

Analysis and Critique of the Advance Market Commitment (AMC) for Pneumococcal Conjugate Vaccines (PCVs) and Impact on Access

EXECUTIVE SUMMARY

This briefing document provides a critical analysis of Gavi, the Vaccine Alliance’s Advance Market Commitment (AMC) pilot for Pneumococcal Conjugate Vaccines (PCVs) and its impact on access to pneumonia vaccines for populations in need. A close and critical review of issues with the AMC model is needed because of the replication of its use for global access to other important vaccines, such as the new COVAX Facility for COVID-19 vaccines, which draws heavily from the AMC mechanism.^{1,2}

Touted as an innovative financial mechanism to incentivize pharmaceutical corporations to address developing-country health needs, the AMC pilot for PCVs (heretofore referred to as “the AMC”) achieved some success but also had shortcomings. Drawing from two evaluations commissioned by the Gavi AMC Secretariat,^{3,4} as well as Gavi’s Pneumococcal AMC Annual Reports,⁵ this document aims to give a critical assessment of the AMC to highlight for stakeholders and Gavi the lessons learned from the practical application of the AMC model, and offers recommendations for reflection and debate in implementation of the AMC model going forward.

Launched in 2009 and scheduled to close in 2020, the overarching goal of the PCV AMC was to reduce morbidity and mortality from pneumococcal diseases, aiming to prevent an estimated 7 million childhood deaths by 2030.⁶ The AMC aspired to achieve four objectives:

1. **Accelerate research and development (R&D)** of pneumococcal vaccines that meet developing-country needs, as specified in the Target Product Profile (TPP), which defined the minimal technical criteria that PCVs must meet to be eligible for AMC funding.
2. **Increase availability** of effective PCVs for developing countries by guaranteeing the initial purchase price, for a limited quantity of the new vaccines, representing value for money and incentivizing manufacturers to invest in scaling up production capacity to meet developing-country vaccine demand.
3. **Accelerate vaccine uptake** by ensuring predictable vaccine pricing for countries and manufacturers, such as through binding commitments by participating companies to supply vaccines at low, long-term sustainable prices after the AMC finances are depleted.
4. Test the effectiveness of the AMC mechanism as an **incentive for supplying** needed vaccines, and to learn lessons for possible future AMCs for other vaccines.

After more than a decade of implementation, the AMC demonstrated success in increasing supply capacity of vaccine manufacturers, and PCV availability in developing countries. However, the AMC failed in fulfilling all of its objectives. Two Gavi AMC Secretariat-commissioned evaluations, one on the AMC’s Process and Design,³ and a second on Outcomes and Impact,⁴ highlighted major weaknesses in the AMC design limiting its success in implementation:

- **R&D not accelerated:** The AMC was flawed from the outset in its selection of pneumococcal disease, which already had a vaccine on the market, since 2000.⁷ PCV was virtually inaccessible to developing countries due to its high price, not because of a lack of R&D. The selection of a disease

with an existing vaccine provided little, if any, incentive for accelerating R&D timelines of other manufacturers who had already begun development prior to the AMC inception.

- **Competition low among manufacturers:** In 2007, US\$1.5 billion was pledged from six donors – Canada, Italy, Norway, Russia, UK, and the Bill & Melinda Gates Foundation – for the launch of the AMC.⁶ While the funding was intended to help encourage competition to reduce the overall price of PCV, in reality the bulk of the money essentially served as a subsidy for Pfizer and GlaxoSmithKline (GSK), which until December 2019 were the only two manufacturers of PCV. Of the \$1.5 billion, \$1.238 billion (82%) was disbursed to Pfizer and GSK. In 2020, a third PCV manufacturer, and the first in a developing country, the Serum Institute of India, was finally awarded a portion of the funding at \$75 million (5%).⁸
- **Lack of transparency and expertise for affordable pricing:** A lack of transparency on costs, capacity, and pricing decisions fed criticism that the AMC acted as a vehicle for private companies to make unnecessarily high profits at the expense of broader vaccine access. The AMC design team lacked critical information and sufficient expertise to appropriately negotiate the original price per dose. If more data from the manufacturers on the costs of production and capacity scale-up had been forthcoming, and if more experts with economic or vaccine-industry experience had been involved, the initial price ceiling of \$3.50 per dose might have been lower but still sufficient to incentivize manufacturers to participate in the AMC. The final subsidy of \$3.50 for the first 21% of supplied doses under each contract *on top of* the \$3.50 tail price (total of \$7.00 per dose) is still high; developing countries may not be able to afford this base price as they lose Gavi support. Additionally, over the past decade of AMC implementation, Pfizer and GSK have provided minimal price decreases (~15%).⁹ PCV remains one of the most expensive among the 12 vaccines supported by Gavi.¹⁰
- **Supply capacity of existing manufacturers did not meet full PCV demand:** During AMC implementation, demand at times exceeded supply despite the large subsidies given to the manufacturers to scale up production capacity. Pfizer and GSK were conservative in expanding their production capacity to only fulfill the number of doses stipulated in supply agreements, but these agreements were based on initial forecasts that were lower than the actual demand. This resulted in supply shortages of up to 29 million doses from 2012 to 2014, delaying 23 country introductions, and leading to an estimated 26 million children born without access to PCV.
- **Lack of improvement in technological capacity for developing countries to produce and supply PCV to their own populations:** No incentive or plan for PCV technology transfer to developing-country manufacturers was included in the design of the AMC. The AMC has yet to prove that it can serve as a model for encouraging long-term, sustainable vaccine production.

Gavi management acknowledged the findings of the two Gavi AMC Secretariat-commissioned evaluations in published responses, though they steered clear of offering serious critique.^{11,12}

In total, five sets of supply agreements⁸ for the PCV AMC were signed between Gavi (and UNICEF, as Gavi's procurement agency) and manufacturers: four with Pfizer and GSK (2010, 2011, 2013, 2018) and one with the Serum Institute of India (2020).

Overall, the evaluations' findings lend support to the criticism that the AMC mechanism in effect increased profits of multinational pharmaceutical corporations at rates higher than necessary to incentivize their involvement to achieve vaccine access in developing countries, while doing nothing meaningful to stimulate competition from developing-country vaccine manufacturers. As recently stated by the Executive Director of the Serum Institute of India, "I attended almost each and every meeting of the AMC since the beginning and therefore I feel extremely depressed with the final outcome when even the small amount could not be available for the developing country vaccine manufacturers. Many years ago, someone asked

me what I thought would be the fate of the AMC. They asked if I thought Serum would end up getting any money out of it. I said that I was 99 per cent sure that most of the money would go to big pharma with maybe a few crumbs left for us.”¹³

Looking forward, as Gavi’s AMC model is replicated for other vaccines, such as future COVID-19 vaccines, this critical analysis of the PCV AMC experience provides an opportunity to learn and avoid having the same flaws in future AMCs, in order to improve and sustain vaccine access to benefit as many people as possible. The following **recommendations** are proposed:

- **Pricing and affordability:** Renegotiate agreements with Pfizer and GSK to bring down the price of their PCVs, which are now at least 36% more than the new lowest global price recently set with the entry of a developing-country manufacturer.
- **Fair profit margin:** Require cost information from vaccine producers to make informed decisions on fair pricing.
- **Country accessibility:** Create a strategy with clear measurable objectives for addressing countries that have transitioned out of Gavi funding eligibility, as well as never-eligible countries.
- **Competition:** Develop a strategy to remove intellectual property (IP) and technological barriers to enable a diverse group of manufacturers, especially within the Developing Countries Vaccine Manufacturers Network (DCVMN), to accelerate development and stimulate real competition.
- **Technology transfer:** Negotiate agreements with requirements for vaccine technology transfer to other potential producers.
- **Clear investment criteria:** Use WHO-based objective criteria to guide AMC financial investments that allocate funding to products anticipated to facilitate optimal access.

BACKGROUND

Two years prior to the World Health Organization (WHO) 2007 recommendation on the use of PCV,¹⁴ the Center for Global Development (CGD) published the 2005 report, *Making Markets for Vaccines*,¹⁵ introducing the concept of the AMC as a financial mechanism that could encourage the development and production of affordable vaccines tailored to the needs of developing countries. The 2013 AMC for PCV Process and Design Evaluation³ framed the AMC concept as “intended to address two perceived failings of global health markets”: 1) pharmaceutical manufacturers are incentivized to focus their R&D on medicines for diseases more prevalent in lucrative markets, such as the US and Europe; and 2) once developed, medicines often reach low-income countries a decade or more after their introduction in high-income markets. As a result, entire generations of children can go untreated or unvaccinated despite the existence of established products able to prevent millions of deaths (e.g. Hib vaccine).

The first PCV to protect young children was PCV7, produced by Wyeth and licensed by the US Food and Drug Administration (FDA) in 2000.⁷ Studies had demonstrated that PCV7 significantly reduced pneumococcal disease burden and related child mortality in both developed and developing countries.¹⁶ With conclusive evidence of the protective effect of PCV in different countries and settings, WHO in 2007 recommended the use of PCV7 in all countries with high pneumonia and under-5 mortality rates, which were predominantly in the developing world.¹⁴

However, implementation of the recommendation was challenging because issues around vaccine development, production and price were not addressed. These issues were not new and had for years prevented many developing countries from procuring PCV. In 2009, an expanded PCV10 (Synflorix; GSK) entered the market,¹⁷ and in 2010, PCV13 (Pneumovax; Pfizer, which had purchased Wyeth) was licensed by the FDA.¹⁸

The AMC uses a forward-looking binding contract from donors and international agencies that guarantees a pre-agreed price for the first doses of vaccines sold to developing countries, under the assumption that vaccine companies can recoup their costs, thus making it an attractive incentive. In exchange, companies guarantee to supply vaccines for a defined duration at the pre-agreed price.⁶ Through these guarantees, the AMC theoretically encourages vaccine makers to develop or build manufacturing capacity to meet supply needs.

PCVs were selected to serve as the first AMC vaccine. The design phase lasted from 2005 to 2008, during which a Target Product Profile (TPP) was developed, an AMC Secretariat was created, an Economic Expert Group (EEG) worked on design and pricing, and an Independent Assessment Committee (IAC) was tasked with preparing a monitoring and evaluation (M&E) plan and legal agreements with manufacturers.¹⁹ In June 2009, the first AMC legal agreements were signed, and in 2010, a decade after the first PCV was introduced in 2000 in developed countries, PCV was finally available for introduction in developing countries.²⁰

By the end of 2019, a total of 60 countries had introduced PCV under the AMC. Of these, 10 are using PCV10 (four countries switched from PCV10 to PCV13 over the duration of the AMC), and 50 have introduced PCV13 (Annex).²¹

KEY FINDINGS

AMC Process and Design Evaluation (2013)

In 2012, a Process and Design Evaluation of the PCV AMC pilot was conducted by Dalberg Global Development Advisors,³ analyzing the “immediate consequences of the [AMC] Pilot’s specific design choices” and “how the key decisions that were made when designing and implementing the Pneumococcal AMC have contributed towards fulfilling the objectives of the AMC Pilot.” The Evaluation did not look at outcomes in terms of how many children were vaccinated, how demand changed as a result of the AMC, or whether or not the AMC was the most effective approach for addressing long-standing challenges to vaccine development, production and price for diseases mostly found in developing countries. These outcomes would be addressed in the Outcomes and Impact Evaluation a few years later.⁴

The Process and Design Evaluation described the motivations of the AMC designers; the trade-offs when it came to decision-making (e.g. short-term vs long-term aims, early-stage vs late-stage product, price setting that benefitted one manufacturer over another); various risks involved with different decisions; and ultimately the consequences of the final design. Overall, the AMC concept was viewed as innovative with a certain level of unavoidable risk and related outcomes that could only be discovered through implementation. The design was grounded in the goal of ensuring that PCV was rolled out in developing countries as soon as possible. As such, the final design used a short-term strategy to ensure this goal was met. However, as the Evaluation revealed, this decision had its advantages as well as disadvantages.

The 2013 Evaluation cited several methodological limitations:

1. The evaluators lacked evidence and full understanding of the global vaccine context and therefore relied on interview responses, which came with a certain degree of bias.
2. Appropriate counterfactuals and control scenarios from which to compare were lacking (e.g. never having an AMC before, nor the existence of a different kind of AMC).
3. The complexity of the design process and the levels of involvement in the design process by individuals interviewed led to bias and subjectivity as a result of partial or incomplete information. Non-response bias was due to the fact that some interviews did not take place as requests were declined. Selection bias was due to the fact that the initial list of individuals interviewed were recommended by Gavi, although broadened through the evaluation process.

4. The evaluators did not have access to manufacturers' data such as costs, expenditures and profit-margin requirements, which they needed in order to evaluate more precisely the extent to which manufacturers were incentivized by the AMC's price ceiling. Rather, the evaluators relied on available but incomplete data, and the use of various scenarios and models.

Key findings from the Evaluation were organized into three focus areas: design process, design elements, and implementation (Table 1).

Table 1. Focus areas of the AMC for PCVs Process and Design Evaluation (2013)

	Focus Area		
	Design Process (2005-2009)	Design Elements	Implementation (2009-2012)
Key Question	How well the process of designing the AMC Pilot was executed, and how this process contributed to the AMC's outcomes to date	How specific AMC design elements contributed to the Pilot objectives	The effectiveness, efficiency, timeliness, transparency, and responsiveness to contextual changes and external factors in both the design and implementation processes to date
Areas of Inquiry	<ul style="list-style-type: none"> • Disease selection • Processes' structure, governance and efficacy • Roles of donors, experts and partner organizations • Expert and stakeholder consultations and communication • Major success factors and trade-offs 	<ul style="list-style-type: none"> • AMC Pilot's price structure and price point • Tail price ceiling • Importance of ensuring donor funding was guaranteed by binding legal agreements • Appropriateness of the Target Product Profile • Importance and accuracy of the assessment of peak demand at 200 million doses • 10-year supply commitment requirement • Limited 3-year purchase guarantee on contracted doses 	<ul style="list-style-type: none"> • Extent to which the AMC has been implemented as designed • Procurement • Prequalification • Governance • Areas of implementation that worked well and challenges during implementation

Overall, the Evaluation found that the **design process** was successfully carried out and proceeded smoothly in large part due to the use and reliance on the original report by the Center for Global Development for the AMC concept,¹⁵ which provided steps to guide development along the way. The design process generated high-level political commitment from the G8 countries, new funding for vaccines, and a range of dedicated champions intent on ensuring that the AMC concept became a reality. Finally, the design process utilized established structures and strengths of different organizations, which saved time and made the process more efficient. The key partners included Gavi, which houses the AMC Secretariat; the World Bank, which manages the AMC funds; and UNICEF, which arranges supply agreements and procurement with manufacturers.

Despite claimed success in the design process, the Evaluation raised several important issues that led to trade-offs and consequences:

1. Disease selection and finalizing objectives

The evaluators noted that the design process itself was done in reverse: the disease was selected before the objectives were finalized. And although the process of designing and developing the AMC was long, designers were only given a 7-week timeline for selecting the disease, which was insufficient time to leverage all available information.

In the end, four objectives (see Executive Summary) were selected, representing the preferences of a wide group of stakeholders, even though the disease selected, pneumococcal disease, already had an existing vaccine. While the inclusion of all four objectives appeased the variety of key stakeholders, the intent of the designers to focus on Objective 2 (increasing availability) and Objective 3 (accelerating uptake) was not sufficiently and explicitly communicated, leaving those who were hopeful of the AMC as a mechanism to achieve Objective 1 (accelerating R&D) confused or disappointed. The objectives created certain expectations, which were not fulfilled equally as the AMC designers selected a late-stage product, which lent itself to achieving short-term outcomes and the use of existing manufacturers, rather than incentivizing new manufacturers to develop new vaccines and compete in the market.

2. Pricing and profits

Among all the **design elements**, the AMC pilot's price structure remains one of continued debate and controversy. The Evaluation explained that based on its analysis, "manufacturers may be earning financial returns greater than what was necessary to incentivize their participation in the Pilot." The Evaluation estimated that returns were likely within the range of 10-20%. Whether or not this is an acceptable profit margin for Pfizer and GSK is highly debatable based on a number of variables; however, issues during the process around price setting were evident:

- First, the AMC designers lacked critical information from the manufacturers on the costs of production and capacity scale-up, which were needed to determine an appropriate price that minimized unnecessary profit but was still sufficient to incentivize manufacturers to join the AMC. Rather, the designers relied on incomplete information and estimates that varied widely to inform their analysis.
- Second, the Evaluation pointed out that the composition of the design group lacked critical expertise needed to negotiate the lowest price. Evaluators concluded that if the design group had more economists and individuals with vaccine industry experience, the price ceiling per dose could have been negotiated lower than US\$3.50, based on a more informed understanding of the market context, costs and price for PCVs.
- Third, communication was not transparent and forthcoming to stakeholders regarding how and why decisions were being made related to the pricing structure. This lack of transparency around pricing remains one that continues to fuel criticism of the AMC as a vehicle for private companies to make unnecessarily high profits at the expense of public money and increased vaccine access.

The "sweet spot" of the AMC's incentive nature would have been to set the price just high enough to encourage manufacturers to participate – covering risks, some opportunity costs and accounting for other factors – but not higher than necessary. However, the information asymmetry between manufacturers and AMC designers led to price setting being largely educated guesswork. Information and analyses suggested that the internal rate of return (IRR) needed to incentivize suppliers would be between 10 and 20%. However, determining a manufacturer's IRR was effectively impossible – or indeed the veracity of this estimated range requirement – due to missing information from manufacturers regarding their fixed and variable costs, capital investments (including dual-use investments), and minimum return requirements. Determining a priori their revenue and unit costs over the lifespan of the AMC was also impossible, as this is dependent on dose volume. Ultimately, the \$3.50/dose price was set based on estimated IRRs of 10-20% over a wide range of investment costs.

Developing-country vaccine manufacturers were expected to earn lower returns from the AMC than multinational corporations. This is because they were expected to receive a much smaller share of the actual AMC subsidy, their development efforts would take longer, and the tail price could decline by the time they entered the market. On the other hand, AMC design analyses suggested that they would still earn IRRs within the 10-20% range while being exposed to a lower risk profile by entering an already established market. Again, actual figures remain untested as they were based on largely unvalidated assumptions at the time.

Manufacturers expressed concern that announcing drastically reduced prices for Gavi countries would reduce its pricing power, thus affecting sales in high-income markets. In reality, this fear was unrealized, as Pfizer has consistently raised its price for PCV13 in the US by 5-6% annually, where the price is now >50% higher per dose compared to 2010.²²

The primary risk exposures of large pharmaceutical manufacturers were capital investments in expanding manufacturing capacity, and opportunity costs associated with expanding production of low-margin products at the expense of not selling higher-margin products. Pfizer stated that their AMC-related investments were “in excess of the \$100 million mark.” GSK indicated a >\$500 million investment in expanded capacity, though a new plant in Singapore was also used to produce PCV for non-Gavi markets as well as other vaccines. Regarding missed opportunity costs, it is impossible to make an economic argument for manufacturers to utilize human and other resources to produce lower-margin products over higher-margin ones. This is not an economic problem but rather a societal and financial-regulation problem, in the face of no standards or mandates regulating the commercialization of life-saving medical products.

Without transparent cost information from suppliers and with only one expert member with prior vaccine industry experience, the AMC pilot designers faced great uncertainty regarding industry costs and profit estimates and lacked the necessary deal-making experience and negotiating power. The Evaluation recognized that pricing the subsidy was one of the most challenging design aspects, and this became even more complex when trying to attract multiple manufacturers with different cost structures.

Overall, the design group was motivated by the following goals in determining the final subsidy payment structure:

- Get vaccines to children in developing countries as soon as possible; this lent to the selection of a late-stage PCV product.
- Set one price ceiling for predictability and to allow for planning and forecasting.
- Ensure both the two existing PCV manufacturers (Pfizer, GSK) participate, thus avoiding a monopoly situation.
- Attract existing manufacturers in the immediate term, while maintaining flexibility for potential price drops once additional manufacturers enter the market.

Grounded in these goals, the final design included two payment structures:

- Manufacturers received a top-up subsidy of \$3.50 for the first 21% of doses in each contract, which was paid out of the \$1.5 billion mobilized for the AMC. This subsidy was intended to offset production costs needed to increase supply based on initial forecasts.
- Manufacturers received a maximum tail price of \$3.50 per dose on all doses over the life of each 10-year supply contract. Out of the \$3.50, Gavi initially pays for \$3.30 and recipient countries provide a co-pay of \$0.20 (with increased country co-financing as governments moved through the transition process).²³

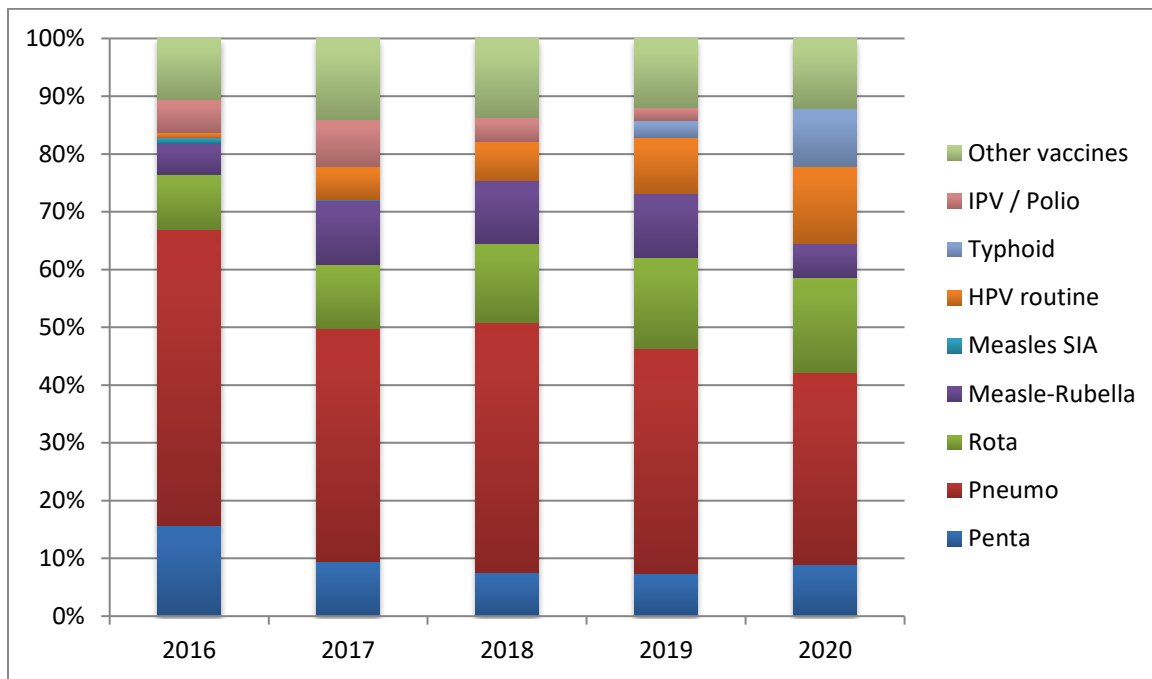
The payment structure put the price per dose at \$7.00, or \$21.00 per child for the three required doses to fully protect a child.

3. Resource mobilization

The final payment structure caused financial distress for Gavi. Gavi ended up bearing 94% of the tail price (\$3.30 out of \$3.50), which was finalized at a higher price than initial estimates and after the launch of the AMC. If the final tail price were set prior to the launch, Gavi may have been able to mobilize an adequate level of resources. Ultimately, the timing of the launch combined with the timing of the final tail price setting caused Gavi's funding crisis in 2011 despite attempts to mobilize additional resources from donors at an emergency meeting in March 2010.²⁴

PCV continues to create challenges for Gavi in resource mobilization as it remains one of the most expensive vaccines supported by the organization. Expenditure figures for the period 2016-2020 indicated that PCV continued to absorb more than 40% of Gavi resources for vaccine procurement, far outstripping any other vaccine it supports (Figure 1).²⁵

Figure 1. Gavi annual expenditure estimates per vaccine, 2016-2020



4. Supply

The AMC designers emphasized legally binding commitments from donors in order to provide guarantees to suppliers, who cited past experiences where, for example, the US government did not follow through on seasonal influenza vaccine purchase intentions. However, other vaccine markets – notably pentavalent – have grown without these formal commitments, instead being based on years of existing high-volume sales relationships between UNICEF/Gavi and manufacturers.

For the AMC designers, allowing countries to choose which vaccine they preferred was important, but this created a mismatch between supply and demand as most countries opted for Pfizer's PCV13, which led to undersupply of this product and a surplus of GSK's PCV10. At least two countries (Bolivia and Senegal) chose to delay introduction until they could access PCV13, despite the availability of PCV10. More attuned demand forecasting could have prevented this.

PCVs are challenging to develop and manufacture, which has delayed entry by other suppliers. However, though the PCV market until very recently remained technically a duopoly, Pfizer has 90% of the global market share by revenue.²⁶ With PCV13 representing Pfizer's single highest revenue-generating product – outstripping even its cancer and chronic-disease franchise products – the company has adopted aggressive market protection tactics that maintain artificially high barriers to entry for potential competitors.

AMC Outcomes and Impact Evaluation (2015)

In 2015, an Outcomes and Impact Evaluation of the AMC Pilot for PCVs was conducted by The Boston Consulting Group.⁴ The independent Evaluation's primary objective was "to assess the extent to which the AMC Pilot has achieved its stated objectives and the overarching goal of reducing morbidity and mortality from pneumococcal disease." The Evaluation also offered lessons for future AMC implementation.

The evaluators drew from a number of resources and data, and used two main counterfactuals in their methodology:

- Vaccine counterfactual: Hib and rotavirus were used to compare against the actual and forecasted performance of PCV. PCV cannot be compared directly to Hib, which was introduced in Gavi countries under a different context, nor to rotavirus, which is less costly to produce than PCV. Nevertheless, these vaccines were deemed the most appropriate for comparison because they were both supported by Gavi, had the same target population, had similar disease burdens, were regarded as underutilized, and had many years of historical data for analysis.
- Market counterfactual: Comparison of PCV introductions in Gavi countries vs non-Gavi countries served as the market counterfactual. This included two types of comparisons:
 - PCV introductions in Gavi-eligible countries receiving AMC support vs non-eligible countries without AMC support (a set of 50 countries with a Gross National Income higher than the eligibility limit); this comparison aimed to understand how the AMC affected a country's interest in introducing PCV.
 - How the AMC facilitated or encouraged the pace of introduction in countries that were supported by the AMC vs countries that introduced PCV without AMC support.

The main limitation of this counterfactual was that it did not control for the fact that Gavi countries receive additional support beyond the AMC in areas such as facilitating vaccine introduction or health systems strengthening that can aid vaccine uptake and delivery.

The findings of the 2015 Evaluation were organized according to the AMC Pilot's overarching goal and four objectives, as follows:

Overarching goal: Reducing morbidity and mortality from pneumococcal disease

The Evaluation concluded that the AMC had accelerated immunization coverage against pneumococcal disease. It cited that 49 million children had been fully vaccinated in 53 countries between 2009 and 2014, averting an estimated 230,000 to 290,000 deaths of children under five years old.

Objective 1: Accelerating the development of vaccines that meet developing-country needs

The Evaluation noted that the AMC stimulated demand as well as innovation from Pfizer and GSK around dose presentation more appropriate for Gavi countries. Supply of PCV was increased and implementation proved that a low-income market exists for PCV. Despite these successes, Objective 1 failed to achieve its focus of accelerating R&D, especially around vaccine licensure and development timelines of other manufacturers, particularly those in developing countries and those with an early-stage product. The evaluators attributed these failures to the initial design of selecting a disease with a vaccine already in existence. The designers, in effect, prioritized a late-stage product that could be rolled out immediately

instead of waiting for a vaccine to be developed, which would require a longer timeframe from development to country introduction. Without other incentives built into the AMC design to support and push other manufacturers to expedite their development timelines, this objective failed.

Throughout implementation, Pfizer and GSK were the only two manufacturers to supply PCV; other manufacturers faced technical, regulatory and clinical delays in their efforts to bring a vaccine to market. Not setting aside funds for a new manufacturer's product creates the risk that the existing suppliers' market dominance will remain a barrier to new entrants. (In December 2019, the third-ever PCV received WHO prequalification from a developing-country vaccine manufacturer, the Serum Institute of India [SII]. In June 2020, SII was awarded a small portion of the remaining \$262.5 million of the \$1.5 billion total subsidy – only \$75 million [5%]. It was announced that the remaining AMC subsidy funds (~\$180 million) will be transferred to a new AMC mechanism for future COVID-19 vaccines.^{8,13})

Objective 2: Bringing forward availability of vaccines

Pfizer and GSK scaled up manufacturing capacity to supply quantities stipulated in supply agreements. However, supply agreements were based on initial forecasts, which in reality were much lower than actual demand. The mismatch between supply and demand combined with a faster-than-estimated pace of uptake led to regular supply shortages throughout implementation, with PCV introductions delayed in approximately 23 countries; the average delay was >12 months in 2012 and 2013. The Evaluation acknowledged that some of the delays were due to country factors outside the control of Gavi, such as political, financial, human-resources, and infrastructure challenges. On the other hand, UNICEF deliberately withheld awarding full quantities to Pfizer and GSK in anticipation of a third manufacturer, which was not realized during the time of the Evaluation. While the decision by UNICEF was intended as an incentive to bring other manufacturers into the AMC, it ultimately created a type of “no-win” situation where the incentive itself was not enough to bring in a third manufacturer at the time, while demand was not met because of supply shortages.

Objective 3: Accelerating vaccine uptake

Positively, uptake of PCV was more rapid than initial forecasts. PCV uptake was also faster than for other Gavi-supported vaccines, namely Hib and rotavirus. To illustrate this point, the Evaluation cited that over six years of implementation, 53 countries introduced PCV while only 19 countries introduced Hib and rotavirus. The reason credited for the success of this objective was the rapid application process for AMC support, which led to more rapid country introductions. In addition, data on the burden of pneumococcal disease were available and accepted by countries, and vaccine efficacy had been proven, communicated and understood. In other words, there was no need to convince countries of the need for and benefits of PCV. Once it became available, countries were quick to apply.

Objective 4: Pilot effectiveness of the AMC mechanism

The Pilot demonstrated that the AMC concept can be successfully implemented; certain design elements can positively affect behavior of donors, manufacturers, and developing countries; and relatively good value for money can be realized in increasing affordability and supply of PCV for developing countries to improve health outcomes. The Evaluation pointed out that R&D was not stimulated as anticipated, supply shortages occurred, competition beyond two existing manufacturers was not realized, and further price drops did not occur due to lack of increased competition. Implementation of the AMC for the first time revealed key lessons:

- Competing objectives (those that satisfy a wide range of stakeholders) can undercut overall outcomes.
- Late-stage products do not stimulate acceleration of R&D; early-stage products require a different set of incentives.

- Productive relationships with manufacturers can support their transition from a Corporate Social Responsibility approach to one of a commercially viable strategy for vaccines supplied in developing countries.
- Financial, political and logistical challenges and barriers need to be overcome to ensure an enabling environment for the future success of the AMC and other similar initiatives.

AMC Annual Reports

In addition to the independent 2013 and 2015 Evaluations, progress towards reaching the overall goal and objectives of the AMC has been monitored through Pneumococcal AMC Annual Reports by the AMC Secretariat.⁵ This work is guided by a monitoring and evaluation (M&E) framework first proposed in the 2008 AMC “Report of the Monitoring and Evaluability Study”,²⁷ which was commissioned by the M&E subgroup of the AMC donors (those who had pledged the initial \$1.5 billion). The study proposed a strategy, implementation plan, associated costs, and timeframe for M&E, which serves as the basis for M&E activities to date, and which are “designed to enable the effectiveness, efficiency and eventual impact of this AMC to be measured over time and to assist with its effective management.” Since 2009, the AMC Secretariat has published annual reports based on the M&E framework, describing progress in the implementation of several key areas: supply and procurement, media and communications, financials, and M&E activities. From the annual reports, two key areas stand out as needing further review, discussion, and adjustments: M&E Framework, and Supply Agreements.

M&E Framework

Of particular interest are M&E indicators used for tracking progress of the first three AMC Objectives of accelerating R&D, increasing availability, and accelerating uptake. The 2019 AMC Annual Report lists progress since 2009 (Table 2).²¹ In analyzing the data, Objective 1 (R&D) showed no progress in accelerating R&D since 2009, while Objectives 2 (availability) and 3 (uptake) demonstrated significant ramp up of availability and uptake of PCV. As noted in the 2013 Process and Design Evaluation,³ the framework lacks targets and process indicators needed to more “meaningfully track progress, guide strategic decisions, learn from any changes in trends and directly attribute them to this AMC.” The 2013 Evaluation recommended that the M&E framework should be improved to add process indicators and targets directly linked to achievement of the four AMC objectives. This should include indicators that address causes of delays in country introduction, and issues around supply meeting demand, competition, and price reductions.

Table 2. Selected non-confidential indicators for AMC progress tracking (calendar year view) in both AMC-eligible and Gavi-supported countries²¹

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Objective 1: to accelerate the development of PCV that meet developing country needs											
Cumulative number of AMC-eligible target product profile (TPP) vaccines	0	2	2	2	2	2	2	2	2	2	2
Cumulative number of AMC-registered manufacturers that have made their registration public	0	4	4	4	4	4	4	4	4	4	4
Objective 2: to bring forward the availability of effective PCV for developing countries											
Annual number of doses of TPP vaccine procured under AMC by year (in millions)	0	7	36	58	58	100	133	164	156	149 ^a	161
Objective 3: to accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers											
Cumulative number of countries that have:	21	21	49	52	59	59	59	60	60	61	62
applied for Gavi support for PCV											
been approved	3	17	37	46	51	55	58	59	59	60	60
introduced TPP vaccines	0 ^b	1 ^b	16	24	38	46	54	57	58	59	60
PCV coverage*	0%	1%	5%	9%	19%	28%	37%	43%	45%	48% ^c	n/a ^{**}
Cumulative number of children vaccinated with PCV with Gavi support (in millions)	-	0.4	4	10	25	46	76	110	146	184	[225] ^{**}

Source: Gavi Secretariat

* Indicator defined as the percentage of eligible population reached across 73 Gavi-supported countries.

** Expected estimate. WUENIC coverage data and WHO-reported number of immunised for 2019 will be available in July 2020.

^a The decrease was caused by a decline in demand from Nigeria, whose coverage rate has been lower than previously estimated, due to a recent survey with new information.

^b Two countries introduced PCV in 2009 but with a vaccine that was not TPP compliant. They switched to a TPP-compliant vaccine in 2011.

^c The annual WUENIC update covers the whole time-series, so at times previous years' coverage figures change too.

Supply Agreements

The AMC Annual Reports present updates on supply agreements and allocation of AMC funds. Of the \$1.5 billion AMC subsidy, \$1.238 billion (82%) went to Pfizer and GSK in seven supply agreements (three with GSK and four with Pfizer) through 2019.²¹ Although the 2020 Annual Report has not yet been released at the time of this writing, an eighth supply agreement was reached in June 2020, with at least a third manufacturer, the Serum Institute of India.⁷ However only \$75 million, or 5%, of the \$1.5 billion AMC subsidy was allocated for the Serum Institute.

Over the last several years, both Pfizer and GSK have reduced their tail price per dose, albeit minimally (Table 3):⁸ for Pfizer from \$3.50 to \$3.40 in 2013, \$3.30 in 2014, \$3.10 in 2017, \$3.05 in 2018, and \$2.90 in 2019; and for GSK from \$3.50 to \$3.40 in 2014,^{9,28} and \$3.05 in 2017.⁹ Important to note however is that both Pfizer and GSK created new multi-dose vial presentations of their PCVs: in 2017, Pfizer produced a new 4-dose vial (in addition to the previous single-dose vial); and in 2018, GSK also produced a new 4-dose vial (in addition to the previous 2-dose vial). The Pfizer price decrease to \$2.90 per dose is for the 4-dose vial (whereby the single-dose vial price is \$3.30 per dose). Multi-dose vial presentations provide production cost savings to the manufacturer.

While on the surface, these small reductions appeared to show a commitment by both Pfizer and GSK to increase value for money by making PCV more affordable and therefore more accessible to developing countries, certain conditions were imposed by Pfizer in the third supply agreement to accelerate the disbursement of their full subsidy payment. Also, although the tail price decreased, the subsidy payment was *increased* to still reach a total payment of \$7.00 per dose, for the doses eligible for the subsidy top-up.²⁹ The rationale or justifications used by Pfizer to secure this condition, or why Gavi and UNICEF agreed to them, is unclear. What is clear is that Pfizer's reduced tail prices were not uniquely a company intention to create increased savings in this case. This arrangement underscores the need for more transparent deliberation and communication about how decisions are made around supply agreements.

Table 3. Status on overall AMC PCV supply commitments⁸

Manufacturer	Date of Signature*	Annual Supply Commitment (Doses)	Tail Price (Per Dose)	Supply Start Date	AMC Funds Allocated
GSK	23 March 2010	30 million	\$3.50; reduced to \$3.05 from 2017**	January 2012	\$225 million
Pfizer	23 March 2010	30 million	\$3.50; reduced to \$3.40 mid 2013 and \$3.30 from 2014. Further reduced to \$3.05 from 2017 and \$2.95 from 2018 for the 4-dose vial only.† Further reduced to \$2.90 from 2019 for the 4-dose vial only.	January 2013	\$225 million
GSK	12 Dec 2011	18 million	\$3.50; reduced to \$3.05 from 2017**	January 2014	\$135 million
Pfizer	12 Dec 2011	18 million	\$3.50; reduced to \$3.40 mid 2013 and \$3.30 from 2014. Further reduced to \$3.05 from 2017 and \$2.95 from 2018 for the 4-dose vial only.† Further reduced to \$2.90 from 2019 for the 4-dose vial only.	January 2014	\$135 million

GSK	22 July 2013	24 million	\$3.40; reduced to \$3.05 from 2017**	January 2015	\$180 million
Pfizer	22 July 2013	26 million	\$3.40 in 2013; \$3.30 from 2014. Further reduced to \$3.05 from 2017 and \$2.95 from 2018 for the 4-dose vial only.† Further reduced to \$2.90 from 2019 for the 4-dose vial only.	January 2016	\$195 million
Pfizer	5 April 2018	19 million	\$2.95 for the 4-dose vial from 2018. Further reduced to \$2.90 from 2019.	January 2018	\$142.5 million
Serum Institute of India	2 June 2020	10 million	\$2.00 for the 5-dose vial	June 2020	\$75 million

* Date of signature represents the first day of the week during which UNICEF signed the supply agreements.

** On 17 March 2016, GSK announced that they are reducing the tail price of their pneumococcal vaccine (PCV10) to \$3.05 per dose from 2017.

† Following various price reduction announcements from Pfizer, doses procured under Pfizer supply agreements were purchased at \$3.40 in 2013 and \$3.30 from 2014 onwards. In 2017, doses procured under Pfizer supply agreements were purchased at \$3.05 for the 4-dose vial and from 2018 onwards, the price is further reduced to \$2.95 for the 4-dose vial. Pfizer announced an additional price reduction for the 4-dose vial from 2019 by 5 cents per dose to \$2.90 per dose.

PCV PRICE: COMMITMENTS FOR GAVI TRANSITIONED COUNTRIES AND CHALLENGES FOR MIDDLE-INCOME COUNTRIES

Countries no longer Gavi-eligible or transitioning from Gavi eligibility are subject to an array of different price agreements.³⁰ Only 13 countries remain eligible to access PCV under AMC terms and conditions.²⁶ Six of these have transitioned and must fully self-finance PCV purchase at the AMC tail price, while 7 remain eligible to receive Gavi support. Non-Gavi middle-income country (MIC) PCV prices can be 5 to 10 times the AMC tail price, and only 30% of self-procuring MICs have introduced PCV. Many countries still consider the price too high to cost-effectively introduce the vaccine into the routine immunization program.

As highlighted by WHO's Market Information for Access to Vaccines (MI4A) study on PCV,³¹ "MICs have voiced affordability of PCV as an important concern. WHO conducted an analysis to identify countries that are likely to be constrained due to vaccine affordability; countries were compared to their peers on factors including other introduced vaccines, vaccine choices, vaccine procurement strength, and the percentage of government expenditure spent on health. The PCV affordability analysis was conducted on 32 non-Gavi, non-PAHO MICs (16 introduced and 16 not introduced) where data were available to support the analysis. For six countries in the analysis, adding PCV to their immunization schedule appears to be an affordability challenge. For these countries, an estimated 53-87% of the immunization budget would need to be spent on PCV."

As of June 2020, the Serum Institute of India's 10-valent PCV (different serotype composition than GSK's PCV10) is now the third PCV product under the AMC, with a price of \$2.00 per dose. However, it is unclear whether or not any countries that have already introduced PCV will switch to this product. Gavi's market-shaping efforts could be utilized to assist countries in understanding the potential epidemiological and economic impact of using this new vaccine relative to others in order to assist countries in making the most informed decisions possible.

CONCLUSION AND RECOMMENDATIONS

While the AMC has undeniably accelerated PCV coverage among children in the poorest countries, and ultimately reduced morbidity and mortality due to pneumococcal disease, the mechanism only achieved some of its objectives, and at times only had partial success towards those achievements. A review of the 2013 and 2015 Evaluations and AMC Annual Reports reveal the consequences of the design and implementation of the AMC to date. These consequences led to several shortcomings ultimately undermining the full success of the AMC.

The 2013 Process and Design Evaluation highlighted that the decision of the AMC designers to prioritize short-term gains (in terms of increasing supply capacity, availability, and uptake) rather than long-term sustainability (in stimulating R&D innovation and competition, and increasing affordability) led to partial success for Objective 2 (increasing availability) and Objective 3 (accelerating uptake), but minimal progress on Objective 1 (accelerating R&D). While a third PCV manufacturer finally entered the market in late December 2019 at the cusp of the AMC's conclusion, evaluation conclusions were that the PCV market alone was attractive enough to incentivize development of new PCVs from developing-country vaccine manufacturers. Significant disappointment has been expressed by developing-country vaccine manufacturers at how the AMC was designed and the miniscule amount of the AMC subsidy left over after payments to Pfizer and GSK.¹³

The 2015 Outcomes and Impact Evaluation was the first review of the AMC's progress towards achieving the overall goal and four objectives of the AMC and found that the overall goal was on track, but also confirmed that Objective 1 on accelerating R&D was not met. It concluded that choosing a disease with a late-stage vaccine product compromised the potential for increasing competition, especially among developing-country producers, and for achieving further reductions in vaccine price.

Gavi's AMC Annual Reports reinforced the Evaluations' findings on Objective 1 and also shed light on the supply agreements with Pfizer and GSK. The small but significant condition by Pfizer in its third supply agreement to ensure a steady \$7.00/dose payment total despite reducing its tail price calls into question the intentions of Pfizer in prioritizing profit over value for money.

Overall, the Evaluations and Annual Reports have served to support, rather than minimize, criticism of the AMC as a mechanism that in effect increases profits of multinational pharmaceutical corporations at rates higher than necessary to incentivize their involvement to achieve broader vaccine access.

MSF's key areas of concern and recommendations to address AMC implementation going forward include:

- **Pricing and affordability:** Despite the AMC, the price of Pfizer and GSK's PCVs is still too high and is significantly more expensive than many other Gavi vaccines used in developing countries.²⁰ Additionally, PCV price commitments through the AMC are only available to Gavi-eligible and Gavi-transitioned countries until 2025 for the Pfizer product, and for 10 years after a country's final year of Gavi support for the GSK product. Although a more affordable third PCV from the Serum Institute of India recently entered, demand from Gavi countries is not yet high (as the bulk of the financial burden falls on Gavi's budget rather than individual government health budgets).
 - *Recommendation:* Gavi should renegotiate agreements with Pfizer and GSK to bring down the price of their respective PCVs and ensure that price commitments are sustained over the long term. To ease the significant burden of current PCV purchases on Gavi's budget, as well as government budgets when they have to assume the full cost themselves, Gavi should allocate financial resources for direct assistance to countries, using technology and impact assessments for informed decision-making when considering which PCV to use.
- **Fair profit margin:** The AMC Pilot used donor money to incentivize manufacturers to produce more doses through the provision of subsidies.³² However, setting a ceiling tail price for PCV and

designing the top-up subsidy that would be awarded in addition to the tail price were difficult due to lack of information on the costs and expectations of manufacturers. Assessment of a fair-pricing strategy is impossible when manufacturers have all of the financial details of the procuring agencies and donors, but reveal none of their own internal costs or expectations.

- *Recommendation:* Gavi should require agreement from vaccine developers and producers to reveal their cost information so as to make more informed and appropriate decisions about vaccine prices.
- Country accessibility: PCVs through the AMC are only available to Gavi-eligible and Gavi-transitioned countries, leaving other developing countries that do not fall into the “poorest” category, as defined by Gavi (e.g. most lower-middle income and middle-income countries), without an affordable option.³² The healthy markets framework, co-developed by the Bill & Melinda Gates Foundation, Gavi and UNICEF, has as its top pillars Total System Effectiveness, Long-term Competition, and Product Innovation, and is used to evaluate Gavi against its market-shaping goals. However, its application to non-Gavi countries is poorly understood and articulated.
 - *Recommendation:* Gavi must create a strategy, with clearly stated, measurable objectives, for addressing the needs of countries that have transitioned out of Gavi eligibility so that they are able to sustain their immunization gains once they are fully self-financing. Additionally, as never-eligible countries continue to struggle with introduction of PCV due to its high price, and seemingly the PCV market outside of Gavi has not been affected by the AMC, Gavi should develop a clear plan to share its experience and benefits with a broader set of countries via other regional or economic groupings (and procurement platforms).
- Competition: For a decade, the AMC failed to stimulate competition from developing-country manufacturers, even though such competition can lower vaccine costs and improve supply production, therefore increasing affordability and accessibility, and ultimately vaccine coverage. Barriers to competition include intellectual property (IP) and technological know-how hurdles – issues that were not addressed in the AMC. The design of the AMC was therefore not conducive to supporting early-stage product development; ultimately, almost the entire duration of the AMC life span saw the same two manufacturers – Pfizer and GSK – being awarded the subsidy.
 - *Recommendation:* Gavi should develop a strategy to remove IP and technological barriers to enable a diverse group of manufacturers, especially within the Developing Countries Vaccine Manufacturers Network (DCVMN), to accelerate development and stimulate real competition. Gavi should particularly aim to stimulate competition from companies in developing countries, and the DCVMN, as these companies have a different business strategy than multinational companies and tend to set prices significantly lower.
- Technology transfer: The AMC contained no incentive nor mandate for vaccine technology transfer to developing-country producers to support long-term sustainability, competition and price drops. If concrete steps are not taken to broaden the manufacturer base, challenges of negotiating affordable prices and ensuring adequate supply will perennially plague Gavi’s efforts (as has been seen with other vaccines, such as for human papillomavirus [HPV]).
 - *Recommendation:* Gavi must negotiate a condition in future AMC agreements – and for any future new AMCs – to facilitate technology transfer to other producers that can demonstrate a commitment towards access and affordability.
- Clear investment criteria: While part of the PCV AMC’s activities were to design a target product profile (TPP) that would guide the development of competitor products and support the AMC R&D objective to accelerate development of new PCVs, this TPP was never used to guide investments as

AMC financing was not structuring to successfully stimulate R&D. Future AMCs should use clear criteria to direct their investments, rather than being "first come, first serve" to manufacturers.

- *Recommendation:* Gavi should guide any future AMC investments by a clear set of criteria (developed by WHO) so that funding is allocated to the products anticipated to facilitate optimal access.

ANNEX. Status of Country Introductions and Approvals of PCV, 2009-2019²¹

Year	Country Introductions of PCV
2009	Gambia, Rwanda
2010	Nicaragua
2011	Benin, Burundi, Cameroon, Central African Republic (CAR), Democratic Republic of the Congo (DRC), Ethiopia, Guyana, Honduras, Kenya, Malawi, Mali, Sierra Leone, Yemen
2012	Congo-Brazzaville, Djibouti, Ghana, Madagascar, Pakistan, Sao Tome & Principe, Tanzania, Zimbabwe
2013	Afghanistan, Angola, Azerbaijan, Burkina Faso, Kiribati, Laos PDR, Mauritania, Moldova, Mozambique, Papua New Guinea, Senegal, Sudan, Uganda, Zambia
2014	Armenia, Bolivia, Cote d'Ivoire, Georgia, Liberia, Niger, Nigeria, Togo
2015	Bangladesh, Cambodia, Eritrea, Guinea-Bissau, Lesotho, Nepal, Solomon Islands, Uzbekistan
2016	Kyrgyzstan, Mongolia, Myanmar
2017	India (select state introduction)
2018	Haiti
2019	Bhutan

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