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THE BOSTON CONSULTING GROUP

Gavi
The Vaccine Alliance

The Advance Market Commitment Pilot for Pneumococcal Vaccines:

Outcomes and Impact Evaluation

The Boston Consulting Group

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Acronyms and Abbreviations

AMC	Advance market commitment
APA	Advance-purchase agreement
AVI	Accelerated Vaccine Introduction
BMGF	The Bill and Melinda Gates Foundation
CAGR	Compound annual growth rate
DALY	Disability-adjusted life year
DTP	Diphtheria-tetanus-pertussis vaccine
FVP	Fully vaccinated person
Gavi	Gavi, the Vaccine Alliance
GNI	Gross national income
GSK	GlaxoSmithKline
Hib	Haemophilus influenzae type B
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSS	Health system strengthening
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
LiST	Lives Saved Tool
M&E	Monitoring and evaluation
MSF	Médecins Sans Frontières (Doctors without Borders)
PAHO	Pan American Health Organization
PATH	Formerly called the Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
PCV 10	10 valent pneumococcal conjugate vaccine
PCV 13	13 valent pneumococcal conjugate vaccine
PCV 7	7 valent pneumococcal conjugate vaccine
PCV3	Received all three doses of pneumococcal conjugate vaccine
PneumoADIP	The Pneumococcal Vaccines Accelerated Development and Introduction Plan
R&D	Research and development
Rota	Rotavirus
SDF	Gavi Strategic Demand Forecast
TPP	Target Product Profile
TRIVAC	Model developed by London School of Hygiene and Tropical Medicine
U-5	Under five years old
UNICEF	United Nations Children's Fund
VIG	Vaccine Introduction Grant
VIMS	Vaccine Information Management System
WHO	World Health Organization
WUENIC	WHO UNICEF Estimates of National Immunization Coverage

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1. Executive Summary

Background

The Advance Market Commitment (AMC) pilot, started in 2005 and officially launched in 2007, was established to reduce morbidity and mortality from pneumococcal disease by accelerating the development, availability, and uptake of pneumococcal conjugate vaccines (PCVs).[i]

This innovative financing mechanism deploys funding commitments of $1.5 billion from six donors (Italy, the United Kingdom, Canada, Russia, Norway, and the Bill and Melinda Gates Foundation). The AMC Secretariat, hosted by Gavi, the Vaccine Alliance, is responsible for providing operational, administrative, and financial support. Collection and disbursement of the AMC funds is managed by the World Bank, while UNICEF issues calls for supply offers and manages procurement.

The intent behind forward financial commitments is to establish the viability of the market, thus reducing the barriers for manufacturers to invest. The AMC pilot sought to assess whether this intent would play out in practice.

Specifically, the objectives of this pilot were to:[ii]

- **Accelerate the development** of pneumococcal vaccines that meet developing country needs (e.g., serotype composition and vaccine presentation) as specified in the Target Product Profile.
- **Bring forward the availability** of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price for a specific quantity of the new vaccines that represents value for money and incentivizes manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand.
- **Accelerate vaccine uptake** by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term, and sustainable prices after the AMC finances are depleted.
- **Pilot the effectiveness of the AMC mechanism** as an incentive for needed vaccines and to learn lessons for possible future AMCs.

Objectives and methodology of this evaluation

The primary objective of this outcomes and impact evaluation is to assess the extent to which the pilot AMC has achieved its stated objectives and the overarching goal of reducing morbidity and mortality from pneumococcal disease. In addition to measuring progress made against each

[i] The Target Product Profile (TPP) specifies naming and production guidelines for pneumococcal conjugate vaccines.
[ii] Wording comes from final AMC objectives document, January 11, 2008. Lack of "conjugate" specification comes from original wording.

objective and estimating the AMC's total impact, the evaluation also captures lessons learned in the pilot.

This evaluation builds on a significant body of data, analysis, and evidence that has been generated by Gavi and its partners over the past 10 years. The independent evaluation team reviewed more than one hundred reports and documents; conducted one or more interviews with 57 representatives from diverse entities (Global health experts, manufacturers, NGOs, academics, funders, in-country representatives, to name a few); and utilized a number of detailed analytical methods, including analysis of counterfactuals, to draw conclusions regarding the achievement of the pilot. The methodology is described in more detail in Section 4.

Summary findings

Overarching goal: Reducing morbidity and mortality from pneumococcal disease

The introduction of pneumococcal conjugate vaccines (PCVs) through the AMC pilot has accelerated immunization coverage against pneumococcal disease across 53 Gavi countries to date,[iii] with 49 million children fully immunized[iv] between 2009 and 2014. Through 2015, these immunizations have averted an estimated 230,000 to 290,000 deaths of children under five years old. Over 3 million under-five deaths are estimated to be averted by 2030, contingent on the immunization continuing.[v] The AMC contributed to this impact by helping to increase supply availability and uptake of PCV.

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

The AMC pilot stimulated demand and brought forward supply but had very little influence on accelerating research and development (R&D) outcomes, in particular vaccine licensure. When PCV was selected for the AMC pilot through a rigorous review process in 2006, two candidates compliant with the AMC Target Product Profile (TPP) were already in advanced stages of development. At the time of selection, it was well understood that the mechanism would not influence development timelines for these late-stage PCV candidates. As expected, both late-stage candidates became available shortly before the first AMC supply agreements were signed in 2010, in line with the companies' pre-AMC expectations.

While some AMC designers and stakeholders recognized that the AMC would have little direct impact on R&D timelines for early-stage candidates, others had great hope for the market entry of a third manufacturer that could increase competitive pressure and reduce the long-term price

[iii] The 53 countries do not include Uzbekistan, which is scheduled to introduce by the end of 2015. An additional four countries are approved for introduction but expected to introduce in 2016 or later.

[iv] Fully immunized, in this context, refers to children with all three doses of PCV.

[v] These estimates are lower than earlier AMC targets due to downward revisions in estimated underlying disease burden, but the AMC is largely on track relative to coverage targets. While based on academic models, these findings are also supported by empirical evidence, as explained further in Section 5.4.

of PCV for Gavi markets. However, to date, the AMC has not succeeded in accelerating the development timelines of other manufacturers. Companies with earlier-stage candidates have faced significant technical and regulatory challenges in developing this complex product, even with direct push funding in some cases (e.g., Serum Institute of India)[vi,1]. This result has highlighted the limitations of this pull mechanism to stimulate the development of an early-stage, technically complex product.

The AMC did have two positive R&D effects: first, it proved that there would be a large low-income country market after the conclusion of the AMC, which likely encouraged many manufacturers to continue to pursue development. Second, the creation of this market stimulated presentation innovation specifically for Gavi markets by existing suppliers (e.g., four-dose vials that eased cold-chain challenges[vii]).

Objective 2: Bringing forward availability of vaccines

The two currently qualified AMC manufacturers, GlaxoSmithKline (GSK) and Pfizer, have built additional manufacturing capacity in response to an unprecedented rate of demand for PCV. Some of this manufacturing scale-up had already been planned and/or begun prior to the AMC, with both companies seeking to serve the robust global market beyond Gavi countries. However, analysis confirms that each company made investment decisions to further expand capacity to serve Gavi markets in response to the AMC and its supply agreements. These decisions were affected by the long-term demand stimulated by the AMC and by the way that the AMC altered supplier economics—i.e., by providing more revenue in the near-term as well as confidence of additional volume that allowed them to achieve scale benefits and thus reduce their costs per vaccine.

While PCV manufacturing scale-up was impressive in its speed and scope, there have been persistent and notable supply shortages over the past five years. These shortages, most notable during 2012 and 2013, resulted in delayed country introductions. They also underscore the tension inherent between the objectives for manufacturing scale-up and for incentivizing the entry of a third manufacturer after GSK and Pfizer. During the first three supply agreements in 2010, 2011, and 2012, UNICEF purposefully opted not to award the full quantities of the strategic demand forecast for 2014, 2016, and 2017 respectively.[viii,2] As a result of these decisions to reserve funds for a potential third manufacturer, GSK and Pfizer did not scale up as aggressively as they otherwise might have.

[vi] Serum Institute has received grant funding from the Bill and Melinda Gates Foundation

[vii] Note: the 4-dose vial is not yet pre-qualified or procured

[viii] At the time, Gavi stated, "*In order to incentivise manufacturers to accelerate the development of new vaccines, to contribute to the creation of a healthy market with multiple suppliers, and to enhance the possibility to access lower tail prices through future offers, quantities have been reserved for award at a later point in time.*"

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Objective 3: Accelerating vaccine uptake

Two pneumococcal conjugate vaccines with appropriate serotype coverage for Gavi geographies, PCV 10 and PCV 13,[ix] became available in Gavi countries just one year after they were available in developed countries, substantially faster than the nine years it took for PCV7 or the eight years it took for the Hib and HPV vaccines. The vaccine was introduced in more Gavi countries (53) in the first six years than either the Hib or rotavirus (rota) vaccines, each of which only had 19 country introductions in the analogous time period. Accordingly, access and coverage in this time period exceeded that of Hib and rotavirus vaccines by three to four times as well. While important contextual differences among PCV, Hib, and rota must be considered in any comparison, it is clear that the PCV uptake, aided by the AMC, was unprecedented.

Other considerations

While the AMC played an important role in accelerating supply availability, country demand, and PCV coverage, these positive outcomes were aided by many other factors. Prior to the AMC, efforts such as the PneumoADIP and Gavi's Accelerated Vaccine Introduction initiative established strong disease burden awareness and generated robust political will for immunization. Similarly, a strong WHO recommendation preceding the AMC was also important in influencing country decisions. Perhaps most importantly, Gavi has provided significant funding support for PCV. Aside from the $851 million in AMC funds (out of the $1.5 billion) that have been disbursed between inception of the AMC and March 2015, Gavi has provided over $1.184 billion in funding support,[3] dramatically reducing the cost of the vaccine borne by the countries. Therefore, while the AMC clearly contributed to accelerated availability and uptake of PCV, it is not possible to attribute these results exclusively to the AMC.

Lessons learned

As a pilot, this AMC has provided proof of concept that an AMC can be practically implemented and that several of its key design elements can improve vaccine-related outcomes and impact.

Beyond the positive outcomes and impact achieved, this pilot has provided a valuable set of lessons learned, which can inform future AMCs or other innovative financing mechanisms:

1. Competing objectives are a natural outcome of a multi-lateral design process that seeks to balance the interests of many stakeholders. But these competing objectives can ultimately undercut outcomes. Having clear prioritization and making hard choices about desired outcomes and objectives aligns stakeholders and leads to greater achievement of those outcomes.
2. Earlier stage products, particularly those that are technically complex, likely require a portfolio of incentive mechanisms to accelerate R&D outcomes. While the pilot AMC was not a true test of early-stage R&D stimulation, the pilot did show the limitations of a pull mechanism for accelerating R&D

[ix] The "10" and "13" after PCV refer to the number of serotypes the vaccines contain. PCV10 is a GSK product; PCV13 is a Pfizer product.

3. Successful engagement with the biopharmaceutical industry, including enabling manufacturers to shift from a CSR-based approach to a commercially viable strategy, is critical to sustainable outcomes. The pilot AMC created a measure of trust and a platform for communication that can be leveraged going forward to contribute to positive outcomes for both the global health community and industry.
4. There are considerable financial, political, and logistical barriers to uptake. Complementary forces to an AMC are critical for creating the enabling environment necessary to overcome these barriers and ensure success for an AMC or related initiatives.

Economic Assessment

The pilot AMC was considered by many to be an innovative mechanism and garnered more attention because of this novelty and innovation. As a result, the AMC likely attracted more donor funds than a traditional vaccine rollout would have generated and ultimately improved Gavi's replenishment.

A key question is whether the AMC delivered good value for the donor investment in the pilot, in terms of outcomes and impact achieved. An attempted calculation of the return on the $1.5 billion invested would not produce a meaningful result given the multiple overlapping and confounding factors that influence outcomes. The AMC pilot generated market outcomes (e.g. increased affordability, sustainable supply) that will ultimately affect future health outcomes, and value for money should be considered through this broader lens. Through certain design elements, the AMC affected donor behavior, manufacturer behavior, and sustainability of country immunization programs that will continue to benefit the global health community and the Gavi population well into the future, creating considerable long-term value.

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2. Introduction and Background

2.1 History of the AMC pilot

There has been a lack of research, development, and country introduction of innovative products targeted at the developing world due to insufficient profitability, which has left large populations vulnerable to preventable and/or treatable diseases. Through a process that began in 2005 and officially launched in 2007, the Advance Market Commitment (AMC) pilot was established to accelerate the development, availability, and uptake of pneumococcal conjugate vaccines (PCVs) appropriate for developing country needs.[x] PCVs protect against pneumococcal infections, and are the most effective prevention against diseases which cause more than 500,000 childhood deaths each year.[4]

As an innovative financing mechanism, the AMC deploys funding commitments of $1.5 billion from six core donors (Italy, the United Kingdom, Canada, Russia, Norway, and the Bill and Melinda Gates Foundation). With these funds, the AMC seeks to achieve its overarching goal of reducing morbidity and mortality from pneumococcal disease by stimulating the development, availability, and uptake of vaccines in Gavi countries and ensuring long-term equitable access to PCVs at affordable prices.

The intent behind forward financial commitments is to establish the viability of the market, thus reducing the barriers for manufacturers to invest. The AMC pilot sought to assess whether this intent would play out in practice. Specifically, the objectives of this pilot were to:[xi]

Accelerate the development of pneumococcal vaccines that meet developing country needs (e.g., serotype composition and vaccine presentation) as specified in the Target Product Profile.

Bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price for a specific quantity of the new vaccines that represents value for money and incentivizes manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand.

Accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term, and sustainable prices after the AMC finances are depleted.

Pilot the effectiveness of the AMC mechanism as an incentive for needed vaccines and to learn lessons for possible future AMCs.

The overarching goal and objectives of this pilot can be seen in Figure 1. This evaluation measures the progress made against each of the outcomes, estimates the total impact, and captures the lessons learned regarding outcomes and impact.

[x] The Target Product Profile (TPP) specifies naming and production guidelines for pneumococcal conjugate vaccines.
[xi] Wording comes from final AMC objectives document, January 11, 2008. Lack of "conjugate" specification comes from original wording.

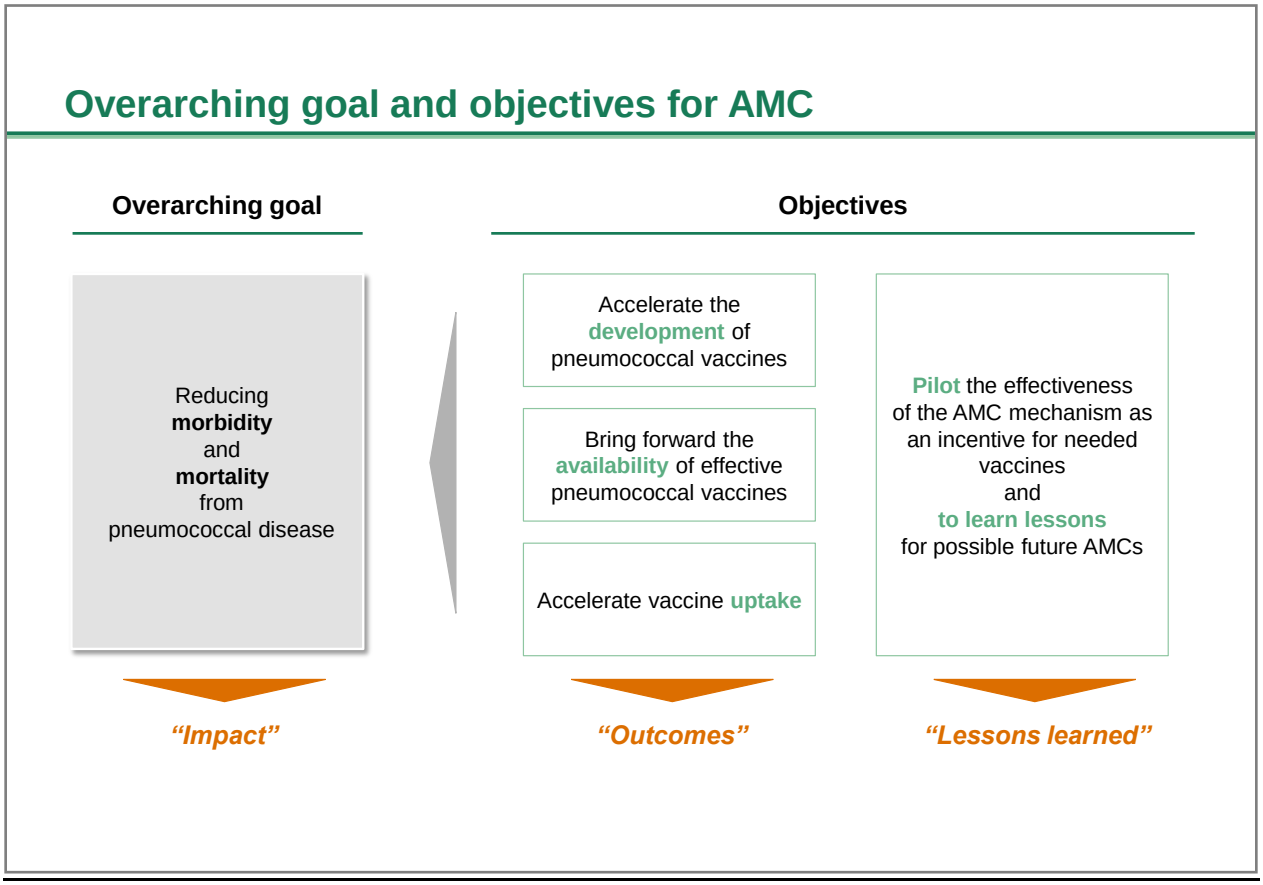

Figure 1

From an operational perspective, the pilot relies on the International Bank for Reconstruction and Development, a World Bank institution, for financial management of funds disbursement to Gavi and oversight of collection of donor funds. UNICEF is responsible for procurement of vaccines. The AMC Secretariat, hosted by Gavi, is responsible for providing administrative support, while the Gavi Alliance provides standard financial and operational support.

The AMC pilot is approximately halfway through its funding commitment period. Three procurement rounds have been completed since the first call for supply offers in 2009. To date, 73 percent of the total AMC subsidy has been allocated to two manufacturers, Pfizer and GSK, across the current six supply agreements. So far, demand is currently 100% met through at least 2018.[xii] Additional forecasted demand will trigger new rounds of tenders. In all, 27 percent of the original $1.5 billion in AMC funds remains available for future allocation, available through the end of the offer period in 2020 (see Figure 2). While two manufacturers have entered into

[xii] Per SDF v12, in which 2019 is the first year that exceeds 146 million doses of demand for the 73 Gavi countries.

supply agreements, another two manufacturers have made their registration public. As of October 2015, 53 AMC-eligible countries have introduced PCV.[5]

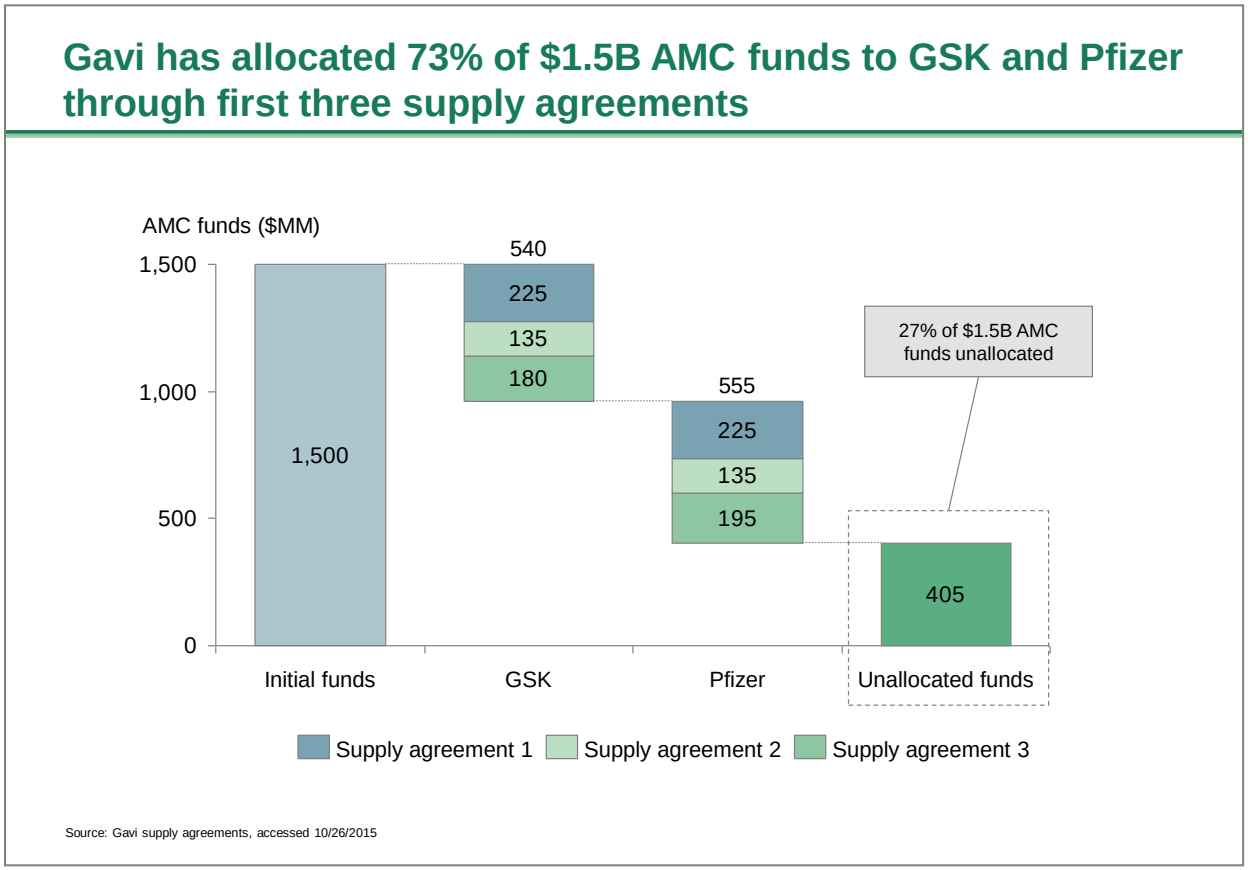

Figure 2

2.2 Context: The global pneumococcal conjugate vaccine market

The only two pneumococcal conjugate vaccine manufacturers with products on the market today are Pfizer and GSK. GSK produces a 10-valent PCV (Synflorix), which was approved for the AMC in 2010 for Kenya and in 2011 for all other countries.[xiii] Pfizer produces a 13-valent PCV (Prevenar 13), which was approved for the AMC in September 2010. Pfizer also has a 7-valent PCV (Prevenar 7) that has been available since 2001, but is not eligible for the AMC.

The global market for pneumococcal conjugate vaccines in 2015 is projected to be $6.5 billion, up from $2.8 billion in 2009 (see Figure 3).[6] Pfizer dominates the global market, with over 90

[xiii] Due to the new administration procedure needed for the novel presentation (two-dose vial without preservatives), AMC eligibility was not extended to other countries until a programmatic assessment was completed in Kenya in 2011.

percent of market share. Global demand was approximately 150 million doses in 2013 and is expected to grow at an average of 8 percent per year until 2025, when it stabilizes at 380 million doses per year.[7] An outsized portion of this growth is due to Gavi markets: Gavi low-income and transitioning countries[xiv] are expected to account for 68 percent of cumulative demand between 2013 and 2025, but will constitute 86 percent of the demand growth. Despite making up the majority of volume, Gavi countries only account for 12 percent of sales during this time period. Middle-income countries will represent another 25 percent of the total sales between 2013 and 2025.[8]

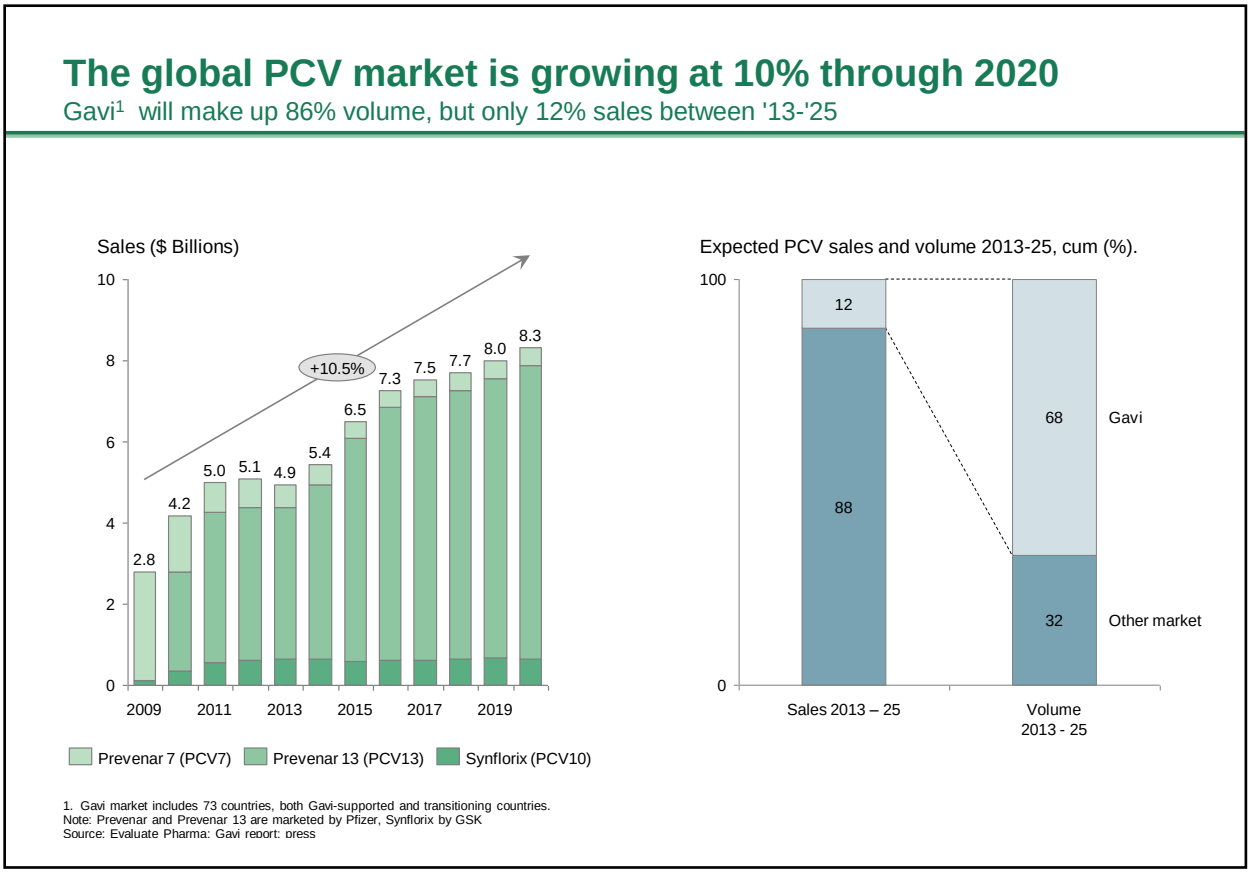

Figure 3

2.3 Previous assessments

From its inception, the pilot AMC established a forward-looking framework for evaluation to ensure the pilot was effectively leveraged for maximum learning. In 2008, a Monitoring and

[xiv] "Transitioning" countries are those in Phases 1, 2, or 3. These were formerly referred to as "graduating" or "graduated." For more information, see "Gavi Eligibility and Transition Policy, version 2.0."

Evaluation (M&E) assessment study was conducted on behalf of the pilot pneumococcal AMC Donor Committee, which led to the adoption of an M&E Framework with four components (see Figure 4).

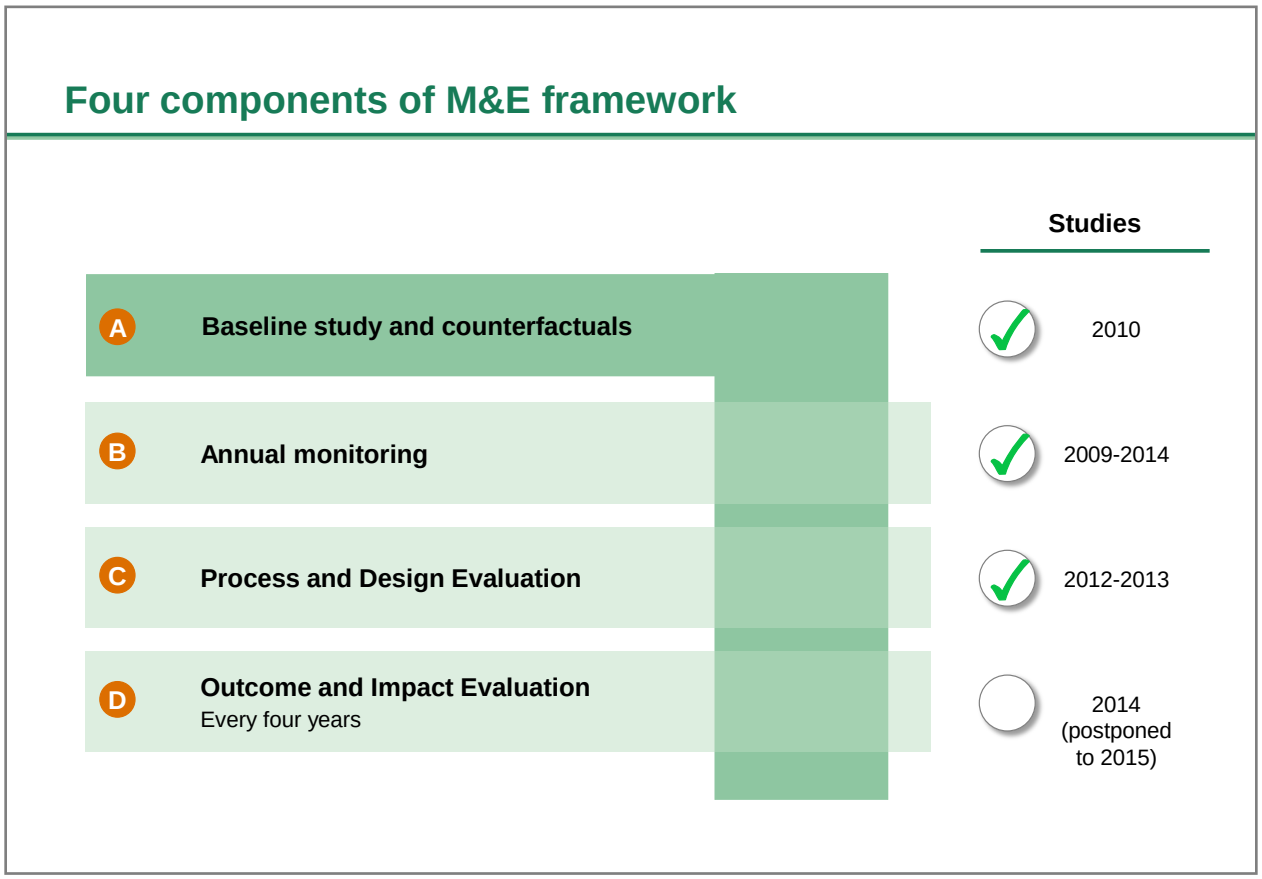

Figure 4

Components A, B, and C of the M&E Framework have generated a significant body of evidence since 2010. This body of evidence will serve as the starting point for the current evaluation, which is part of Component D. In particular, the 2010 baseline study (Component A) has provided a selection of indicators related to the objectives of the AMC, along with baseline estimates of each. As described in the methodology section, our evaluation of outcomes and impact builds upon this selection of indicators. In addition, the baseline study provided models for specific counterfactual scenarios, which will be updated with current information. The annual monitoring (Component B) has provided AMC annual reports since 2010 that summarize the progress against key indicators and give an overview of the implementation activities each year. A process evaluation (Component C), completed in 2013, provides perspective on how the AMC was executed, highlighting the key design challenges and future opportunities. This analysis served as one input into our assessment of lessons learned and future opportunities for AMCs.

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3. Objectives and Scope of this Evaluation

3.1 Objectives of this evaluation

The primary objective of this evaluation is to assess the extent to which the pilot AMC has achieved its overarching goal of reducing morbidity and mortality from pneumococcal disease and the supporting objectives around development, availability, and uptake of the vaccine. The evaluation also builds upon past reports to elucidate lessons learned for future AMCs. It addresses design and implementation issues in order to explain the extent to which results were achieved, including analysis of counterfactuals.

This outcomes and impact evaluation focuses on the critical insights that can only be understood following a sufficient track record of pilot AMC performance. As Gavi enters its fourth strategic period (2016 to 2020), innovative financing will continue to play a critical role in accelerating equitable uptake of vaccines and shaping markets for vaccines and other immunization products. The lessons learned from this evaluation hold implications for the financing of the other vaccines within the Gavi portfolio. Many of these lessons learned also extend beyond Gavi and shed some light on immunization programs sustainability in low-income settings.

3.2 Scope of this evaluation

The scope of this evaluation includes the following:

- A review of the original AMC rationale and the extent to which the pilot AMC is achieving its overall goal and four specific objectives.
  - Performance is judged using a selection of indicators that was heavily informed by the 2010 baseline study (see List of Key Indicators).
  - Performance is judged in the absolute as well as the relative, using specific, clearly defined counterfactuals. These counterfactuals use and build upon the counterfactuals discussed in the 2010 and 2013 reports.
  - Actual and projected progress toward goals and objectives includes analysis of historical pipeline candidates, supply availability, uptake, and impact. Projections rely on existing forecasts that are updated with new inputs as needed; generation of wholly new forecasts was beyond the scope of this evaluation.
  - Assessment of impact is based on existing model-based estimation of changes in impact measures. The analysis of raw empirical data or generation of new mathematical models is beyond the scope of this evaluation.
- An understanding of how the AMC design (e.g., product choice) and implementation may have contributed to these outcome and impact measures.
  - Examination of design choices and implementation will be targeted to those deemed relevant to the outcomes and impact indicators. Our initial perspective on relevancy leverages the 2013 process and design evaluation recommendations.
- Summary of the lessons learned to improve the current pilot or future AMCs.

4. Methodology

4.1 Methodology for Objective 1

Objective 1: Accelerating development of TPP-compliant vaccines

Key data sources

- Evaluate Pharma database (accessed August/September 2015)
- Clinicaltrials.gov
- Industry and press search
- Gavi publications and internal Gavi documents
- Expert interviews with manufacturers, PCV experts, Gavi Secretariat

Methodology

The current pneumococcal conjugate vaccine pipeline[xv] was determined through an initial August 2015 search on Evaluate Pharma and clinicaltrials.gov for all vaccines with the indication for pneumococcal infection prophylaxis. This list was then narrowed down through research and interviews to determine which were conjugate vaccines and TPP-compliant. In addition, new candidates were surfaced through interviews that were added to the pipeline.

The 2006 pipeline was gleaned from a 2006 document on the vaccine candidates for the AMC pilot. The projection of this pipeline to 2015 used industry success rates and average timelines from published reviews.[9,10]

The historical and projected size of the PCV market came from a September 2015 search on Evaluate Pharma and from a November 2014 Supply and Procurement Roadmap on Streptococcus pneumoniae published by Gavi. Evaluate Pharma does not necessarily capture all public markets, and thus the additional Gavi report was used in addition.

Evaluation of the current candidates and qualitative information on manufacturer behavior since the announcement of the AMC came from expert interviews. Information on ongoing presentation innovation came from interviews with the respective manufacturers as well as interviews with the Bill and Melinda Gates Foundation (BMGF), PATH, and former industry executives.

[xv] The search was limited to conjugate vaccines only, as these are the only vaccines currently appropriate for infant immunization.

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4.2 Methodology for Objective 2

Objective 2: Bringing forward availability of vaccines

Key data sources

- AMC annual reports
- UNICEF shipping data
- UNICEF supply availability data
- UNICEF product menu
- UNICEF PCV update note
- Gavi country application data
- Gavi country introduction dates
- Vaccine Information Management System (VIMS), updated September 2015
- Industry and press searches
- Interviews with manufacturers, PCV experts, UNICEF, Gavi Secretariat

Methodology

Contracted volumes and detail on the supply agreements came from the AMC annual reports through 2015. In addition, information on actual shipments was found in UNICEF shipping data through September 1, 2015. Progress on supply availability came from the UNICEF product menu for Gavi, the UNICEF PCV update note (July 2014), and AMC annual reports.

Country delay analysis was based on three data sources: original introduction date on the country application for Gavi support, UNICEF supply availability dates, and actual introduction dates from Gavi. Additionally, non-Gavi country introductions came from Vaccine Introduction Management System (VIMS). Delays due to supply availability are calculated as the time period between the original introduction date requested on the application[xvi] and the date of supply availability for that country. Delays due to all other factors, including in-country factors, are calculated as the time between when supply became available and actual country introduction. It should be noted that these other factors may still be effects of supply delays, and that further breakdown of cause is not known. These are not exact measurements—some of the delays before supply became available may still have occurred even with available volume due to other factors. However, it provides an approximation of the proportion due to supply shortages.

Manufacturer investment in capacity comes primarily through press releases, articles, and interviews with the manufacturers.

[xvi] Original date on application may not always be realistic, as in some cases it may precede Gavi approval. However, it is currently the best proxy for earliest possible introduction date.

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4.3 Methodology for Objective 3

Objective 3: Accelerating uptake of vaccines

Key data sources

- WUENIC coverage data
- UN World Population Prospects (UN WPP) surviving infants, as of 2015
- Gavi country introduction dates
- Vaccine Introduction Management System (VIMS) introduction data
- Industry and press search
- Interviews with UNICEF, principal investigators of empirical studies, Gavi Secretariat

Methodology:

Coverage data comes from WHO UNICEF Estimates of National Immunization Coverage (WUENIC) for all Gavi and non-Gavi countries. Coverage is calculated as the number of target children immunized with the last dose of vaccine (numerator) divided by total number of target children (denominator). WUENIC provides coverage data for all countries through 2014, and includes information available to WHO/UNICEF through July 7, 2015. This latest version may include retroactive revisions of previous years.

WUENIC data comes from three sources, which are standardized as much as possible across countries: administrative data, country-reported data, and high-quality surveys.[xvii] Coverage data can be overestimated, particularly in countries with weak health systems, because the numerator is often overestimated and the denominator often underestimated. In administrative data, vaccines administered to children outside of the target population (e.g., over the age of one) may be counted as part of the target population. In survey data, families that maintain vaccination records may be more likely to get their children routinely immunized. In addition, census data may be outdated, leading to an underestimation of the denominator.

One limit of WUENIC data is that it only captures coverage data for the year of introduction if the vaccine is introduced before the month in which the survey is performed or administrative data collected.

In addition to WUENIC data, UN World Population Prospect (WPP) data was used for number of surviving infants and Gavi country introduction dates used for introductions. VIMS data was used for non-Gavi country introduction dates. VIMS data was also used to determine country GNI per capita as of 2013 and to identify the Threshold 50 countries for the market counterfactual (see below). Gavi provided information on country application dates and

[xvii] Full description of WUENIC methodology can be found at: http://www.childinfo.org/files/Immunization_WUENIC_guide_and_mark-up.pdf.

approvals for PCV and rota. Press research and interviews were used to determine relevant event timing for rota and Hib vaccines.

4.4 Methodology for overarching goal

Overarching goal: Reducing morbidity and mortality from pneumococcal disease

Key data sources

- Output from Lives Saved Tool[xviii] (LiST) using Gavi Strategic Demand Forecast (SDF) v8
- Gavi-modified output from LiST using SDF v11 (from early 2014)
- Output from TRIVAC[xix] with SDF v8 (from Dec 2013)
- WUENIC coverage (as of July 2015)
- SDF v12 for projected coverage (published October 2015)
- Publications from major medical journals
- Book of Abstracts from the International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD), 2014
- Interviews with M&E experts, modeling teams, epidemiologists, principal investigators for empirical studies, external modeling consultants, Gavi Secretariat

The methodology and structure of both models is well-documented in separate publications.[11,12] These models were chosen for this evaluation because their application to immunization programs in Gavi countries have been peer reviewed and well accepted. However, the outputs of these models have been adjusted to account for more recent knowledge of inputs. The models and the methodology behind them were vetted with external experts and our independent advisory board, who agreed that they were the most applicable models for Gavi interventions. In addition, the existence of the correct country-level inputs and assumptions meant that these existing models could be run with more accuracy and precision than developing estimated inputs for new models. Any development of new models was considered beyond the scope of the report, as noted in the RFP.

Timing and context of these estimates

The last official runs of LiST and TRIVAC were performed in December 2013 and early 2014. Since then, the LiST output has been adjusted by the Gavi Monitoring & Evaluation team to account for previous overestimates in disease burden and updates in coverage forecasts, but the models have not been officially re-run by the academic teams. The Gavi-adjusted version of the output was used in our calculations. Both of these models were being updated and re-run concurrent to our evaluation; results are expected to be published in Q1 2016, with several improvements from previous runs including the official SDF v12, most recent underlying

[xviii] Academic model from Johns Hopkins University.
[xix] Academic model from London School of Hygiene and Tropical Medicine.

disease burden estimates, improved assumptions, and corrections to previous structural errors. Therefore, our estimates are only meant to serve as approximations for the purposes of this evaluation until the next series of official results becomes available.

Calculations

The impact estimates were derived from the latest runs of LiST and TRIVAC. Adjustments were made to standardize assumptions across years and update the coverage inputs to reflect the latest projections. The low estimate of impact (morbidity and mortality) is based on TRIVAC and the high estimate is based on LiST. These low and high estimates are not representative of an official confidence interval; rather, they represent different ways in which deaths averted can be estimated. An official uncertainty range is being calculated with the current re-run of the models, and will be available for future evaluations. The use of a range, rather than a point estimate, is to prevent false precision. The range indicates structural uncertainty, as it is not known which model is more accurate.

The official SDF v12 was used to estimate projected coverage. The ratio between annual doses in SDF v12 and annual doses in the version of the SDF used in the model was multiplied to the number of fully vaccinated persons in the model. This calculation assumes that wastage fractions (the percent of doses shipped that do not go towards vaccinating someone) do not change. However, as four-dose vials are introduced, or the mix of product changes, it is likely the wastage fraction will change.[13]

The low estimate was calculated using the 2013 run of TRIVAC, which was based on SDF v8. This required an update from SDF v8 to SDF v12. In order to do this, the annual numbers of fully vaccinated persons (FVPs),[xx] deaths averted, cases averted, and Disability-Adjusted Life Years (DALYs) saved were adjusted proportionally by a ratio of that year's doses in SDF v12 to that year's doses in SDF v8. This was applied to aggregated Gavi countries, by year, for years 2009 to 2020. These adjustments were reviewed by the TRIVAC modeling team as well as an independent advisory board.

The high estimate was calculated using the 2015 adjustment of LiST, which incorporated SDF v11. This output was not an actual run of the model, but an adjustment of the 2013 LiST run performed by Gavi using SDF v8. Gavi's adjustments incorporated SDF v11 and included significant downward revisions to the underlying disease burden, which reduced the number of deaths averted per 1,000 fully vaccinated persons. Because Gavi's adjustment was only performed for the next strategic period (2016 to 2020), our first adjustment was to calculate the number of deaths averted per 1,000 fully vaccinated persons for the updated period and apply it to the remaining years (2009 to 2015, 2021 to 2030). While this approach simplifies the calculation of number for deaths per 1,000 persons vaccinated by ignoring the variation of disease burden in countries in the extrapolated years, it provides a straightforward approach

[xx] A fully vaccinated person is one who has been vaccinated with the last dose of a vaccine.

that can be performed without the annual disease burden data by country[xxi]. The second adjustment we made was to account for changes from SDF v11 to v12. We adjusted aggregate deaths averted each year by a ratio of doses in SDF v12 to doses in SDF v11 for that year. These adjustments were reviewed by the LiST modeling team as well as an independent advisory board.

Lastly, the morbidity estimates (cases averted and DALYs saved), are based on TRIVAC, as LiST does not produce morbidity estimates. Cases averted and DALYs saved from the TRIVAC SDF v8 run were adjusted in the same way as deaths averted per 1,000 fully vaccinated persons was above. This set of numbers was used as the low estimate and the high estimate was produced by applying the low-to-high percentage range each year from deaths averted each year. These calculations assume that cases averted, DALYs saved, and deaths averted are all proportional to each other.[xxii]

Biases and limitations of these estimates

These estimates face the same shortcomings as the LiST and TRIVAC models, which are well documented in separate publications.[14,15] While inputs such as coverage and population data themselves have limitations (noted in separate publications[16]), this section focuses on the limitations of the model structures and assumptions.

Although estimates have historically been revised downwards as input data is updated, we consider these estimates of morbidity and mortality to be, on the whole, conservative, as they do not account for the following.

- **Partial vaccination:** One or two doses of PCV are shown to have efficacy, but the effect of partial vaccination is not included in this analysis.
- **Herd immunity:** Indirect protection offered throughout community, even in those who are not vaccinated and those older than the target population, is achieved when a significant portion has been vaccinated. This is because chains of infection are disrupted, which stops or slows the spread of disease. This protection is not included in the analysis.
- **Antibiotic resistance:** The role of vaccines in preventing antibiotic resistance, and other indirect effects in both immunized children and older age groups, is not included.
- **Over-five deaths:** Both models focus on the under-five population, and thus estimated impact is given as deaths averted before the age of five. However, there is evidence that

[xxi] Note: In extrapolating the data for 2009-2015, the assumption of a constant number did not make a significant difference because the total number of deaths averted during that period is quite small.

[xxii] This is an oversimplified relationship between DALYs, cases averted and deaths averted. However, not enough has been quantified regarding the relationship between these metrics to validate a less straightforward approach.

deaths over the age of five represent a significant portion of childhood pneumococcal deaths.[xxiii,17,18,19]

- **India introduction date:** In the models, India is assumed to introduce PCV in 2021, although there are strong indicators it may start introducing in some states before then.

Biasing factors that act in the opposite direction exist, though it is our opinion based on extensive expert consultation that these affect the estimates to a lesser extent. These include:

- **Serotype replacement:** The models do not include the potential increase in non-vaccine-type serotypes and a potential corresponding increase in pneumococcal disease is not included.
- **Confounding factors:** The models do not account for the fact that the persons at greatest risk for disease are often the least likely to get vaccinated. This would reduce the average vaccine effectiveness.
- **Delay in immunization schedule:** The models do not account for the chance that the first dose may be given after the risk of infection starts. In some countries, the first dose of PCV is given to many children later than the recommended 2 months of age.[20]
- **Choice of clinical endpoint:** The models use x-ray confirmed pneumonia as a proxy for fatal pneumonia, although this has not been validated. Half of the deaths in the PCV trials and most children hospitalized for pneumonia do not have x-ray confirmed pneumonia, and vaccine efficacy against non x-ray confirmed pneumonia is lower.[21]

Empirical studies

A number of empirical studies were reviewed through study abstracts, published articles, and interviews with principal investigators. The findings are used to provide context for the models as well as provide validation for inputs and assumptions used. Analysis of the empirical data was limited to published conclusions or conclusions provided directly by the study teams.

4.5 Counterfactuals

Two counterfactuals, one focused on other vaccines and one focused on non-Gavi markets, were used in our analysis to put the absolute performance of PCV into relative perspective (see Figure 5).

[xxiii] Estimates of deaths occurring between five and 19 in 2010 range from 1.5 million to 2.3 million, which represent 21 to 33 percent of under-5 deaths. Under-5 deaths in 2010 are estimated to be approximately 7 million.

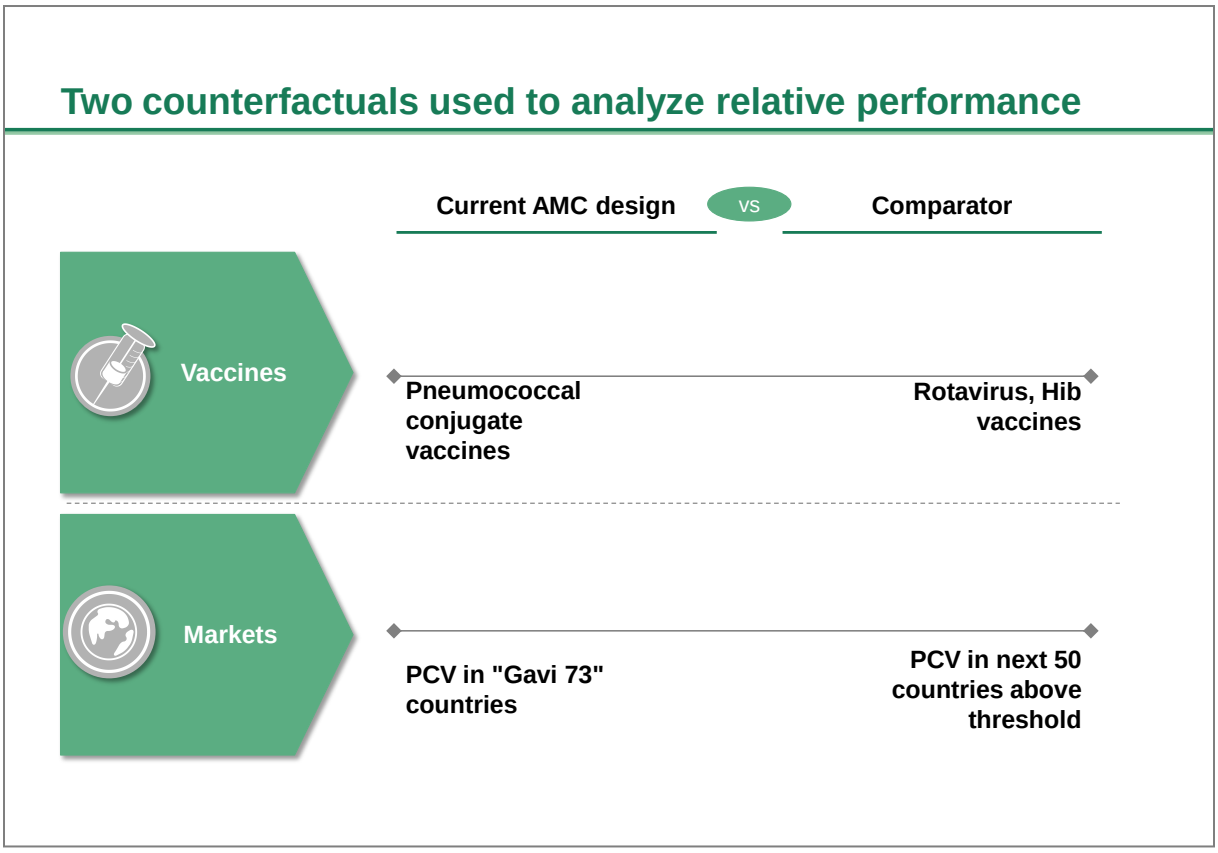

Figure 5

Vaccines counterfactual

The vaccines counterfactual examined the actual and forecasted performance of PCV in Gavi countries versus the actual performance of rota and Hib-containing vaccines (hereafter referred to as Hib vaccines) in Gavi countries. This comparison allows us to assess PCV procurement, interest, and uptake relative to past Gavi vaccines that were managed through the standard Gavi support. Although Hib and rota cannot pose exact "what if" scenarios of PCV through a standard Gavi support, they are valuable real-life examples that help describe the state of the world without the pneumococcal AMC.

Rota and Hib were selected through careful analysis in two earlier evaluations[xxiv] and the design of this evaluation reconsidered and reaffirmed their appropriateness. Both of these vaccines are part of the Gavi portfolio, purchased through a normal financing mechanism, with enough years of historical data to provide insight. Both were also considered "underutilized" vaccines as of 2010, and address disease burden on the same scale as pneumococcal disease.[22] In addition, both vaccines cover the same target population as PCV.

[xxiv] See AMC Baseline Evaluation (2010) and AMC Process and Design Evaluation (2013).

Rota provides an example of a "new" vaccine that is being introduced into Gavi countries at approximately the same time as PCV. Two suppliers provide rota vaccines to Gavi, similar to PCV. Additionally, the work of the Rotavirus ADIP has generated evidence of clinical need and awareness of the disease in a similar manner to the PneumoADIP, which helped stimulate demand and give confidence to the manufacturers. In addition to the ADIPs, rota and pneumo both benefitted from the Accelerated Vaccine Introduction (AVI) initiative, established in 2008 to facilitate the rapid and large-scale introduction of these vaccines[23].

The Hib vaccine, on the other hand, represents an older vaccine that has enough historical data to represent adoption across all Gavi countries. The Hib vaccine also requires suppliers to build in the fixed costs investments at a similar level as PCV,[24] even if the scientific barriers are lower. In addition, Hib has substantial use in the developed world, similar to PCV.

Assumptions and limitations of the vaccines counterfactual

We recognize that comparing PCV to rota or Hib is not an equal comparison. The vaccines and diseases themselves are quite different, as is the context of each introduction.

The rota vaccine is less costly to produce, as suppliers do not incur the same level of fixed cost investments as they would if they had to build protein conjugation lines into their production plants (such as for the PCV and Hib vaccine).[25] A previous rotavirus vaccine, RotaShield, carried the rare but serious side risk of intussusceptions, which led WHO to place age restrictions around their recommendation for other rota vaccines until 2009. This may have lowered the coverage achieved within countries.[26] To counterbalance, however, the rota vaccine given to 90 percent of children in a two-dose product, which requires fewer points of contact with each child than the three-dose PCV. Lastly, the rota vaccine also faced more severe supply shortages in the early years than did PCV, and still faces supply constraints in 2015.

The Hib vaccine was introduced into Gavi countries in a very different context. Hib was first introduced in 1997 as a monovalent vaccine, before Gavi existed. Beginning in 2001, Gavi offered Hib as part of the pentavalent vaccine. Hib introduction at this time represents a scenario in which global initiatives do not achieve their goals as successfully, as the timing of policy interventions was suboptimal. In particular, a well-funded and dedicated Hib initiative did not exist until 2005, as opposed to PCV and rota, which benefitted from both an ADIP and the AVI initiative. Additionally, WHO only made a global recommendation in 1998 once it became clear very few countries were using this highly effective vaccine (which had been available since the 1980s), and affordable pricing of Hib only came about after the WHO recommendation increased demand. Hib faced supply shortages in the first five to seven years after introduction.

Gavi support for both Hib and rota preceded support for PCV. Therefore, it can be assumed that Gavi and its partners applied the lessons learned in each vaccine introduction to the next

vaccine. As a result, we would expect to see some improvement over time, even absent the AMC mechanism. An explanation of the relative expectations, versus the relative outcomes, is included in the description of findings in order to elucidate a valid comparison.

Market counterfactual

The market counterfactual examined the actual and forecasted uptake of PCV in Gavi countries versus the actual uptake of PCV in the "Threshold 50" countries, as described below. This allows us to compare interest and introduction of the same vaccine in countries that had the AMC tail price and Gavi support versus countries that were of similar economic context but did not have the AMC price or Gavi support. Although this is meant to test the AMC, the standard Gavi support (in the form of financial support to countries, vaccine introduction grants, and health system strengthening funds) has enormous influences in country affordability. To help account for this, two additional analyses were included: the difference in uptake of rota vaccine between Gavi and Threshold 50 countries, and the Gavi countries versus the non-Gavi PAHO countries, which also have access to relatively low prices through the Revolving Fund.[xxv,27]

The Threshold 50 countries were defined as those countries with the lowest 2013 GNI per capita that were not eligible for Gavi support under the AMC. GNI per capita for these countries ranges from $2,990 to $9,940, versus the 73 Gavi countries with a range of $260 to $7,350.[xxvi] Within these 50 countries, 20 have chosen to introduce PCV so far. A comparison of all 73 Gavi countries versus all 50 threshold countries was performed, as well as a comparison of the subset of each group that has introduced PCV (see Figure 6). The list of countries in each category is included in Figure 7.

[xxv] Weighted average Revolving Fund price for PCV is $14.12 to $15.68

[xxvi] The high end of the Gavi range comes from countries that are in Phase II or beyond of Gavi transition, such as Azerbaijan.

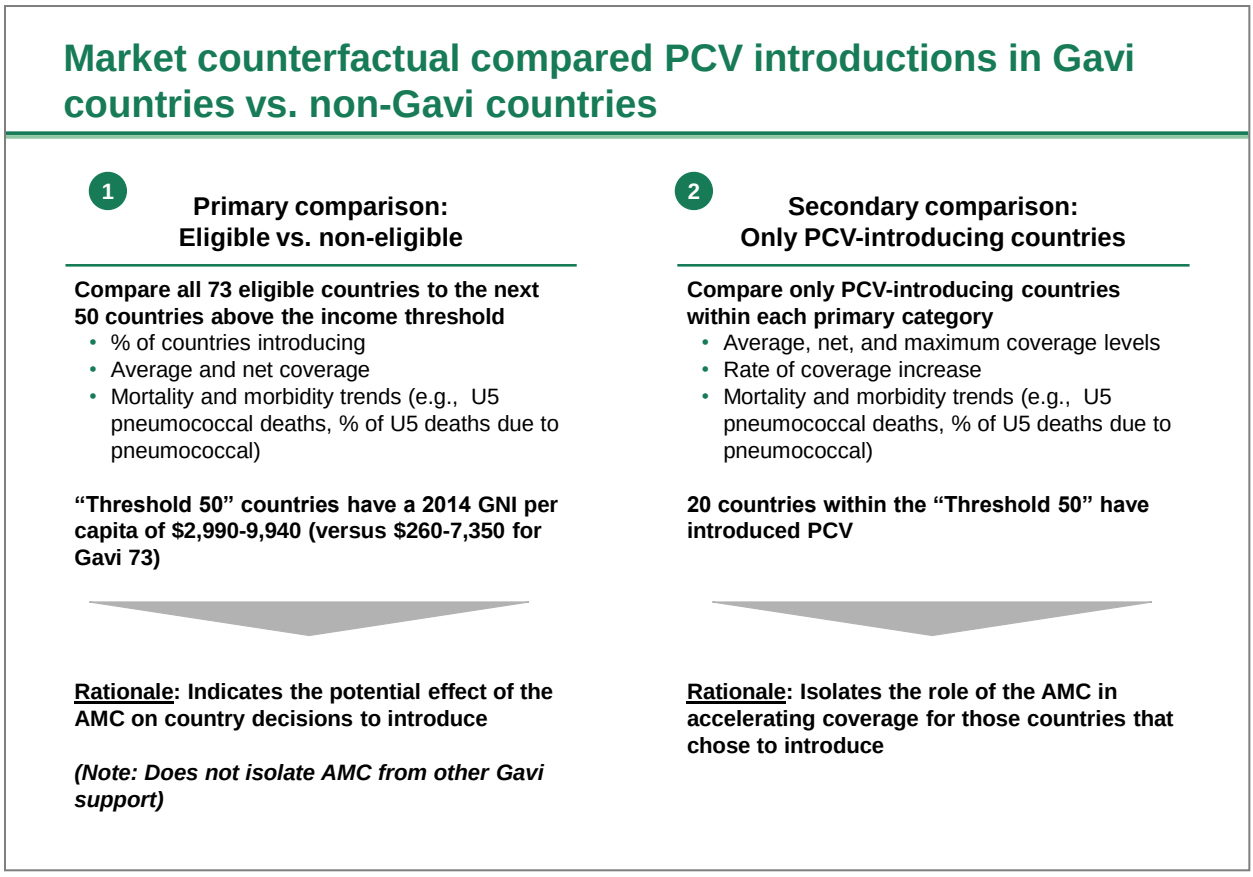
Market counterfactual compared PCV introductions in Gavi countries vs. non-Gavi countries
1
Primary comparison:
Eligible vs. non-eligible
Compare all 73 eligible countries to the next 50 countries above the income threshold
% of countries introducing
Average and net coverage
Mortality and morbidity trends (e.g., U5 pneumococcal deaths, % of U5 deaths due to pneumococcal)
"Threshold 50" countries have a 2014 GNI per capita of $2,990-9,940 (versus $260-7,350 for Gavi 73)
Rationale: Indicates the potential effect of the AMC on country decisions to introduce
(Note: Does not isolate AMC from other Gavi support)
2
Secondary comparison:
Only PCV-introducing countries
Compare only PCV-introducing countries within each primary category
Average, net, and maximum coverage levels
Rate of coverage increase
Mortality and morbidity trends (e.g., U5 pneumococcal deaths, % of U5 deaths due to pneumococcal)
20 countries within the "Threshold 50" have introduced PCV
Rationale: Isolates the role of the AMC in accelerating coverage for those countries that chose to introduce

Figure 6

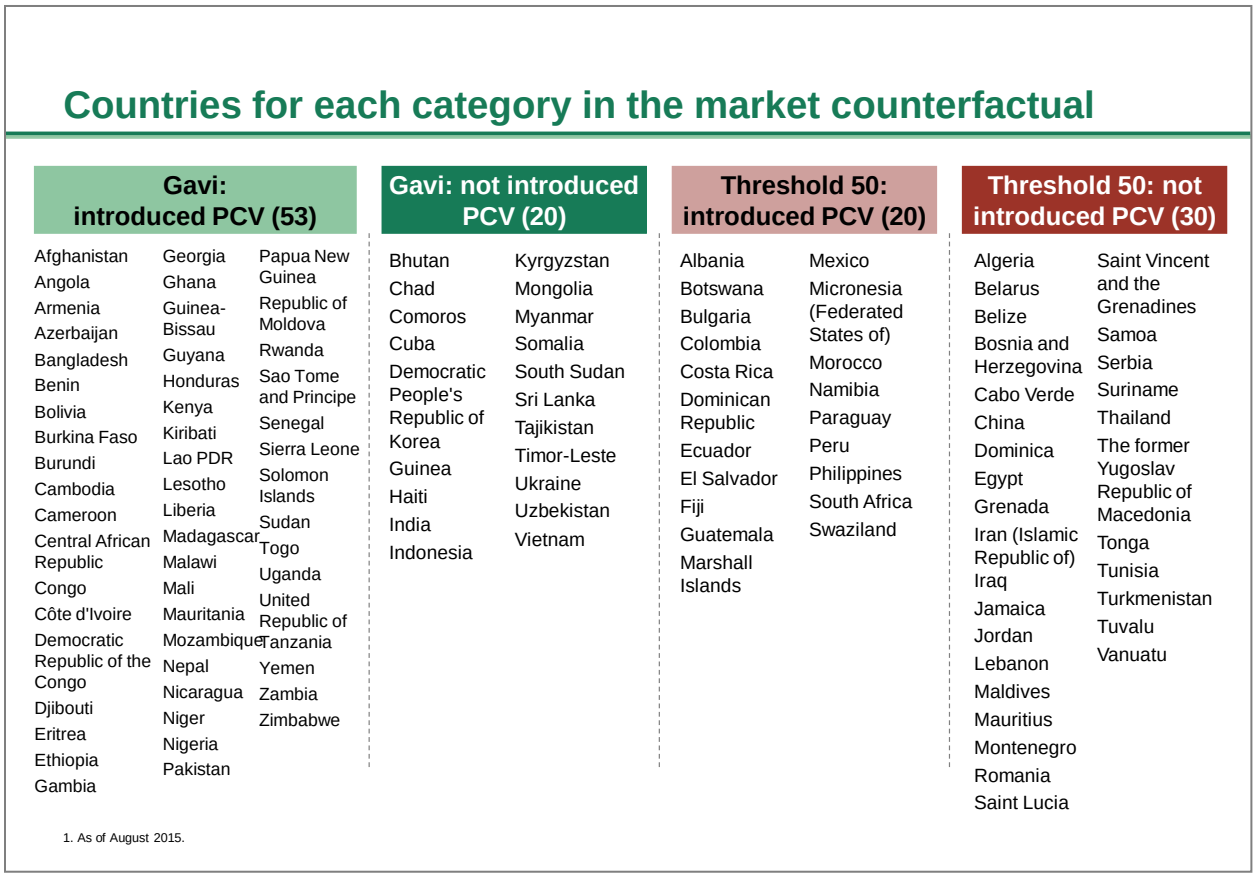

Figure 7

Assumptions and limitations of the market counterfactual

As mentioned above, the largest limitation of the market counterfactual is that it does not fully account for the fact that Gavi countries receive financial support for PCV, vaccine introduction grants, and health system strengthening funds, while the Threshold 50 do not. This is partially addressed by the inclusion of rota as a control in the market counterfactual, but the differences between PCV and rota pose their own challenges. Additionally, although the GNI per capita ranges overlap, the overlap is small. The low end of the Threshold 50 range ($2,990) is still higher than 63 of 73 of the Gavi countries.

4.6 Expert and stakeholder interviews

Through the course of this evaluation, 57 topic experts and relevant stakeholders were interviewed one or more times. These interviews were used to collect and understand data and technical information, as well as to gather a range of perspectives on the pilot AMC, review and validate our findings, and refine lessons learned. Inevitably, some of these stakeholders carry biases, may only be exposed to partial information, or may unconsciously filter information based on their positions or preferences. We sought to mitigate these potential challenges by

interviewing a broad range of stakeholders representing a diversity of positions and experiences. For the full list of interviewees, see Appendix I.

4.7 List of key indicators used

Fifteen key indicators guided the analysis of each outcome or impact (Table 1). These indicators were heavily based on the baseline report conducted in 2010 for the AMC. The only indicator that was not fully analyzed was Indicator 5, number of doses offered to UNICEF per year, as this is part of the strategic confidential information provided as part of procurement processes. A table summarizing the indicator findings for each objective is included at the bottom of each "key findings" section of the report.

Indicator	Category	Indicator Description
1	Obj. 1 (Development)	# of suppliers (multinational and developing country)
2		# of products with WHO prequalification and # of products eligible for AMC
3		# of clinical candidates that are consistent with TPP (broken down by development step)
4		# of manufacturers publicly registered with AMC
5	Obj. 2 (Availability)	# of doses of TPP vaccines offered to UNICEF/year
6		# of doses of TPP vaccines contracted/year
7		Vaccine price (absolute price and price trend)
8	Obj. 3 (Uptake)	Per-year and cumulative # of AMC eligible countries that have introduced TPP vaccines (first child vaccinated)
9		# of AMC-eligible countries that have applied for Gavi PCV support
10		Cumulative # of doses of TPP vaccines shipped to AMC eligible countries
11		% PCV3 coverage of eligible population in AMC eligible countries
12		Cumulative # of children vaccinated with AMC-supported pneumococcal vaccines
13	Goal (Health Impact)	Cumulative # of pneumococcal disease cases averted due to TPP vaccines in AMC eligible countries
14		Cumulative # of DALYs due to TPP vaccines in AMC-eligible countries
15		Cumulative # of deaths averted due to TPP vaccines in AMC-eligible countries

Table 1

4.8 Causal pathways

This evaluation, where possible, is based on facts, data analysis, and recorded documents to provide evidence for its conclusions. These sources are cited as endnotes and explained in the methodology section where relevant. Where there is no existing data, we have relied on expert interviews with those who were involved in the AMC or have been closely following its development and implementation. To increase the confidence in our findings from interviews, we sought out many perspectives, including both supporters and critics of the AMC. We interviewed 57 experts from a wide array of fields, many of them multiple times. All of this provides a significant evidence base from which to draw conclusions.

However, where evidence is not clearly available, we must rely on subjective judgment and interpretation. This is particularly important when trying to causally link the AMC mechanism and certain outcomes or impact. Here, we rely on the "theory of change" laid out in the Gavi PCV results framework (replicated in Appendix IV). This framework provides a logical underpinning for how and why the AMC intends to create desired outcomes in childhood pneumococcal disease burden. By laying out the logical steps of how different parameters (inputs, processes, and outputs) enable certain outcomes and impacts, the framework articulates potential causal pathways.

Conclusions that are based on the kind of causal logic outlined in this framework have been vetted by our expert interviews as well as reviewed with an independent advisory board. However, these conclusions must be read not as fact but as subjective interpretations, based on lines of reasoning from which we can draw plausible conclusions. We have tried to make clear with our language and citations where conclusions are based on fact and where they are based on likely explanations considering potential causal pathways.

In addition, the language used in this report is intended to differentiate between contribution and attribution. In many cases, the AMC was a contributing factor to the specific outcomes, but it cannot be definitively said that the outcomes would not have happened in the absence of the AMC, or that the AMC was the sole enabler. In cases like this, language such as "contributed" is specifically used, rather than "caused."

5. Findings: Outcomes and Impact

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

5.1.1 Key findings

When PCV was selected as the AMC pilot product in 2006, it was well understood that the mechanism was unlikely to influence the development timelines of the two TPP-compliant candidates (Pfizer's PCV13[xxvii] and GSK's PCV10) that were already in advanced stages of development at that time. As expected, both late-stage candidates came to market shortly before the launch of the AMC, in line with the companies' pre-AMC strategies.

There is no evidence that any of the early-stage manufacturers successfully accelerated their product development timeline after the announcement. Although all of the other candidates were quite early stage at the inception of the AMC, some forecasts in 2008 and as late as 2010 expected a third manufacturer to come to market around 2015 or 2016.[28,29] This has not happened to date; manufacturers have faced technical, regulatory, and clinical delays that have made it unlikely for a third product to enter the market before 2018.

Design elements that would have aided early-stage candidates—such as reserving a portion of the pool for later entrants or developing country manufacturers—were discussed but not included. There is no consensus on whether the exclusion of design elements to aid these manufacturers was based purely on a trade-off with incentivizing supply availability or due to the fact that the pipeline projections underestimated the challenges manufacturers would encounter in PCV development. However, the resulting lack of R&D outcomes makes clear the limitations of a pull mechanism to stimulate the development of an early-stage, technically complex product.

The AMC did have two significant positive influences on R&D. First, it encouraged manufacturers with early-stage products to continue development by establishing that there would be significant demand for PCV after the conclusion of the AMC and phasing out of supply under initial contracts. This has led to a strong R&D pipeline, with approximately 14 manufacturers pursuing TPP-compliant PCV programs. Second, it encouraged investment by the two existing manufacturers to develop product presentations more suitable for Gavi countries, in particular multi-dose vials that help ease cold-chain challenges and lower the cost—and in turn price—per dose. GSK had created a two-dose vial from the beginning, and both GSK and Pfizer are developing a four-dose vial presentation with preservatives. These improvements require new product design, new formulations, and clinical studies. That manufacturers have gone above and beyond the minimum TPP requirements to understand and adapt their product to the unique challenges in Gavi markets is a success of the AMC.

[xxvii] At the time, PCV13 was being developed by Wyeth. Pfizer subsequently bought Wyeth and acquired the product. Pfizer/Wyeth is referred to as Pfizer in this document for consistency.

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5.1.2 Summary of key output indicators

Key indicator	Result
# of suppliers (multinational and developing country)	2
# of products with WHO prequalification and # of products eligible for AMC	2
# of clinical candidates that are consistent with TPP (broken down by development step)	14 (for full breakdown, see Figure 8)
# of manufacturers publicly registered with AMC	4

Table 2

5.1.3 Detailed analysis

The effect of the AMC on late-stage products in 2007

The only two pneumococcal conjugate vaccine manufacturers with products on the market today are Pfizer and GSK, both of which would have had PCVs on the market in the absence of an AMC. GSK produces a 10-valent PCV (Synflorix), which was approved for the AMC in 2010 for Kenya and in 2011 for all other countries.[xxviii] Pfizer produces a 13-valent PCV (Prevenar 13), which was approved for the AMC in September 2010. Pfizer also has a 7-valent PCV (Prevenar 7) that has been available since 2001, but is not eligible for the AMC.

It is likely that neither of these manufacturers would have discontinued development after 2006 in the absence of the AMC, as both had reasons to bring their vaccines to market. GSK had already invested in a new vaccine manufacturing facility that would help produce PCV for low-income markets. Pfizer was developing PCV13 because of the projected pediatric growth in middle-income countries and projected global sales for an adult indication. Pfizer's PCV7 was already a blockbuster product, the first vaccine to reach $1 billion in annual sales, with nearly $2 billion in sales by 2006.

The effect of product choice on Objective 1

The selection of pneumococcal conjugate vaccines for the AMC shifted the focus of the pilot from spurring R&D investment to increasing supply capacity. Originally, six disease candidates were considered for the pilot AMC: HIV, HPV, malaria, pneumococcal, rotavirus, and tuberculosis. Some of these faced scientific and early-stage development barriers, in which case

[xxviii] Due to the new administration procedure needed for the novel presentation (two-dose vial without preservatives), AMC eligibility was not extended to other countries until a programmatic assessment was completed in Kenya in 2011.

a pilot would have tested the ability of an AMC to act as a "pull mechanism" accelerating early-stage R&D. For pneumococcal disease, an existing marketed vaccine and two more late-stage vaccines ensured little risk of scientific failure or monopoly. Pneumococcal disease was therefore chosen for the pilot so that the supply-building capability of the mechanism could be quickly tested.[30]

The degree to which this choice minimized the importance of Objective 1 is debated among stakeholders and reflects issues in how the pilot objectives were prioritized and communicated, internally and externally (see Figure 8). Stakeholders agree that the pilot had minimal effect on the late-stage candidates, and Gavi explicitly claimed no responsibility for the two vaccines that have come to market to date.[31] However, the intent regarding early-stage manufacturers is unclear. Some pipeline projections at the time of the AMC design expected a third and possibly fourth manufacturer to come to market around 2015/2016, although this may have not been completely realistic.[32] Regardless, the final AMC design did not explicitly reserve any portion of the $1.5 billion for a later entrant. Some stakeholders suggested that this was purely an underestimation of the technical and regulatory hurdles manufacturers would face, while others thought it a deliberate trade-off for supply availability.[33] Either way, this left some stakeholders disappointed that the $1.5 billion may go entirely to two multinationals; these stakeholders point to the absence of a third manufacturer as the reason for minimal price reduction.[34] More importantly, the lack of a third manufacturer highlights the limitations of a pull mechanism in stimulating the development of early-stage and technically challenging products.

Given that the paths of the existing PCVs were unaffected and no additional manufacturers have entered the market, Objective 1 had not been fully achieved by 2015. To avoid this foreseeable outcome, Objective 1 should have been more explicitly deprioritized in the pilot framework. For future AMCs, technical complexity of the chosen product and stratification of the starting pipeline should be considered. If acceleration of early-stage candidates is to be a future objective, either a different structure or a combination of pull mechanisms and other supporting incentives would likely be needed.

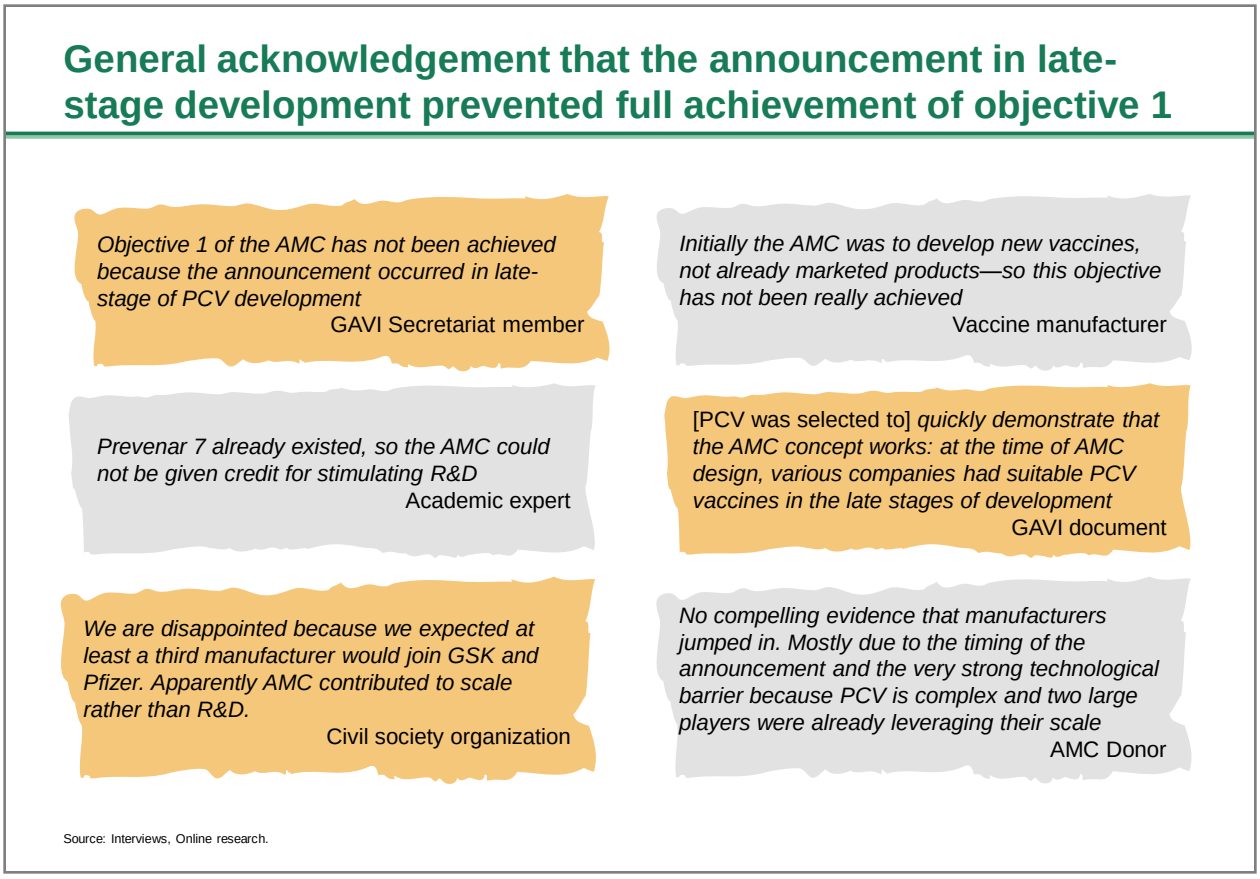


Figure 8

The pneumococcal conjugate vaccine pipeline today

Beyond the TPP-compliant PCVs currently available on the market, it is important to understand the existing PCV pipeline candidates for two reasons: to assess the potential for another manufacturer to enter the market while AMC funds remain available and to explore the implications of the AMC on the PCV market when all AMC funds have been committed to suppliers under contracts (or after expiration).

A conjugate pneumococcal vaccine is very difficult to manufacture; of those in Gavi's portfolio, PCV is considered to be the hardest vaccine to make. A vaccine with X serotypes requires making X different polysaccharides at scale and conjugating each onto the same carrier protein. Any company developing a PCV product must have certain advanced technical capabilities to succeed, to say nothing of the technical and financial challenges of scaling production and financing clinical trials.[35] One manufacturer mentioned that an R&D team of 150 people was needed for PCV, right from the earliest phases.[36] Global leaders in the vaccine industry such as Merck and Sanofi have struggled to bring a product to market, underscoring the difficulty of developing PCV.

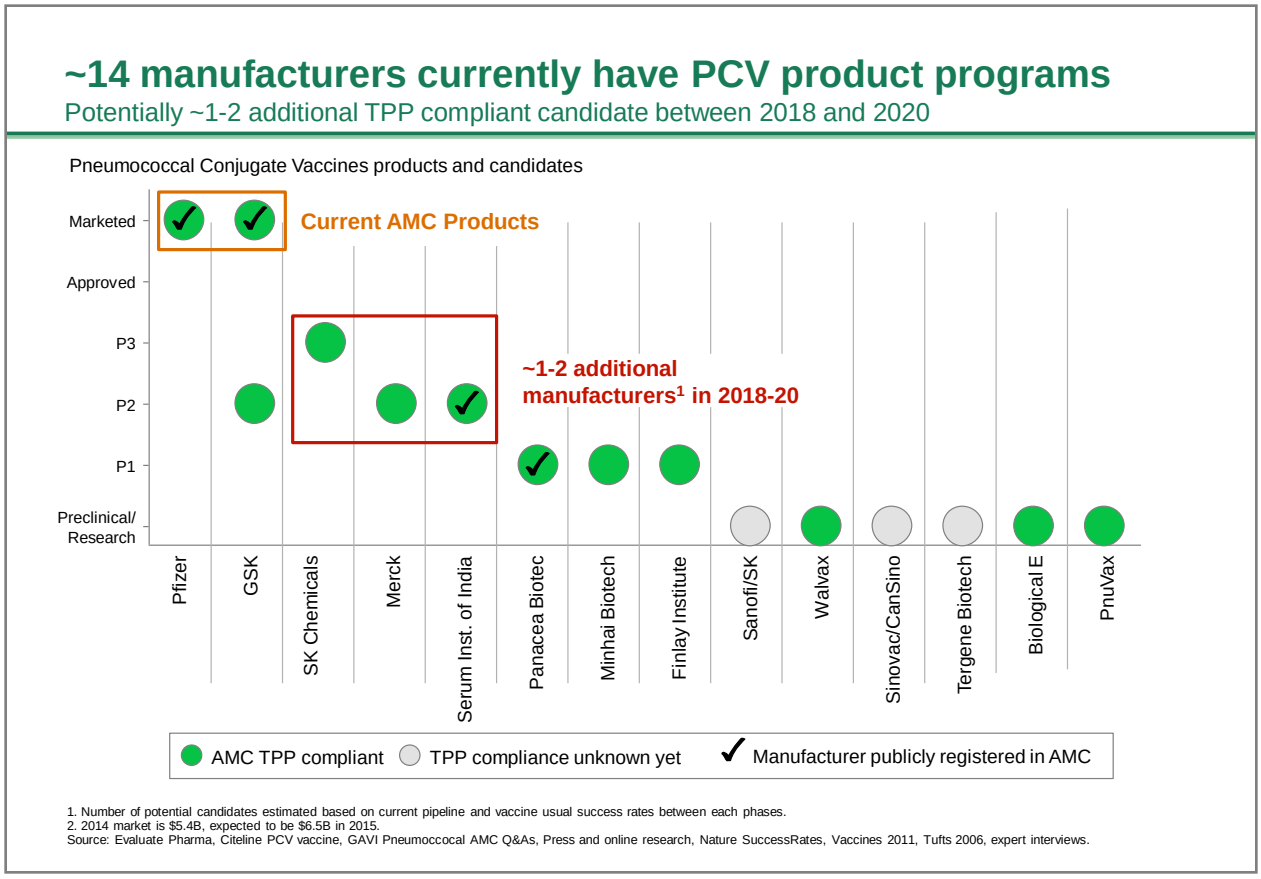


Figure 9

Currently, there are approximately 14 manufacturers with confirmed PCV programs whose vaccines are confirmed or potentially TPP-compliant[xxix,37,38] (see Figure 9). This pipeline has grown stronger over the last several years, as many of these companies only recently developed the baseline capabilities to produce a conjugate vaccine. While none of the nine early- or preclinical-phase candidates can be said to have entered development because of the AMC, expert interviews suggested that some may have stayed in the pipeline because of the large low-income market enabled by Gavi and the AMC.

Pfizer and GSK are included as part of the 14, as they are continuing to explore presentation innovations for their marketed products. In addition, GSK has another product in the pipeline (GSK2189242A), a next generation recombinant conjugate vaccine currently in Phase 2 trials.[39]

[xxix] Not all candidates have 13 serotypes, but all have or are expected to have sufficient serotype coverage as designated in the Target Product Profile (TPP), including the three required serotypes.

Merck, Sanofi, and SK Chemicals are the only other multinational companies with current PCV programs. Of all the manufacturers not yet at market, Merck is the closest competition for Pfizer's Prevenar 13 in the developed world, as it is the only late-stage candidate that is likely targeting the $6-plus billion market in the developed world market.[40] Competing in the developed markets requires clinical trials in those countries, as well as sufficient manufacturing capacity and know-how.[41]

Merck recently re-entered clinical trials after remaking its product. Previously, Merck's first PCV15 product failed Phase 2 trials. This led to Merck and Serum ending their three-year partnership at the end of 2014. Merck had initiated the partnership with Serum to access the manufacturing economies of scale that Serum could provide and to offer low-cost PCV for the developing world. The product, however, was developed entirely by Merck and was kept separate from the PCV product that Serum was developing on its own.[42] After failing Phase 2 trials, Merck dropped the program and ended the partnership. Recently, however, Merck remade its product and has entered Phase 2 trials.[43,44]

Sanofi entered into a partnership with SK Chemicals to co-develop a PCV product. If successful, the vaccine will be manufactured at SK's South Korean facilities and Sanofi will commercialize the vaccine. The current vaccine is still preclinical.[45] Separately, SK also has its own PCV program with a product in Phase 3 trials.[46]

The developing country manufacturers are not targeting the U.S. or Europe due to clinical and capacity hurdles, and are instead primarily motivated by the growth in middle- and low-income country markets. These companies have the potential to gain significant share in middle-income countries.. Given that the low end of the Pfizer price range in these countries is $15 to $40,[47,48,49] these markets would still be extremely profitable for such companies.[xxx] In addition, the Gavi volume would help them achieve greater cost efficiencies.

Two Indian manufacturers, Serum Institute of India and Panacea Biotec, have made their registration with the AMC public.[50] Biological E Limited is another well-established Indian manufacturer with a PCV research program, while Tergene is an Indian biotech start-up with claims of a PCV research program. In addition to India, China has at least three PCV programs: Walvax, Minhai Biotech, and Sinovac/CanSino.[xxxi] Pnuvax is a Canadian company that has received funding from the Bill and Melinda Gates Foundation. Finlay Institute is a Cuban organization with a vaccine in clinical trials; however, their strategy does not seem to include access to Gavi markets.[51] Of all of these, Serum and Panacea are the most serious candidates for Gavi markets in the near term, and are discussed below. Details on the remaining manufacturers in Figure 9 are included in Appendix II.

[xxx] Profitability is assumed, based on an expected marginal cost of less than $2.00; Source: Expert interviews.

[xxxi] China National Biotec Group (CNBG)/Lanzhou and CNBG/Chengdu may also have PCV programs, however, their current status has not been confirmed.

We believe that Serum is the next manufacturer most likely to make it to market with a TPP-compliant vaccine. After its partnership with Merck ended in 2014, Serum continued development of its own PCV10, which is now in Phase 2 trials. This vaccine was developed by Serum from the ground up with financial and technical backing from the Bill and Melinda Gates Foundation. Though investment in the vaccine was made prior to the AMC, the candidate is comprised of 10 serotypes that provide coverage specifically for Africa and the Indian subcontinent (different from GSK's PCV10).[52] For Serum, successfully developing a vaccine as complicated as PCV and scaling it up for middle- and low-income markets would position the company between developing country manufacturers and multinationals in size and capability.[53] While pipeline experts expect Serum's PCV10 product to come to market before the AMC expires in 2020, the full $1.5 billion may be allocated before then. However, Serum has already committed to the Gates Foundation on a quantity-dependent price, quoted at close to $2.00.[54] To reach this low price, Serum plans to produce multi-dose vials to reduce manufacturing costs.[55]

Panacea Biotec has also actively demonstrated interest in the AMC and is the only company to attribute R&D actions to the launch of the AMC. Although the company had a PCV in its pipeline in 2006, Panacea claims that the announcement of the AMC led it to refocus efforts and prioritize the product. To date, Panacea has completed Phase 1 trials in children.[56]

Analysis of the current PCV pipeline indicates that the earliest another manufacturer will come to market is 2018, although projections in 2006 suggested that a third manufacturer was expected by 2015 or 2016. Thus the current pipeline is strong but slower than expected (see Figure 10). There are many candidates in early clinical trials, but fewer candidates in late-stage trials than would have been expected by projecting the 2006 pipeline forward. We attribute this delay to the technical and scientific challenges of developing PCV. For instance, the failed Merck/Serum partnership would have been in later stage trials by now. Instead, a modified version of this candidate is restarting Phase 2. This example underscores the challenging reality of developing a technically complex product; earlier stakeholder expectations did not necessarily account for these challenges (e.g., failed developments or rework required by several manufacturers).

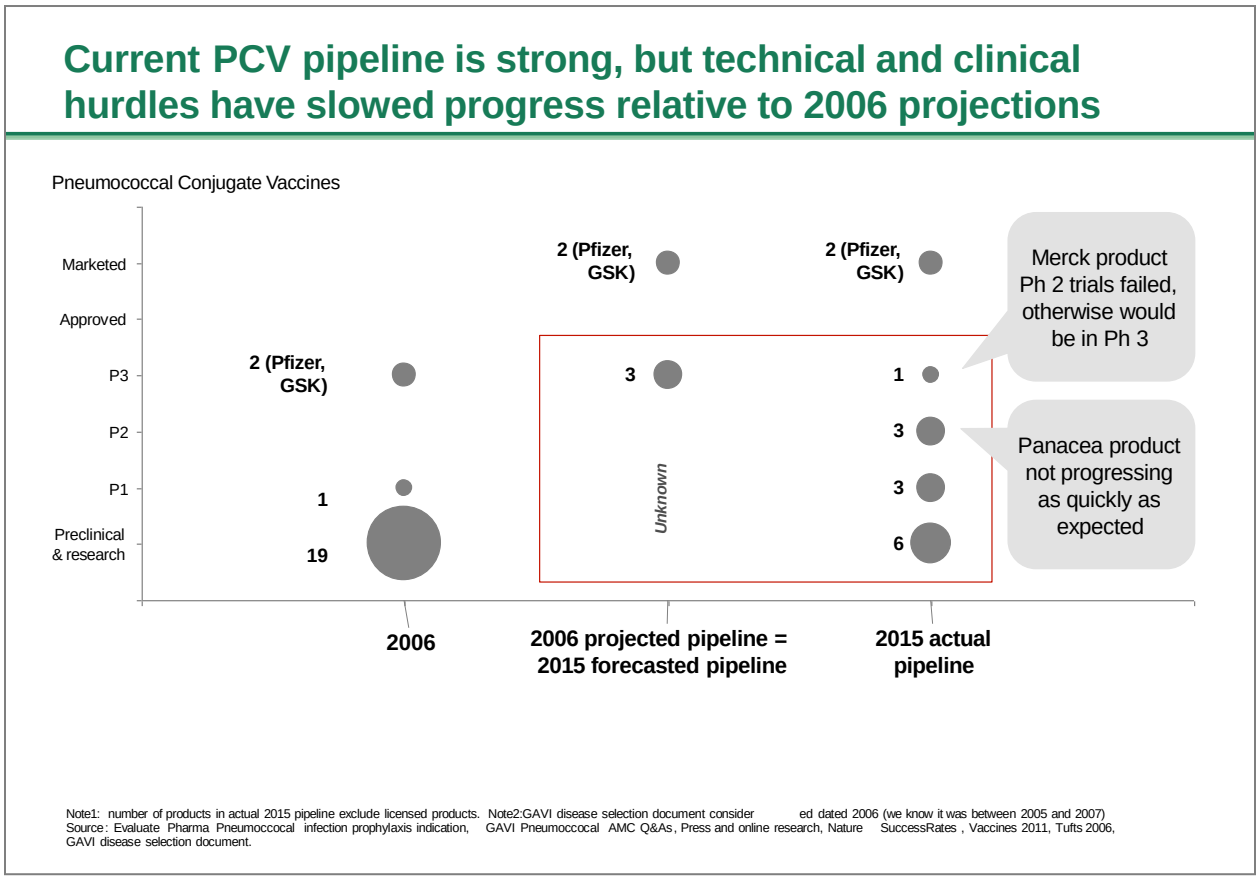


Figure 10

Presentation Innovation

Since the announcement of the AMC, Pfizer and GSK have both invested in product presentation improvements for Gavi markets. These two manufacturers have demonstrated a commitment to understanding the unique needs of healthcare systems in Gavi countries and adapting their products to address these. Primarily, product presentation improvements address cold-chain capacity constraints and stability. Vaccines require refrigeration within a narrow temperature range until the point of delivery, but the refrigerated capacity along the delivery chain in developing countries is often quite limited.

From the start of the AMC, both Pfizer and GSK have provided Gavi with vials rather than the single-dose pre-filled syringes they provide for most other markets. This helps reduce storage by up to two-thirds and avoids the risk of transmission of blood borne diseases through the reuse of non-auto-disabled syringes.[57,58]

To further conserve storage space, GSK offers a two-dose vial presentation without preservatives. Although this caused large challenges at the beginning of the AMC, including additional usage instructions due to lack of preservatives and delay in WHO prequalification,

countries have implemented the correct administration training programs and confirmed the capacity advantage this offers.

In specific response to Gavi needs both GSK and Pfizer are developing a four-dose vial that includes a preservative. Such an undertaking requires investment both in product development as well as clinical programs. The four-dose vial has three advantages: it alleviates the cold-chain capacity constraints in Gavi countries, increases the supply capacity for manufacturers at the filling and packaging steps, and reduces the manufacturing cost and therefore the price.[59]

5.2 Objective 2: Bringing forward the availability of vaccines

5.2.1 Key findings

PCV10 and PCV13 were available in developing countries just one year after they were introduced in developed countries, which is much faster than any other Gavi vaccines. The suppliers were able to support uptake in Gavi markets at an unprecedented rate. To accomplish this, both Pfizer and GSK invested in additional capacity to manufacture additional doses of PCV for Gavi markets.

PCV10 and PCV13 were second-generation pneumococcal conjugate vaccines with better serotype coverage outside of developed markets, and so making the vaccine available to emerging markets (including Gavi countries) quickly was likely part of the original, pre-AMC strategy. In addition, the investments in capacity also served markets other than Gavi countries, and, in some cases, were decided before the announcement of the AMC. Although the degree to which the AMC drove these investments is unclear, discussions with manufacturers confirm that the AMC and its supply agreements certainly influenced these investment decisions. These decisions were affected by the long-term demand stimulated by the AMC and by the way that the AMC altered supplier economics—specifically, by providing confidence of additional volume that allowed them to achieve scale benefits and thus reduce their costs and increase profitability in all markets (Gavi, middle income, and developed world).

It is important to note that the actual supply was not increased quickly enough to completely meet demand. This resulted in supply shortages of up to 29 million doses from 2012 to 2014 that delayed an estimated 23 country introductions and resulted in up to 26 million Gavi children born without access to the vaccine. However, because of the additional publicity and legally binding agreements associated with the AMC, it is likely that the delays were rectified more

quickly than would have happened without the AMC. For comparison, Hib delays lasted up to seven years beyond the first introductions, and rota delays are still ongoing[xxxii]. Both manufacturers appear to be on track now to meet demand for 2015, with the exception of demand from Nigeria.[xxxiii]

The supply shortages were due primarily to technical issues that manufacturers faced when scaling such a complex vaccine, although the manufacturers could have planned to scale capacity much more aggressively. For instance, manufacturers confirmed they were unable to internally justify capacity investments beyond the awarded supply volume, suggesting a better outcome could have been achieved if supply agreement volume had not been withheld. In addition, deviances between actual purchases and forecasted demand make supplier production teams more conservative in planning, highlighting the importance of forecast accuracy and transparency. In addition to the supply shortages, non-supply factors contributed to country delays, including political issues, national funding disruptions, or insufficient in-country human resources.

5.2.2 Summary of key output indicators

Key indicator	Result
# of doses of TPP vaccines offered to UNICEF/year	Not calculated—see methodology section
# of doses of TPP vaccines contracted/year	See Figure 11
Vaccine price (absolute price and price trend)	Lowest tail price is $3.30/dose[xxxiv]

Table 3

5.2.3 Detailed analysis

Context: Supply agreements signed under the AMC

Countries have been applying for PCV support and introducing PCV much faster than other vaccines in Gavi's history.[xxxv] Twenty-six countries applied for PCV support before the first

[xxxii] Note that there are important contextual differences between PCV, Hib, and rota, discussed further in the Methodology section. Any comparison must consider the multitude of contributing factors driving differences among the vaccines.

[xxxiii] Nigeria is still undergoing a phased roll-out begun in 2014. The country was prepared to do a national roll-out, but was delayed due to supply shortages. Had full supply been available in 2015, they would have started and completed the roll-out earlier.

[xxxiv] Pfizer has committed to price of $3.10 per dose for a four-dose vial, but this product is not yet prequalified and therefore not eligible through the AMC

[xxxv] Inactivated polio vaccine (IPV) is the exception. For further detail on the uptake of PCV, see Objective 3.

vaccine was even approved for the AMC, leading to extremely high early demand. The large number of countries introducing at once was intensified by the pent-up demand within each country resulting from a several-year delay between approval and introduction. Manufacturers were able to supply sufficient volume to support 53 country introductions in the last six years by increasing availability from 3 million doses in 2010 to 107 million doses in 2014.

Over the course of three supply agreements, signed in 2010, 2011, and 2013, UNICEFhas contracted 73 percent of the target peak annual demand of 200 million doses for AMC countries (see Figure 11).[xxxvi,60] As a result, 73 percent of the $1.5 billion AMC funds have been allocated between the two existing manufacturers, with $405 million left to be committed under future call for supply offers.[61] Pfizer and GSK each have been awarded about half of the contracted volume.[xxxvii]

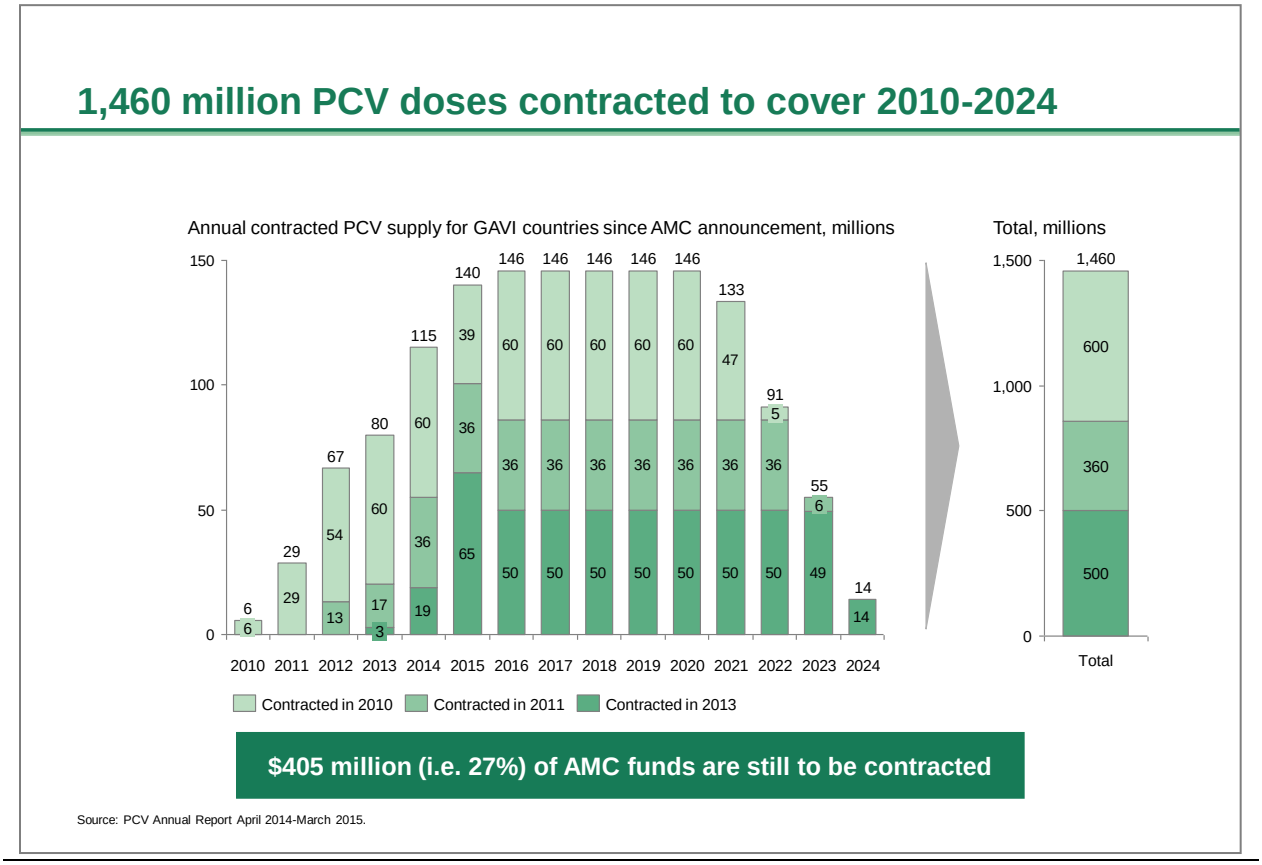


Figure 11

[xxxvi] For AMC design of supply agreements, peak demand was expected to be 2016. This differs from more recent forecasts used for planning and procurement forecasts.

[xxxvii] For more information on supply agreements, see AMC annual reports.

PCV10 and PCV13 were introduced in Gavi countries just one year after they became available in developed countries.[62] This is extremely fast relative to the nine years it took to bring the first-generation PCV7 to Gavi countries,[63] the eight years required for the HPV vaccine, or the 12 years required for the Hib vaccine (see Figure 12).[64,65] The AMC was a contributor to this shortened gap, but was not the exclusive driver. As PCV10 and PCV13 were second-generation vaccines designed for better serotype coverage outside of developed countries, it was likely that Pfizer and GSK were planning on making the vaccines available outside of developed countries more quickly.

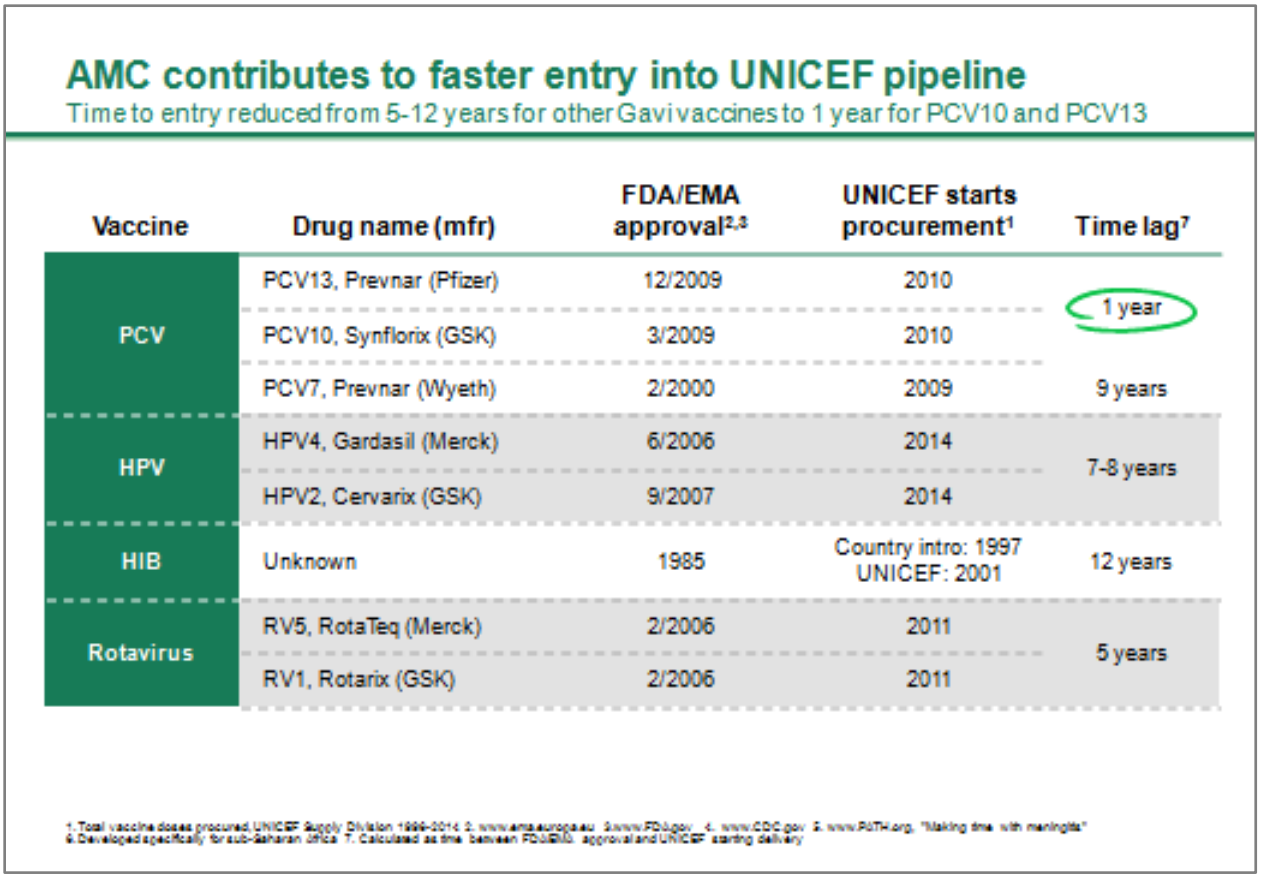


Figure 12

Manufacturer investment in capacity

GSK and Pfizer made investments to increase PCV capacity to serve both Gavi and other markets, enabling increased production volume. GSK invested in new assets to serve Gavi markets starting in 2009, whereas Pfizer waited until 2011 to make significant investment.[66]

GSK spent $510 million on a new vaccine manufacturing plant in Tuas, Singapore, which opened in June 2009.[67,68,69] The decision to build this plant, which is targeted at middle- and low-

income markets, was made in 2004, a year before investment in a pilot AMC was even announced.[70] GSK stated that the decision was based on price levels similar to the AMC average price, and that volume from Gavi countries was a core assumption.[71] GSK's pre-AMC price and volume assumptions are unknown, and so whether they would have invested differently after the AMC is unclear. In addition, the plant is shared across several vaccines, all for low-income markets, and thus the portion of the investment that is attributable to the AMC is unknown.

Since 2011, Pfizer has announced multiple investments in new capital, process improvements, and efficiency measures across its Prevenar supply network, in part for Gavi markets. In 2011, Pfizer invested $200 million in its Grange Castle facility in Ireland, one of the key production sites for Prevenar, a move that it says was spurred by AMC volume.[72] Recently, in February 2015, Pfizer announced an additional $175 million investment in its packaging plant in Puurs, Belgium. The plant has the capacity to produce 75 million doses, which will cover the 74 million doses per year Pfizer has committed to date for Gavi markets in addition to serving developed country markets.[73]

Actual shipments vs. commitments

Despite the significant investments that manufacturers have made in expanding capacity and the fast ramp-up of volume, there are still gaps between cumulative committed doses and actual shipped doses. Between 2009 and 2015, there has been a cumulative gap of 14 percent between doses committed and actual/expected doses shipped, with the largest absolute differences in 2012 and 2013 (see Figure 13). This gap has improved in the last year, and both manufacturers appear to be producing more doses than are being requested for shipment and to be on track to meet commitments in 2015.[74] Some of the 14 percent gap is due to forecasted demand that did not materialize, mainly from introduction delays due to non-supplier factors, such as political issues, national funding disruptions, or insufficient in-country human resources. However, a large part of the gap—especially in 2012 to 2014—was driven by manufacturer technical or capacity issues and inability to ship doses being requested.

UNICEF rates PCV supply "limited" or "very limited," with minimal progress since 2009 (see Figure 14). This rating is similar to the rota vaccine, but much lower than the HPV or penta vaccines. Manufacturers indicated they were not meeting demand in 2011, and the AMC annual reports in 2012, 2013, and 2014 highlight manufacturer struggles to meet demand (see Figure 15). In 2012 and 2013, many countries were forced to delay introduction due to limited supply. In 2014, supply of PCV13 was deemed sufficient, but PCV10 capacity constraints continued (see Figure 15). However, by 2014, UNICEF was able to manage the deficit to prevent more country delays, in large part because few new countries were applying by that time.

It took Pfizer five years to produce sufficient supply to meet Gavi's needs due to technical challenges associated with ramping up the production of an incredibly complex product.[75] At the beginning of the AMC, Pfizer was using existing assets to accommodate the Gavi volume, but have since moved to new assets.[76] The tech transfer of a challenging product to manufacture

may have been underappreciated when planning supply. In contrast, in an interview for this evaluation, GSK did not recognize any large supply issues,[77] although these shortages existed and were especially impactful for Bangladesh and Nigeria (see Figure 16).

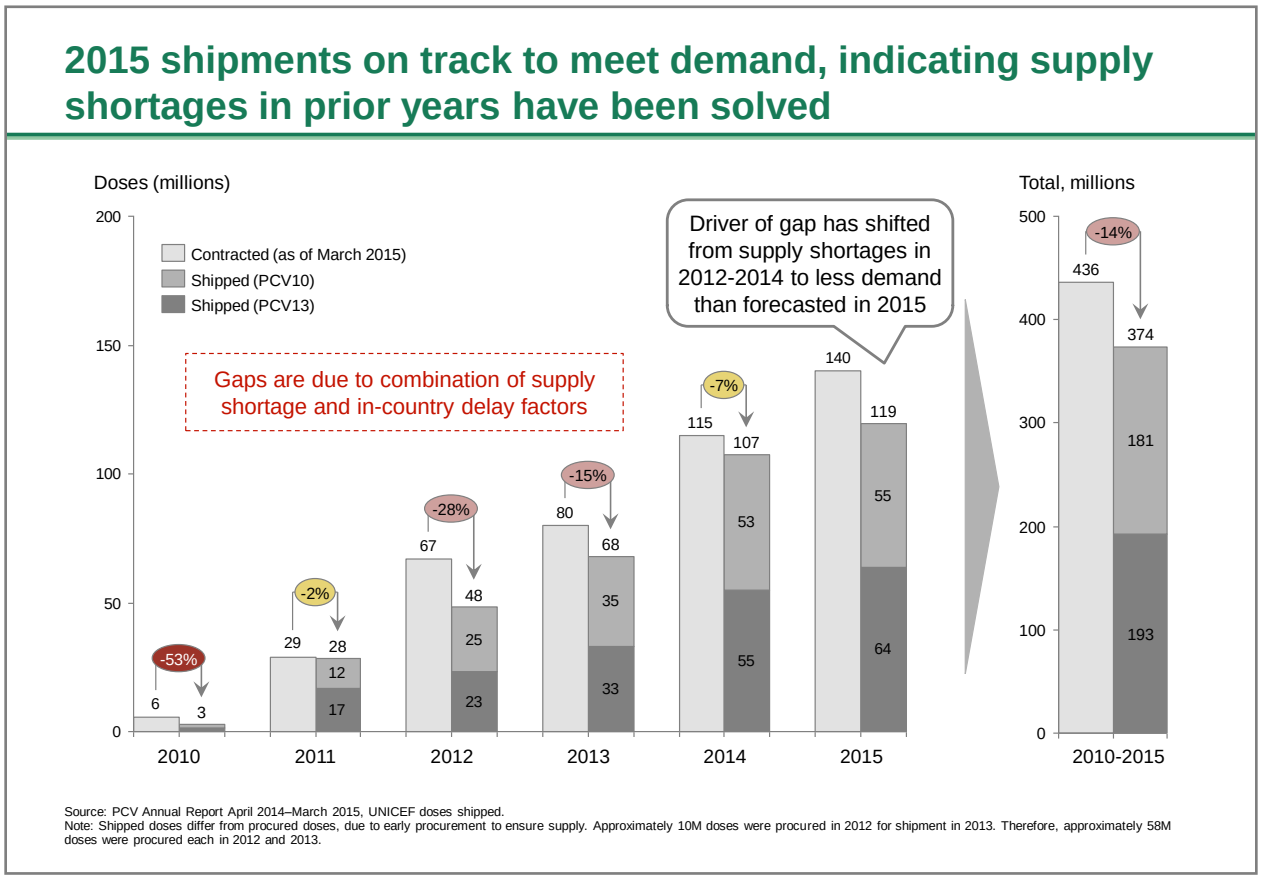


Figure 13

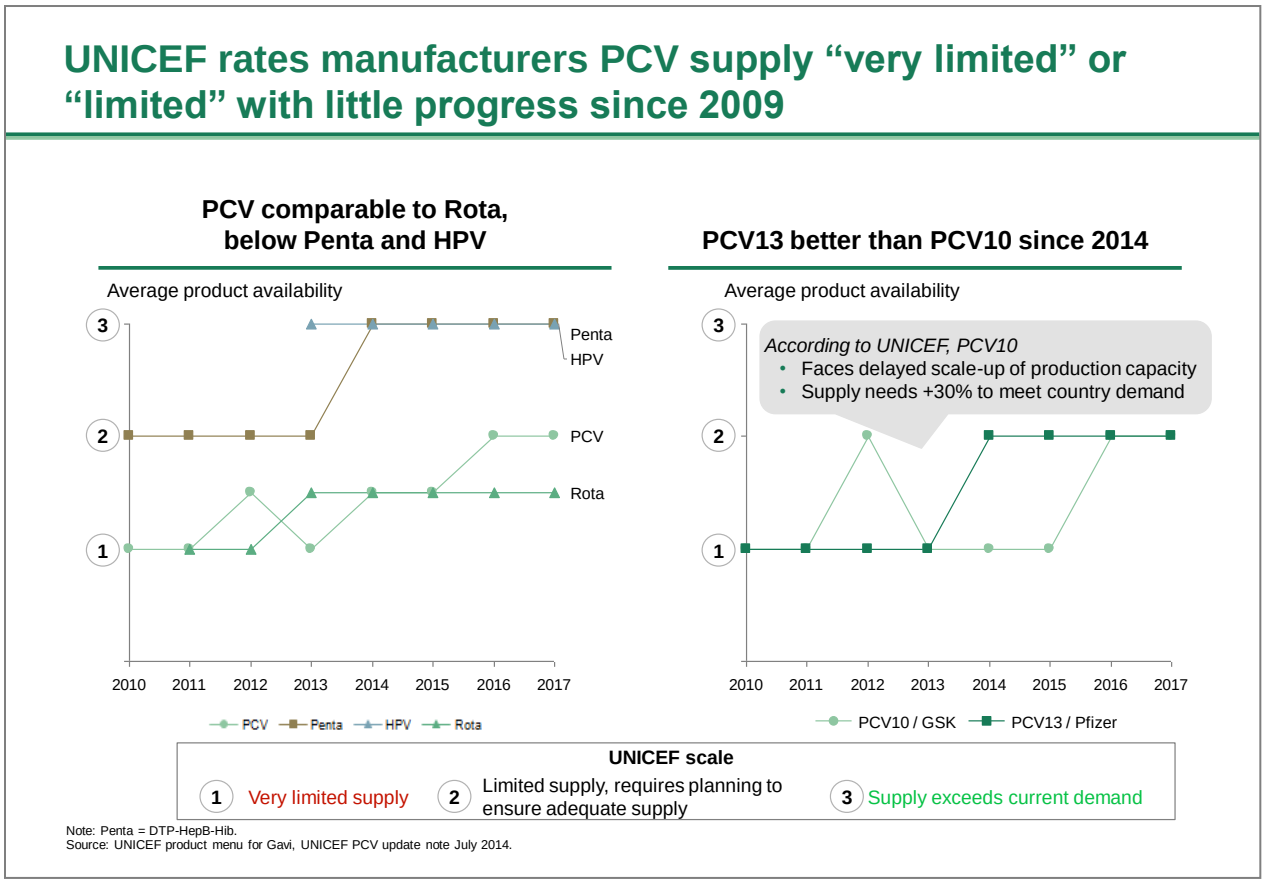

UNICEF rates manufacturers PCV supply "very limited" or "limited" with little progress since 2009
PCV comparable to Rota, below Penta and HPV
Average product availability
3
2
1
Penta
HPV
PCV
Rota
2010
2011
2012
2013
2014
2015
2016
2017
PCV
Penta
HPV
Rota
PCV13 better than PCV10 since 2014
Average product availability
According to UNICEF, PCV10
Faces delayed scale-up of production capacity
Supply needs +30% to meet country demand
PCV10 / GSK
PCV13 / Pfizer
UNICEF scale
1 Very limited supply
2 Limited supply, requires planning to ensure adequate supply
3 Supply exceeds current demand
Note: Penta = DTP-HepB-Hib.
Source: UNICEF product menu for Gavi, UNICEF PCV update note July 2014.

Figure 14

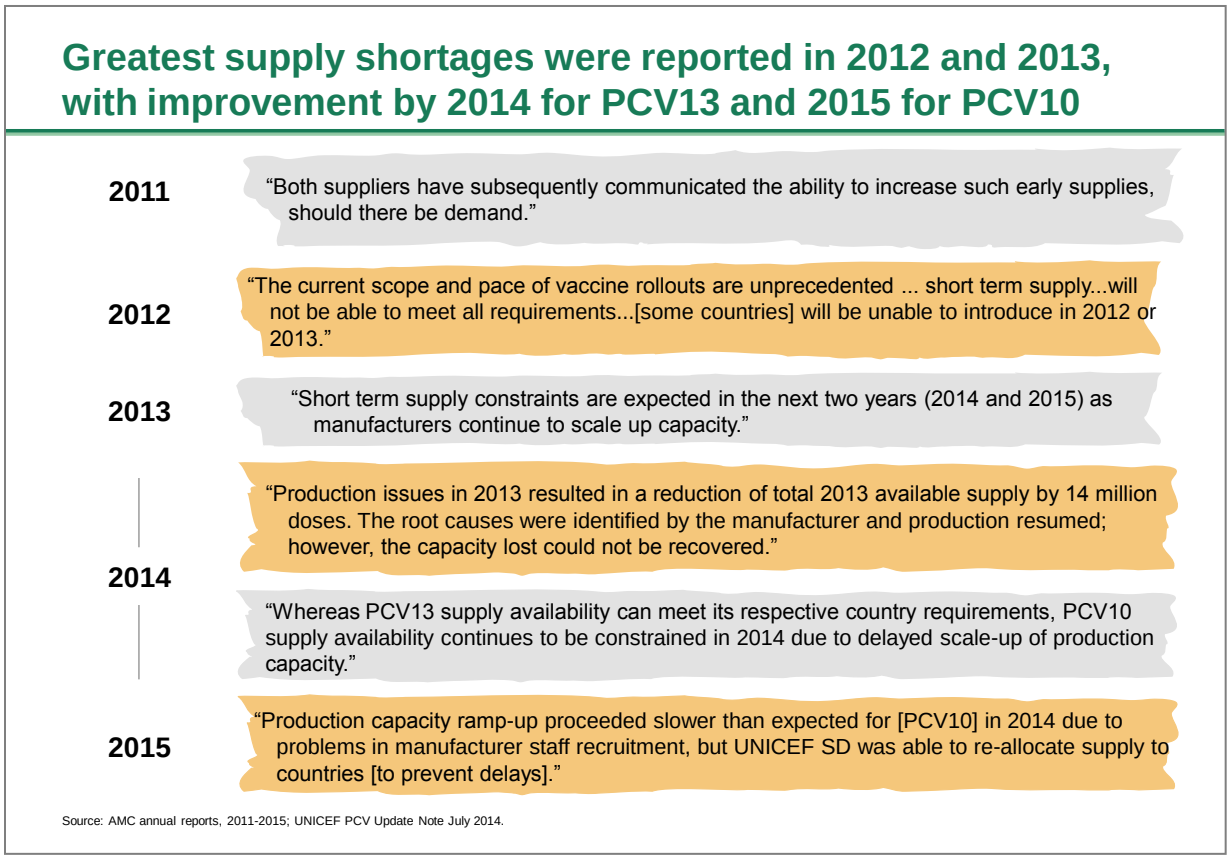


Figure 15

The supply shortages in 2012 and 2013 played a large role in the country delays that happened during those years. The analyses of supply-related delays each year corroborate the reported capacity constraints in 2011, 2012, and 2013 (see Figure 16).[xxxviii] Of the countries that wanted to introduce in 2011, only Pakistan was delayed due to supply shortage. On the other hand, nearly every country that wanted to introduce in 2012 and 2013 was delayed in part due to supply shortages. This raised the average delay from 5.7 months in 2011 to 13.7 months in 2012 and 14.0 months in 2013.[78,79] Only one country was originally planning on introducing in 2014, which helped ease the running delays.

[xxxviii] Calculation of these supply delays assumes that the earliest possible introduction date was the date originally requested on the application to Gavi. In some cases, these dates are unrealistic, exaggerating the amount of supply delay due to supply shortages. However, there are also secondary effects of supply shortages that may have increased the months of delay attributed to "additional, non-supply related delays." Therefore, these effects are considered to balance each other out.

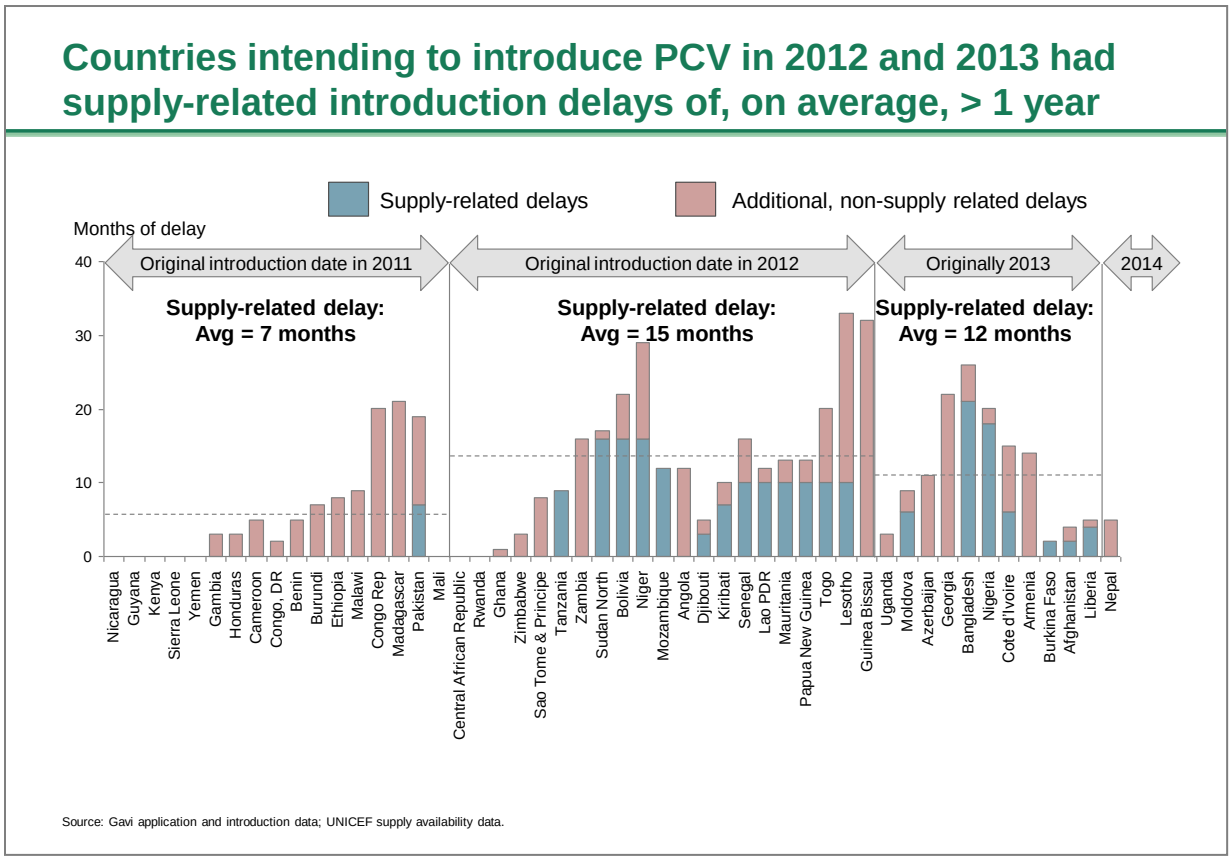


Figure 16

Challenges in demand forecasting

Demand forecast accuracy is extremely important to manufacturers in the context of the AMC, where purchase guarantees were minimal.[xxxix] For participating manufacturers, the long-term strategic demand forecast helps inform their capacity investment decisions (e.g., building new plants or new lines), and the near-term operational forecasts help inform their one- to two year production plans (e.g., how much to make and where to hold inventory).[xl] In particular, the manufacturers have experienced differences between near-term operational forecasts and actual purchases that have potential long-term implications for supply availability.

[xxxix] Purchase guarantees consisted of 20 percent, 15 percent, and 10 percent for the first three years, respectively. Manufacturers confirmed that they consider this level of purchase guarantee to be irrelevant.

[xl] Pipeline manufacturers also use these forecasts to make decisions, but this is less relevant in the context of the outcomes.

Both participating manufacturers have recently experienced shortages of up to 20 percent between what countries estimate as their annual requirement at the beginning of a year versus what they actually purchase.[80] As a result of these shortages, manufacturers have started to second-guess and adjust downward the forecasts when creating their production plans:

> *The confidence level of the signal we send to our [internal] manufacturing colleagues is undermined if we send the wrong signal. People are second guessing our volume, which isn't good for supply.*
>
> **– Current supplier, commercial team[81]**

There is a higher risk of running into supply shortages if manufacturers continue to be increasingly conservative when creating production plans. As Gavi and UNICEF work to make their forecasts more accurate, they should continue to communicate to manufacturers the changes in methodology, so that manufacturers can amend their own adjustments. For instance, countries submit requests for financial support to Gavi, which Gavi approves as the Endorsed Program Costs (EPC). Historically, moral hazard has meant that countries tend to request more than they need, inflating the projected amounts. As Gavi works with countries to make these estimates more realistic, this change should be communicated to manufacturers, so that manufacturers do not continue to reduce the estimates.

5.3 Objective 3: Accelerating the uptake of vaccines

5.3.1 Key findings

The introduction of PCV in Gavi countries and coverage ramp-up across the Gavi population was very steep relative to other Gavi-supported vaccine introductions, and the AMC was a significant contributor to this unprecedented success. By 2014, the fifth year that the vaccine was available through Gavi, the 46 countries that had introduced PCV represented 49 percent of the Gavi population and PCV3 coverage across all 73 countries reached 28 percent. Within the countries that had introduced, coverage was 58 percent. This rate of uptake by countries was faster than the comparable rate for Hib or for rotavirus vaccines, even with important contextual differences taken into account.

Counterfactual analysis revealed that four times the number of Gavi children had access to PCV by the fifth year that the product was available as did the number of children for Hib or rota. Similarly, three times as many Gavi children were covered with the last dose of PCV by that point as were covered with the last dose of Hib or rota. The primary driver of this fast uptake was the rate of country introductions: a large number of country introductions happened within a relatively short time period after the AMC launch in 2009. The build-up of applications before a product was approved meant that there was a large waiting market, and the increased supply availability due in part to the AMC enabled this many introductions. Additionally, PCV uptake is slightly faster than Hib or rota once introduced within a country, albeit to a lesser extent. This is

inferred by PCV's comparable absolute coverage during the first several years, relative to Hib and rota, even though it faced higher contextual hurdles than the other two vaccines.[xli]

In addition, the markets counterfactual reveals a stark difference in the rate at which Gavi countries chose to introduce versus comparable non-Gavi countries. Access and coverage of PCV within Gavi countries exceeds access and coverage within the 50 countries in the next tier of GNI per capita (the "Threshold 50") by a factor of 1.7. Rota has had a lower uptake in Gavi countries than in the Threshold 50, suggesting that this difference is not due purely to the structure and support of Gavi. In addition, a comparison of Gavi countries to the PAHO countries with access to reduced prices relative to high-income countries through the Revolving Fund shows that PCV coverage is much closer to the well-established Hib program than it is to the rota program.

In interpreting these results, it is important to note other factors that also contributed to these positive coverage outcomes. The Gavi support for PCV was enabled by the WHO global recommendation for PCV in 2007, which in turn was catalyzed by the output of the PneumoADIP team between 2003 and 2008, and the Accelerated Vaccine Introduction initiative established in 2008. Without one of these factors—the AMC and Gavi financial support, the PneumoADIP or AVI, or the WHO recommendation—uptake would not have been so quick. The increased global coordination to inform political health decisions is one example of how PCV benefitted from all of the lessons learned based on previous introductions.

Interviews have confirmed that price decrease and co-financing policy ultimately drove country behavior. What had previously been seen as an expensive vaccine suddenly became very affordable for Gavi countries, due to the combination of the guaranteed tail price and Gavi financial support for PCV. Gavi co-financing was feasible because of the tail price; the pre-AMC price of $30 to $40 for middle-income countries would not have been feasible to co-finance. As long as a country is co-financing the same amount, they likely would have behaved the same under a wide range of tail prices.

[xli] Most of Hib roll-out was done by replacing the trivalent DTP vaccine with pentavalent, which would help facilitate coverage increase. There is a two-dose and a three-dose rota vaccine, but 90 percent of immunized children are vaccinated with the two-dose vaccine, making it easier to achieve full coverage. While rota has greater age restrictions than PCV, the lack of a third dose may balance this effect.

BCG

5.3.2 Summary of key output indicators

Key indicator	Result
Per year and cumulative # of AMC- eligible countries (73 Gavi countries) that have introduced TPP vaccines (first child vaccinated)	54 through end of 2015[xlii] (see figure 18)
# of AMC-eligible countries (73 Gavi countries) that have applied for Gavi PCV support	59 through Sep 2015[xliii] (see figure 23)
Cumulative # of doses of TPP vaccines shipped to AMC eligible countries (73 Gavi countries)	Projected 374 million doses through end of 2015
Percent of PCV3 coverage of eligible population in AMC eligible countries (73 Gavi countries)	28% in 2014[82] (58% in the 46 countries that had already introduced by 2014)
Cumulative # of children vaccinated with AMC-supported pneumococcal vaccines	49 million through 2014

Table 4

5.3.3 Detailed analysis

Access and coverage to PCV across the Gavi population

Both access to PCV[xliv] and coverage of PCV3 within the total Gavi target population has risen dramatically. The percentage of Gavi infants with access has grown at an annual rate of 61 percent per year since 2011, and reached 49 percent of the target population in 2014 (see Figure 17). India, home to 31 percent of the Gavi birth cohort, makes up over half of the remaining population without access. Meanwhile, the percentage of infants who have received the third dose of PCV has grown at an annual rate of 82 percent per year since 2011, and in 2014, reached 28 percent of target population. These annual growth rates will level off, of course, as countries complete introductions. Through 2014, this has resulted in a cumulative 49 million children vaccinated with the last dose of PCV through the AMC.[83,84]

[xlii] Includes Uzbekistan, expected to introduce by the end of 2015.

[xliii] Fifty-nine countries have applied; 58 countries have been approved (Guinea applied in 2011 but never re-submitted).

[xliv] Access to PCV defined as born in a country in which PCV has been introduced.

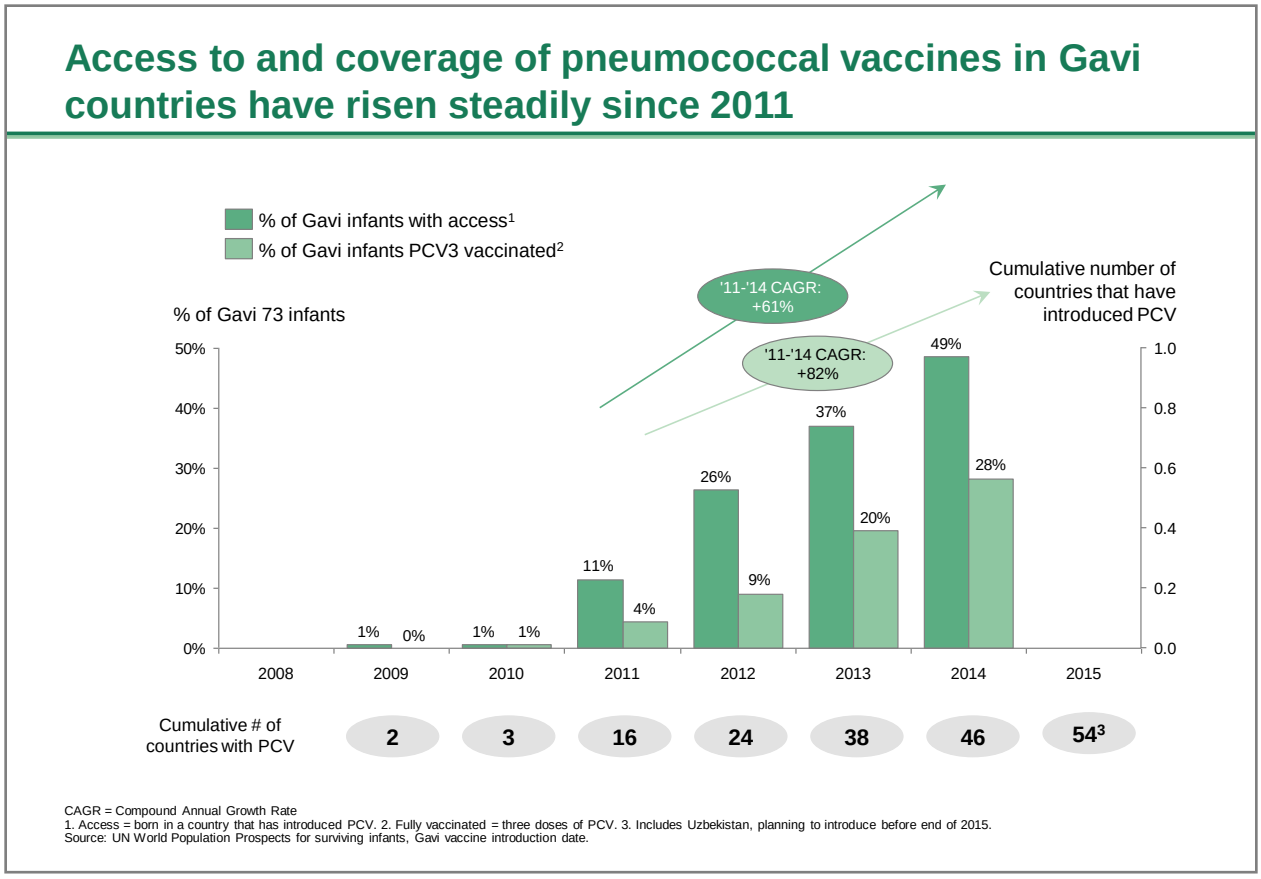


Figure 17

While the Gavi 73 coverage rate is 28 percent, the coverage rate in the 46 Gavi countries that had introduced as of 2014 is 58 percent. The equivalent DTP3 coverage rate is 81 percent, representing the potential coverage of a mature program. As PCV coverage stabilizes in the countries that have introduced it, the 58 percent is expected to approach 81 percent.

BCG

Vaccines counterfactual

A comparison to the Hib and rota vaccines reveals that PCV has achieved its current level of coverage fast (see Figure 18). In year five of availability through Gavi, average PCV access in Gavi countries exceeded the same year for rota and Hib by over 400 percent and exceeded coverage by over 300 percent.[xlv]

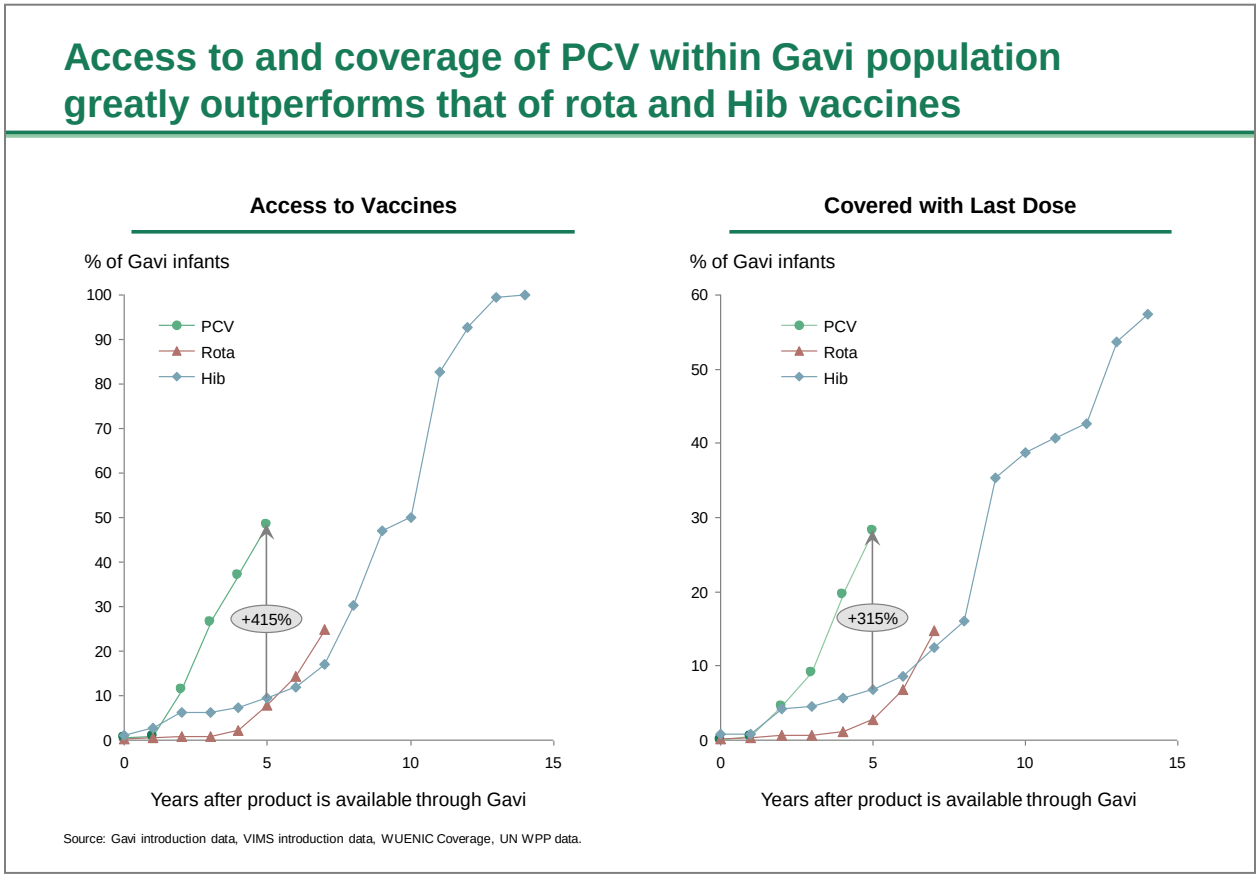


Figure 18

The main driver of this strong access and coverage across the Gavi cohort is the number of countries that have chosen to introduce the vaccine. Gavi countries demonstrated interest in introducing PCV immediately upon the announcement of the AMC pilot in 2007. Between May 2007, when Gavi sent a non-binding letter of interest to the Gavi-eligible countries at the time, and April 2010, when the first TPP-compliant product was approved, 26 countries had submitted applications for PCV. An additional 23 countries sent in applications in 2011, three in 2012, and

[xlv] As noted earlier, Hib and rota faced greater supply challenges, but the AMC played a part in increasing the supply availability. Interestingly, the rota and Hib curves start to look more like PCV in years five and seven, respectively. This could be due to greater supply as well as to the effects of the Rota ADIP and Hib initiative, which had a later launch relative to Gavi support than the PneumoADIP did.

seven in 2013. The cumulative number of countries submitted, approved, and introduced each year can be seen in Figure 19.[xlvi]

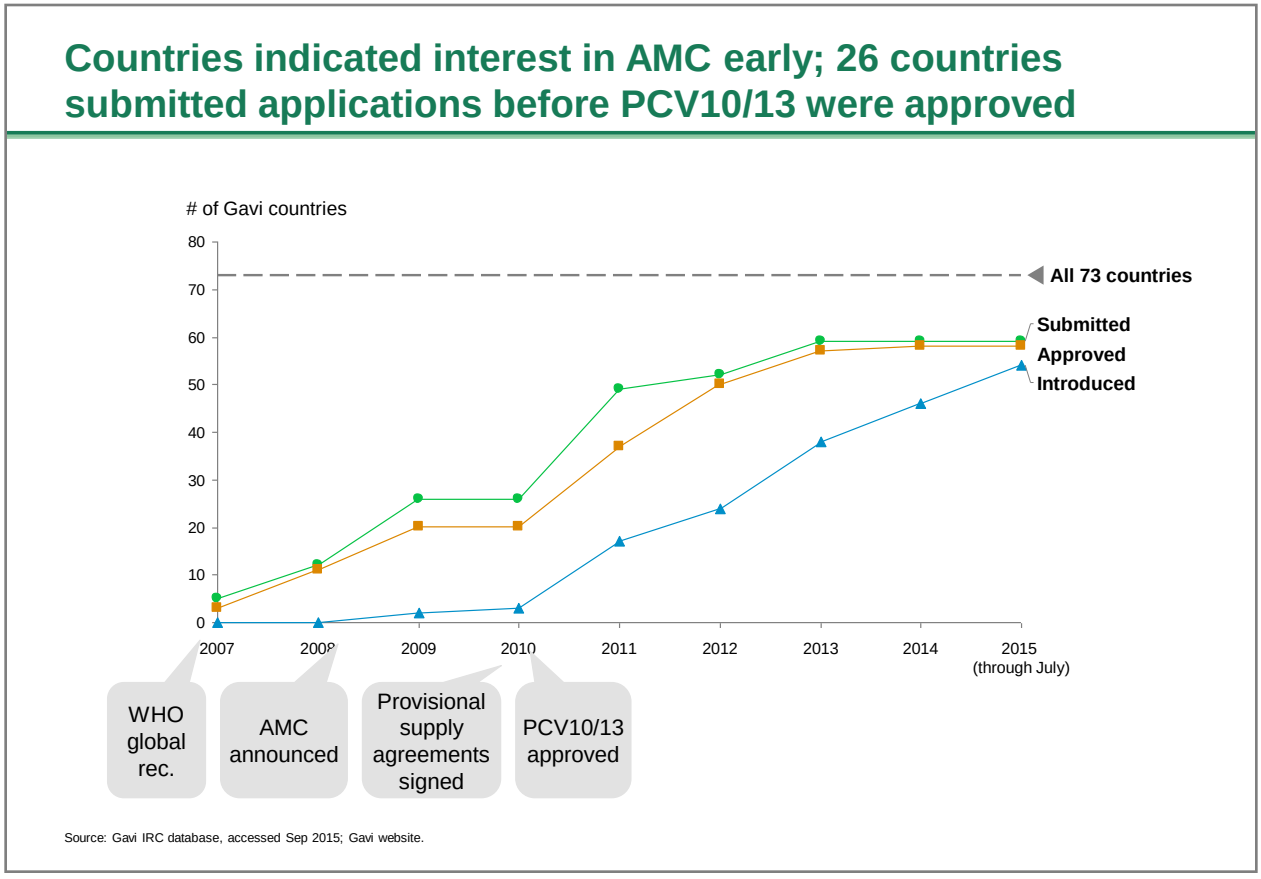
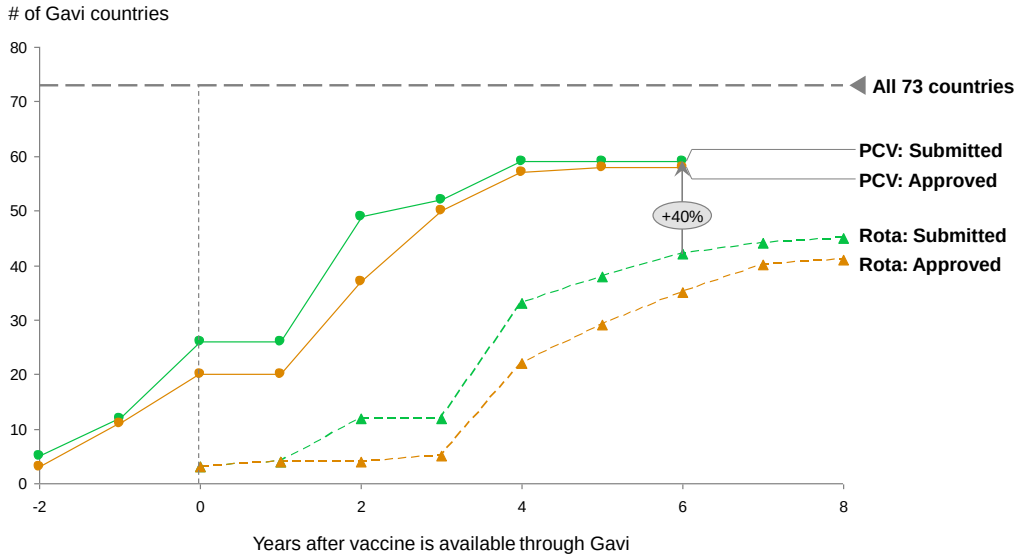


Figure 19

This pace of application is rapid compared to application for rota vaccine support. By year six of vaccine availability through Gavi, 40 percent more countries had applied for PCV support than rota (see Figure 20). Applications for both have leveled off since 2013, but PCV has done so at a much higher level. Of the fifteen countries that have not yet applied, five are not eligible due to insufficient DTP3 coverage as per Gavi's application eligibility criteria (<70 percent), while six are transitioning from Gavi support, meaning they are not eligible for Gavi financial support but can access vaccines under the AMC terms and prices. The remaining four—the Comoros, the Democratic People's Republic of Korea, India, and Tajikistan—had not applied as of August 2015.[85,86,87]

[xlvi] Note that the large gap between approved and introduced in the early years is due to the fact that no product was yet available. This gap persisted through 2013 due to the supply shortages.

Gavi PCV applications outpace Gavi rotavirus vaccine applications by 40%



Source: Gavi IRC database, accessed Sep 2015; Gavi website.

Figure 20

This rapid application process translated into a rapid series of country introductions. Since 2009, 53 countries have introduced PCV, with an additional five countries approved to introduce. In an analogous time period with Gavi support, Hib and rotavirus each only had 19 country introductions (see Figure 21). An examination of each vaccine's timeline highlights factors that were critical in this acceleration. In particular, Gavi's financial support for PCV (both the AMC and non-AMC financial support) was preceded by three crucial factors:

- A well-established set of clinical findings in low-income settings
- The comprehensive disease burden available by region/country
- A strong WHO recommendation for inclusion of PCV in every country's national immunization program

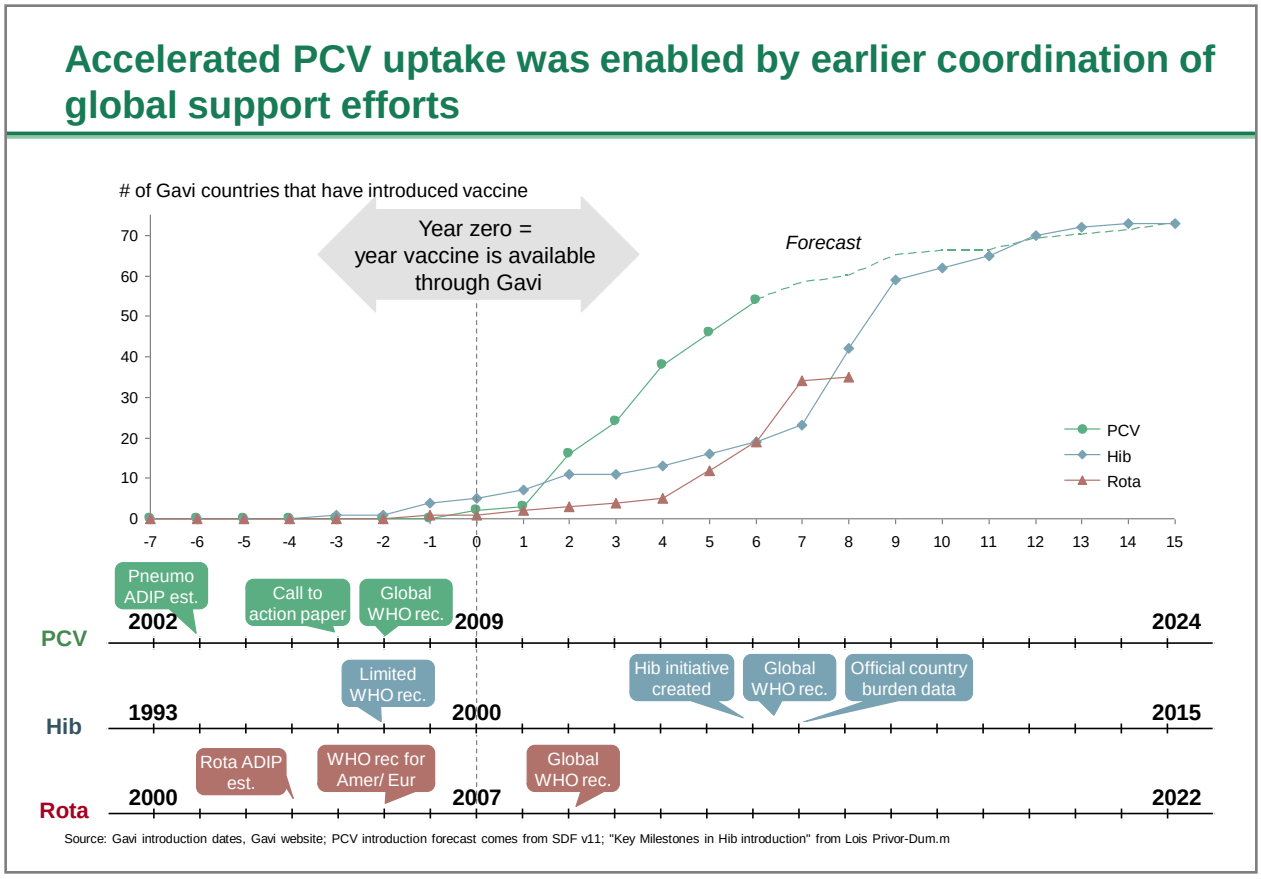


Figure 21

The first two—clinical findings and disease burden by country—were achieved and marketed through the efforts of the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) and the Accelerated Vaccine Introduction initiative. The global WHO recommendation was announced in a 2007 position paper that cited the established vaccine efficacy and substantial disease burden. All three factors were in place before Gavi began to offer financial support. The financial support from Gavi partly broke down one of the last barriers to swaying political decision-making, and made PCV adoption a straightforward decision for many eligible countries. It is also important that PCV supply in the first several years faced smaller constraints than Hib or rota vaccines, although the available supply was due in part to the AMC.[xlvii]

[xlvii] See Objective 2.

On the other hand, the Hib vaccine had a different sequence of events, which led to a longer, more drawn-out process of changing political decision-making.[xlviii] In particular, introductions were slow because of a lack of information around the disease burden within countries as well as supply constraints, and only eight additional countries introduced the vaccine in the first five years that Gavi offered support. Only once the Hib Initiative was established and the WHO provided a strong recommendation did Hib adoption take off at a rate similar to PCV. This shows that financial subsidy alone is not enough to influence political decision-making to introduce new vaccines; a clear disease burden and forecasted impact are necessary, too.

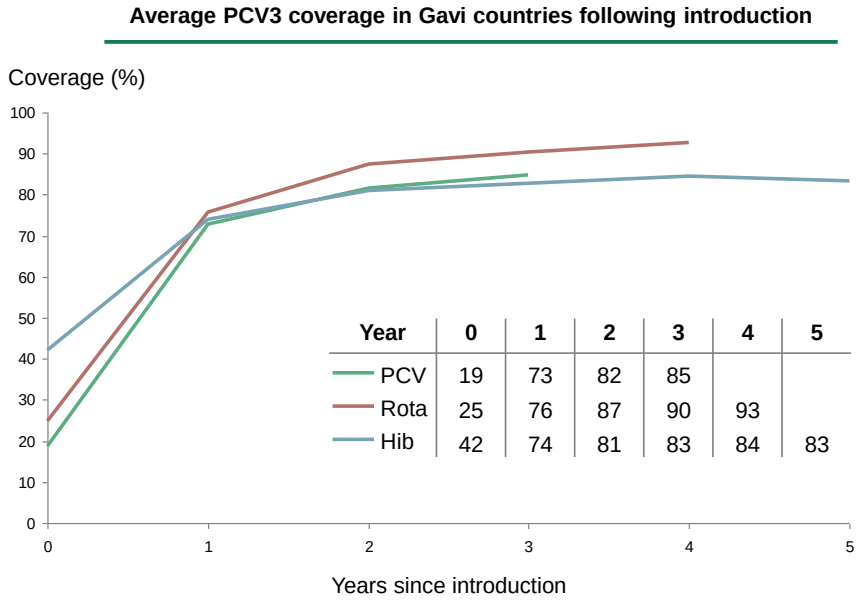
The Rota ADIP was established in 2003, at the same time as the PneumoADIP. WHO issued a recommendation for the rota vaccine in 2005, but only for the Americas and Europe, where clinical trials had demonstrated safety and efficacy. The recommendation was only extended to all countries in 2009, when clinical evidence had been established in countries with high mortality.[88] Gavi had added the rota vaccine to its portfolio in 2006, but, until 2009, only supported introduction in countries covered by the limited WHO recommendation. Even then, applications did not rise sharply until 2011 (Year 4 in Figure 21). Even once the Rota ADIP was established, and the WHO recommendation and Gavi support were in place, introductions rose less steeply than PCV.

This is important in explaining the results of the counterfactual comparison to Hib and rota. The creation of PneumoADIP stemmed from learnings based on the Hib and rota experiences, and is an example of Gavi sophistication and improvement over time. Without any one of these three components—Gavi financial support (the AMC and non-AMC funding from Gavi), the PneumoADIP, and the global WHO recommendation—country uptake would not have been so rapid.

On the other hand, the PCV coverage levels achieved within each country are not much different from those of Hib and rota. In general, the PCV coverage during the ramp-up period is nearly equal to the equivalent years for Hib and rota coverage (see Figure 22). However, given the higher contextual challenges that PCV faced, outlined below, this still reflects well on PCV.

[xlviii] When Gavi was established in 2000, the alliance immediately began to subsidize Hib as part of routine immunization programs. Although Gavi encouraged administration via the pentavalent vaccine, Gavi also offered support for monovalent or tetravalent (DTP-Hib) vaccines. Only eight countries introduced the vaccine between 2000 and 2004. As a result, in 2005, Gavi invested in the Hib initiative to build the case for Hib adoption, similar to what PneumoADIP did for PCV. The strong WHO global recommendation followed in 2006. After 2006, the Hib adoption curve looks similar to the PCV adoption curve post-2009.

PCV ramp-up is similar to other Gavi vaccines, but exceeds relative expectations based on vaccine context



Note: Year 4 and year 5 excluded for Gavi countries because of only 3 or fewer countries contribute data.
Source: WUENIC coverage data, as of July 10, 2015; no WUENIC data from before 2008.

Figure 22

Hib has a higher Year 0 coverage than PCV did (see Figure 22). This is to be expected, given that in most countries Hib was introduced through the pentavalent vaccine, which replaced the existing DTP vaccine. However, from Year 1 onward, the two vaccines are within two percentage points of each other. This reflects well on PCV, as PCV is a harder vaccine to introduce than the pentavalent vaccine. For penta to replace DTP, limited additional storage volume was needed, and no additional human resources were required for administration because no additional injection was given.[89,xlix] However, PCV required additional storage volume as well as three additional injections. All other factors being equal, PCV would have been expected to have slower uptake than Hib, so the fact that it did not differ in a meaningful way is very positive for PCV introduction.

The rota comparison is less straightforward. PCV3 coverage in introductory years is consistently about five percentage points below rota last-dose coverage (see Figure 22), although this may be explained by dosing schedule. The rota vaccine, on average, has less opportunity for drop out.

[xlix] However, more human resources may be needed to handle logistics and overhead.

Nearly all children are vaccinated with a two-dose rota vaccine, which requires fewer points of contact with each child.[l,li]

Market counterfactual

As an alternative to the vaccine counterfactual, the Gavi countries can be compared to sets of countries that are not eligible for the AMC through a "market counterfactual".[lii] In particular, the Gavi countries are compared to the next 50 countries with the lowest GNI per capita that are not Gavi-eligible. These 50 countries range in their 2013 GNI per capita from $2,990 to $9,940, versus $260 to $7,350 for the 73 Gavi countries.[90] Though the economic contexts of the threshold countries are not equivalent, they are comparable.

Although both Gavi countries and these Threshold 50 countries began to introduce PCV around the same time (2009 and 2008, respectively), the rate of Gavi countries that introduced PCV by 2014 exceeded that of the Threshold 50 by nearly double; i.e., 74 percent of Gavi countries have already introduced PCV, compared to 40 percent of the Threshold 50 countries (see Figure 24). These Threshold 50 countries do not have access to the AMC price, do not receive Gavi financial support, and are not the direct focus of the PneumoADIP efforts. Although they may receive some indirect benefit—for instance, product presentation innovations that are also appropriate for their countries, related clinical studies, or the resulting global WHO recommendations—they do not have the low price or price guarantees of the AMC. Most of the retail and hospital prices in these countries range from $30 to $60 per dose,[91,92] and the countries are not aided by a Gavi subsidy. The threshold countries also do not have access to the health system strengthening (HSS) support funds or Vaccine Introduction Grants (VIGs) that Gavi provides. The countries within this Threshold 50 group that choose to introduce must have enough intrinsic political will and available funding to enable introduction. The implications of this market counterfactual are explored in the following sections.

Gavi PCV uptake is relatively high when examined through the lens of the market counterfactual. Gavi introductions, access, and coverage all exceed the threshold countries by a factor of 1.5 to 2 (see Figure 23). Rota has lower access and lower coverage in Gavi countries than in the Threshold 50, suggesting that the pattern seen in PCV is not entirely due to standard Gavi support (see Figure 24).

[l] The two prequalified rotavirus vaccines currently available through Gavi are Rotarix and RotaTeq, which require two and three doses, respectively. Rotarix currently makes up about 85 percent of procured doses for Gavi, or approximately 90 percent of Gavi children covered for rota.

[li] In addition, fewer countries have chosen to introduce rota than PCV (48 percent vs. 66 percent of Gavi 73 countries by April 2015). It is possible that the countries choosing to introduce each have different health system strengths.

[lii] See Methodology section for a full description of "Threshold 5"" countries.

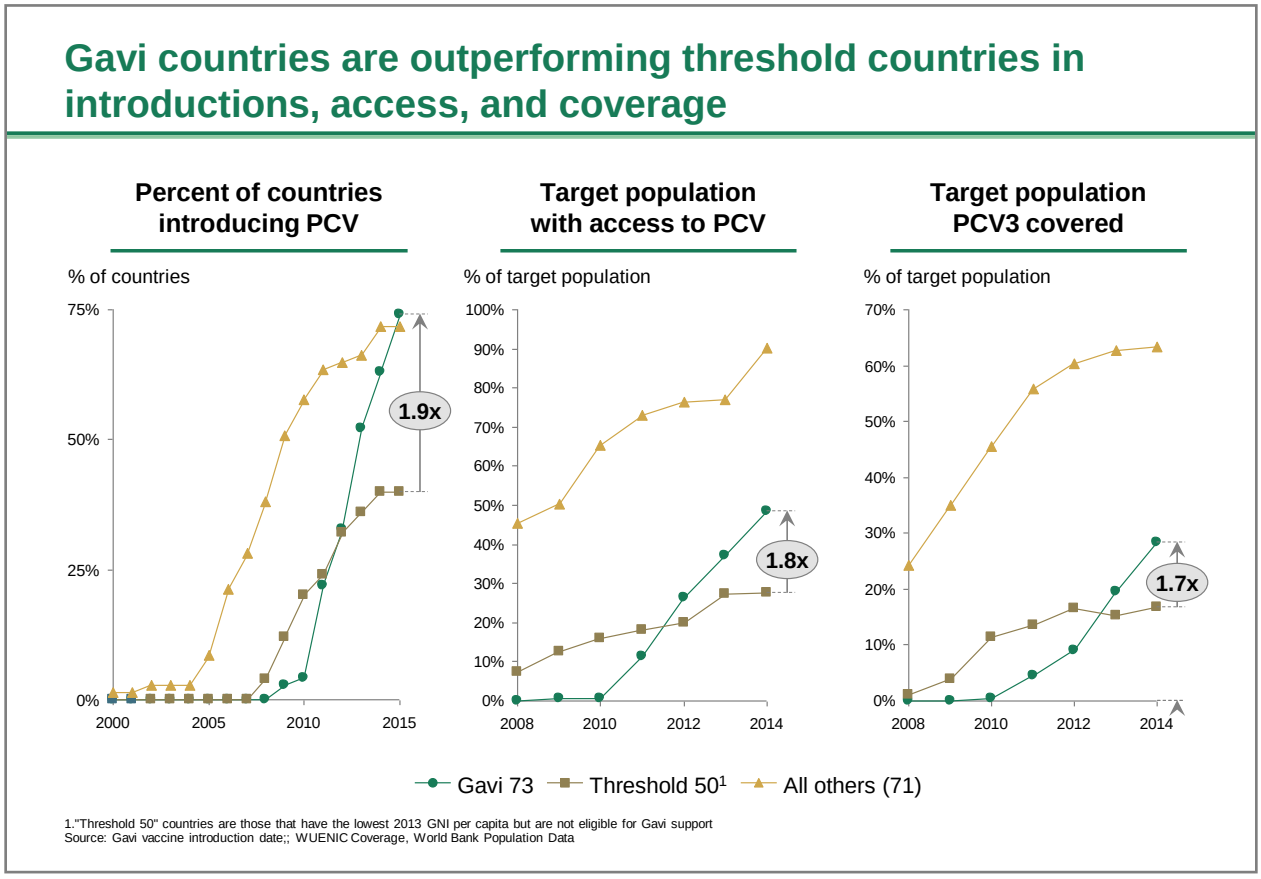

Gavi countries are outperforming threshold countries in introductions, access, and coverage
Percent of countries introducing PCV
% of countries
75%
50%
25%
0%
2000
2005
2010
2015
1.9x
Target population with access to PCV
% of target population
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2008
2010
2012
2014
1.8x
Target population PCV3 covered
% of target population
70%
60%
50%
40%
30%
20%
10%
0%
2008
2010
2012
2014
1.7x
Gavi 73
Threshold 50[1]
All others (71)
1."Threshold 50" countries are those that have the lowest 2013 GNI per capita but are not eligible for Gavi support
Source: Gavi vaccine introduction date;; WUENIC Coverage, World Bank Population Data

Figure 23

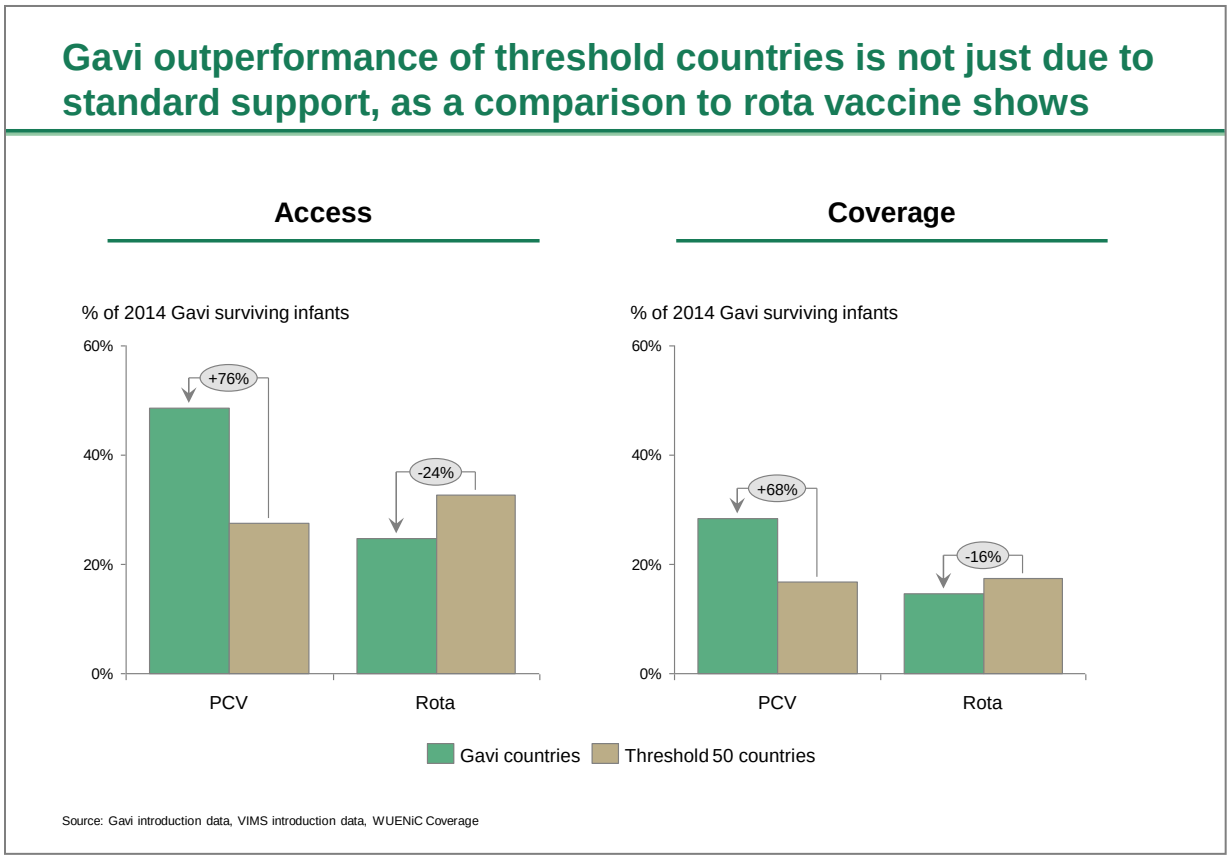


Figure 24

Alternatively, Gavi countries can be compared to the PAHO countries that are not Gavi eligible, but have access to the Revolving Fund (see Figure 25).[liii] These countries have access to a weighted average price of either $14.12 or $15.68, depending on the product, although they also have higher GNIs per capita than the 73 Gavi countries.[liv,93,94] There is a gap of 36 percentage points between coverage in countries with access to the AMC and those with access to the Revolving Fund price.[95,96] This gap is substantially closer to the equivalent gap for Hib (32 percentage points) than it is to the equivalent gap for rota (60 percentage points). Given that Hib is a well-established vaccine while rota is a new vaccine on the same timeline as Hib, this suggests that the AMC has contributed to closing the gap between these country groups.

[liii] Countries included are all WHO Americas region countries, excluding AMC-eligible countries, and excluding the USA, Canada, Mexico and Brazil (Mexico and Brazil are taking part in tech transfer deals, and so are not participating).

[liv] GNI per capita for the selected countries ranges from $3,340 to $21,570.

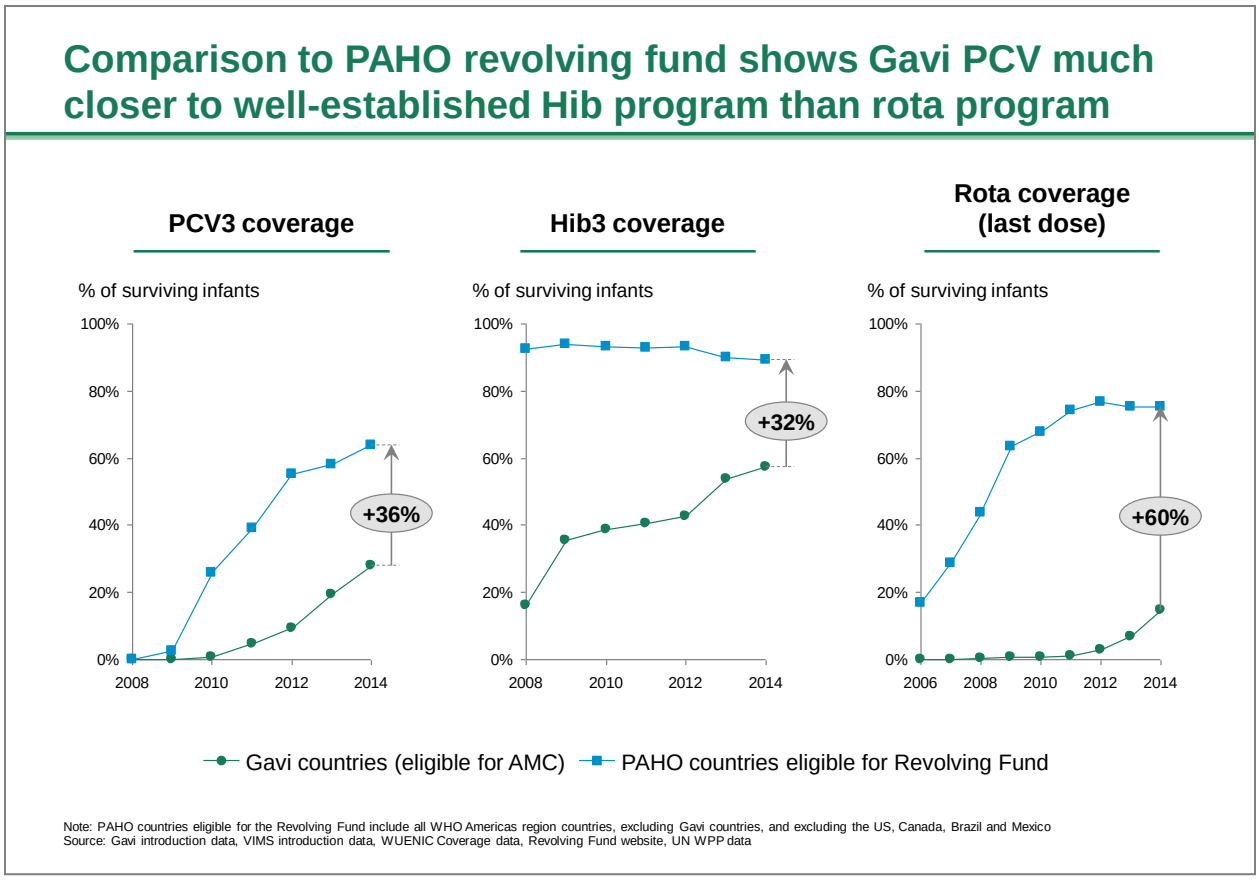


Figure 25

5.4 Overarching goal of reducing the mortality and morbidity from pneumococcal disease

5.4.1 Key findings

Vaccination in Gavi countries under the AMC program has contributed to an estimated 230,000 to 290,000 under-five pneumococcal deaths averted through 2015, with an estimated 670,000 to 970,000 under-five deaths averted projected by 2020. In 2013, the WHO estimated that more than 500,000 young children die each year from pneumococcal disease, with the vast majority of these deaths occurring in developing countries. By 2020, PCV immunization in Gavi countries is expected to avert 80,000-150,000 deaths per year, making a significant difference in global childhood pneumococcal deaths.[97]

In addition to deaths averted, reduction in morbidity (cases averted and DALYs saved) is significant, with 6 million to 7.5 million pneumococcal disease cases averted through 2015, and 14 million to 17 million DALYs saved over the same period. Annual estimates can be seen in

Figures 26, 27, and 28. These figures all represent health impact due to PCV immunization in AMC eligible countries. While 100 percent of the morbidity and mortality averted due to vaccination cannot be explicitly attributed to the AMC, the AMC's progress along the first three objectives (development, availability, and uptake of vaccines) all contribute to this overarching goal.

In addition, the relevant empirical studies were reviewed to provide context and support for the inputs used in the models. This included studies related to the vaccine effectiveness on reducing invasive pneumococcal disease (IPD) cases and carriage in Gavi countries, as well as studies that demonstrate the likely conservative nature of these estimates.[lv]

5.4.2 Summary of key output indicators

Timeframe & indicator	Estimated range
2009-2015: U5 deaths averted	230,000–290,000
2009-2015: U5 cases averted	6M–7.5M
2009-2015: U5 DALYs saved	14M–17M
2009-2020: U5 deaths averted	670,000–970,000
2009-2020: U5 cases averted	20M–29M
2009-2020: U5 DALYs saved	40M–58M
Annual U5 deaths averted in 2020	80,000–150,000
Annual U5 cases averted in 2020	2.6M–4.7M
Annual U5 DALYs saved in 2020	4.9M–8.8M
2009-2030: U5 deaths averted	[LiST estimate only] 3.2M[lvi]

Table 5

Impact is reported as a range to avoid false precision. It is important to note that the low and high values represent different ways of calculating health impact (e.g. different models), rather than being ranges of statistical uncertainty. Confidence intervals were not available for the previous output estimates; however, the next published output will include these.

[lv] These impact studies are conducted in specific settings that may not be generalizable to the entire Gavi population. They do, however, provide a sense of direction and magnitude of the modeled impact estimates.
[lvi] TRIVAC output did not provide data beyond 2020.

The estimate of 3.2 million deaths averted by 2030 represents a difference of 3.8 million from the 2008 estimate of 7 million deaths averted. This difference of 3.8 million deaths averted is largely due to factors other than the outcomes of the AMC, primarily the downward revisions in the underlying disease burden (total childhood mortality and proportion of pneumococcal deaths) that have come about through better information. In addition, separate models were used to calculate these figures, creating structural differences in the estimates. One AMC-related factor, the delay of India's introduction, contributed to the difference, but this explains only 200,000 of the 3.8 million.

Additionally, it should be noted that the modeled estimates given here, both low and high, are conservative,[lvii] for the reasons listed in the methodology section. A further explanation of considerations, limitations, and scope of this analysis is included in the Methodology section of this report.

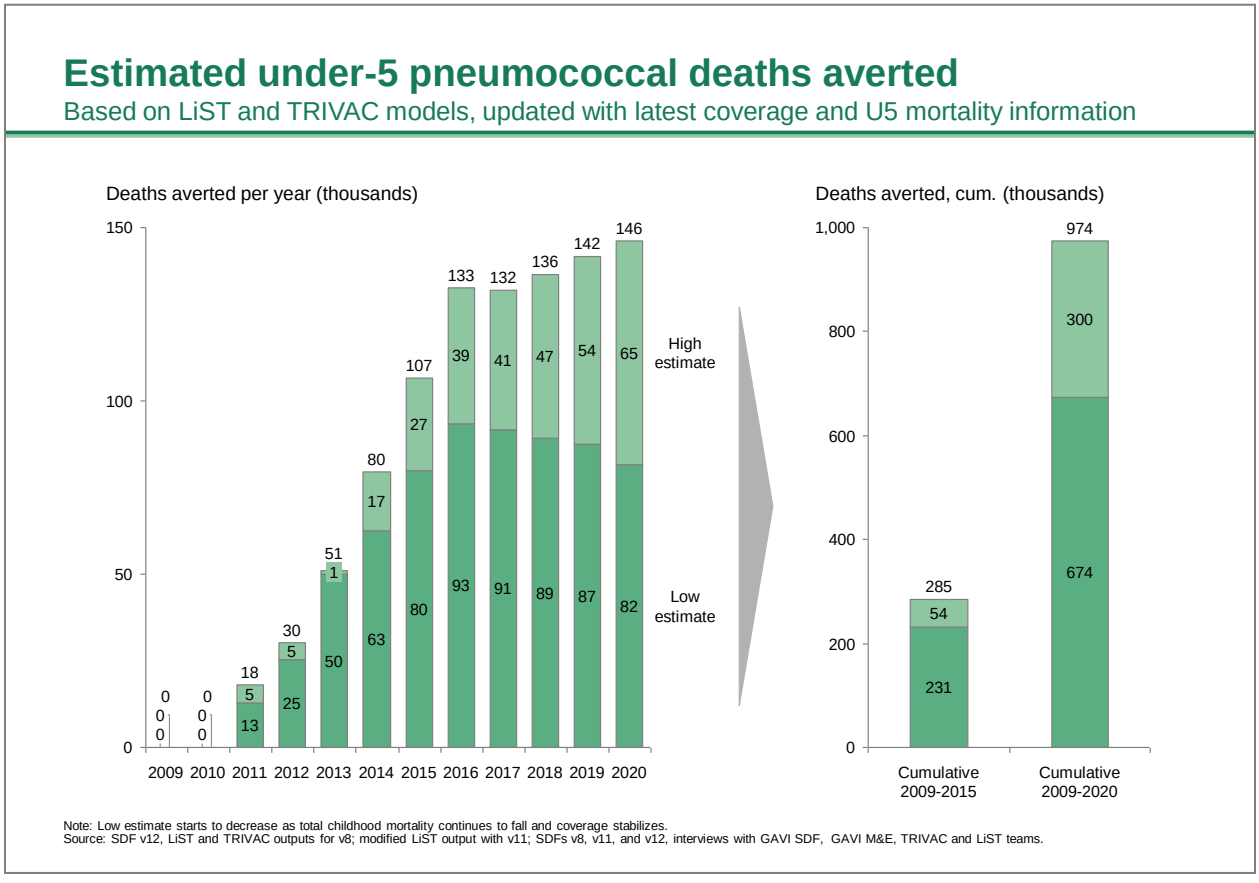


Figure 26

[lvii] Expert opinion, through both Gavi and external experts.

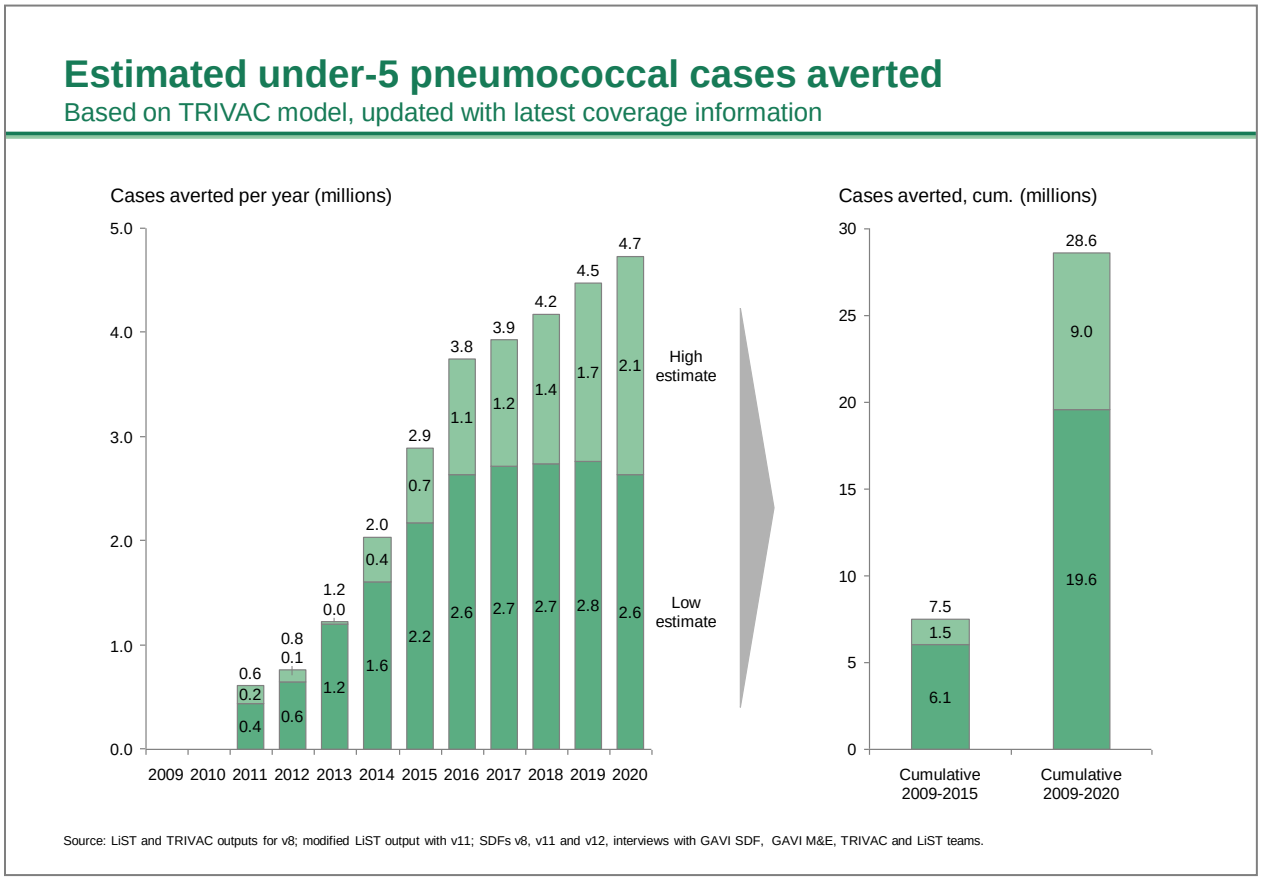

Estimated under-5 pneumococcal cases averted
Based on TRIVAC model, updated with latest coverage information
Cases averted per year (millions)
5.0
4.0
3.0
2.0
1.0
0.0
2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020
0.6
0.2
0.4
0.8
0.1
0.6
1.2
0.0
1.2
2.0
0.4
1.6
2.9
0.7
2.2
3.8
1.1
2.6
3.9
1.2
2.7
4.2
1.4
2.7
4.5
1.7
2.8
4.7
2.1
2.6
High estimate
Low estimate
Cases averted, cum. (millions)
30
25
20
15
10
5
0
7.5
1.5
6.1
28.6
9.0
19.6
Cumulative 2009-2015
Cumulative 2009-2020
Source: LiST and TRIVAC outputs for v8; modified LiST output with v11; SDFs v8, v11 and v12, interviews with GAVI SDF, GAVI M&E, TRIVAC and LiST teams.

Figure 27

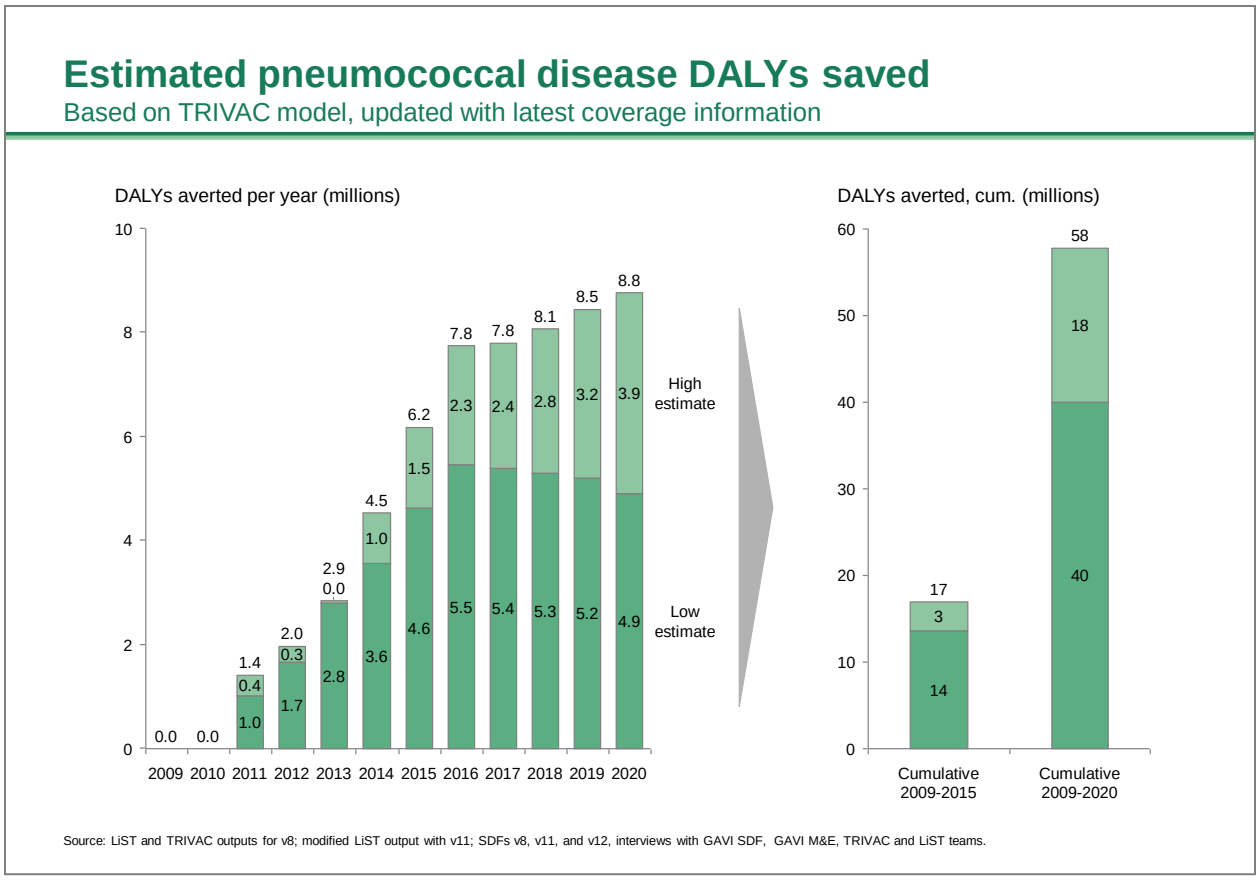


Figure 28

5.4.3 Detailed analysis

Comparison to previous impact estimates

Our projection of more than three million under-five deaths averted by 2030 is an estimate that updates the latest LiST/TRIVAC output to reflect the most recent coverage estimates. Over time, the mortality impact estimates of the AMC have changed significantly as new models are utilized and new estimates for model inputs are provided. Therefore, for several reasons unrelated to the progress of the AMC, the latest deaths averted estimate differs from early estimates.

For example, the 2008 estimates expected 900,000 deaths averted by 2015 and over 7 million by 2030.[98,99] This estimate came from PneumoADIP, not using LiST.[100] In addition, two major changes have happened since then that influence the modeling methods:

- Estimates of underlying disease burden have been revised downward by over 40 percent[101]
- Assumed India introduction date has been moved from 2016, to 2018, to 2021

The first of these two factors, the downward revision in underlying disease burden, plays the largest role in reducing the impact estimates. The underlying disease burden is the number of under-five pneumococcal deaths that would have occurred without vaccination, and is a function of total child mortality estimates, proportion due to pneumonia, and proportion of pneumonia due to pneumococcal disease.[102] Estimates for each of these factors have been dramatically over the last 10 years. For instance, the total child mortality alone has come down by 20 percent: the number of global under five deaths that happened in the year 2005 was revised from 10.1 million (UNICEF 2006 estimate)[103] to 8.2 million (UNICEF 2014 estimate).[104] Proportion due to pneumonia and proportion of pneumonia due to pneumococcal disease have similarly been revised downwards.[105] The change in number of deaths averted is proportional to the changes in underlying disease burden data.

The second change is related to how PCV introduction played out, and is therefore, potentially related to the AMC. Originally, India was assumed to gradually introduce PCV in its states between 2016 and 2018.[106] Introduction in India has since been pushed back to 2021.[107] This delay leads to over 200,000 fewer deaths averted by 2030.[lviii]

Evolution of the impact models

Health impact estimates are included in this evaluation of the AMC mechanism with the understanding that these ranges will continue to evolve as input estimations are revised and assumptions are improved. In particular, a comprehensive re-run of the two academic models used in this evaluation (LiST and TRIVAC) is occurring during Q4 2015, with published output expected in Q1 2016. These re-runs will also use the latest version of the Strategic Demand Forecast, SDF v12, to forecast coverage. The re-runs will also produce statistical uncertainty ranges.

Application of empirical data

These impact estimates come through modeling the pre-intervention and post-intervention mortality and morbidity using global underlying disease burden estimates, coverage estimates, and vaccine efficacy estimates. This kind of impact modeling is currently the best method to understand historical global impact, and the only method of projecting future impact.

Ideally, these modeled estimates could be validated by comparison to empirical measurements of pneumococcal deaths before and after vaccine introduction. We explored numerous ongoing and completed empirical studies that measure case or carriage reduction after PCV introduction, both through interviews and literature reviews (see Figure 29 and Figure 30). In addition, further lists of ongoing studies are available through external resources.[108]

[lviii] Estimated by combining percent reduction in cumulative 2015 to 2030 doses between SDF v2 and SDF v11, with India FVPs in LiST V11 estimates.

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Empirical studies primarily focus on morbidity, but confirm directional findings in reduction of cases

Empirical studies interviewed as part of this evaluation

Location	Principal Investigator	Parameters	Key Findings
Gambia	Dr. Grant Mackenzie	• 2008-9 as "before" • 2013-14 as "after" • PCV7 introduced in 2009, switched to PCV13 in 2011	• IPD[1] incidence rate reduced by 56% in 2 to 4 age range • IPD incidence rate reduced by 55% in all ages
Kilifi, Kenya	Dr. Anthony Scott	• 2009-10 as "before" • 2011-12 as "after" • PCV10 introduced Jan 2011	• 65% effectiveness against U5 carriage • 95% effectiveness against U5 Vaccine-Type IPD
Malawi	Dr. Naor Bar-Zeev	• Morbidity baseline since 1997 • PCV13 introduced Nov 2011 • *Ongoing measurement*	• Serotype replacement not yet observed
Latin America	Dr. Dan Weinberger	*Ongoing measurement*	*Not ready to report*[2]

1. IPD = "invasive pneumococcal disease"
2. These studies will provide valuable evidence in non-sub-Saharan-Africa settings once complete.
Source: Interviews with principal investigators.

Figure 29

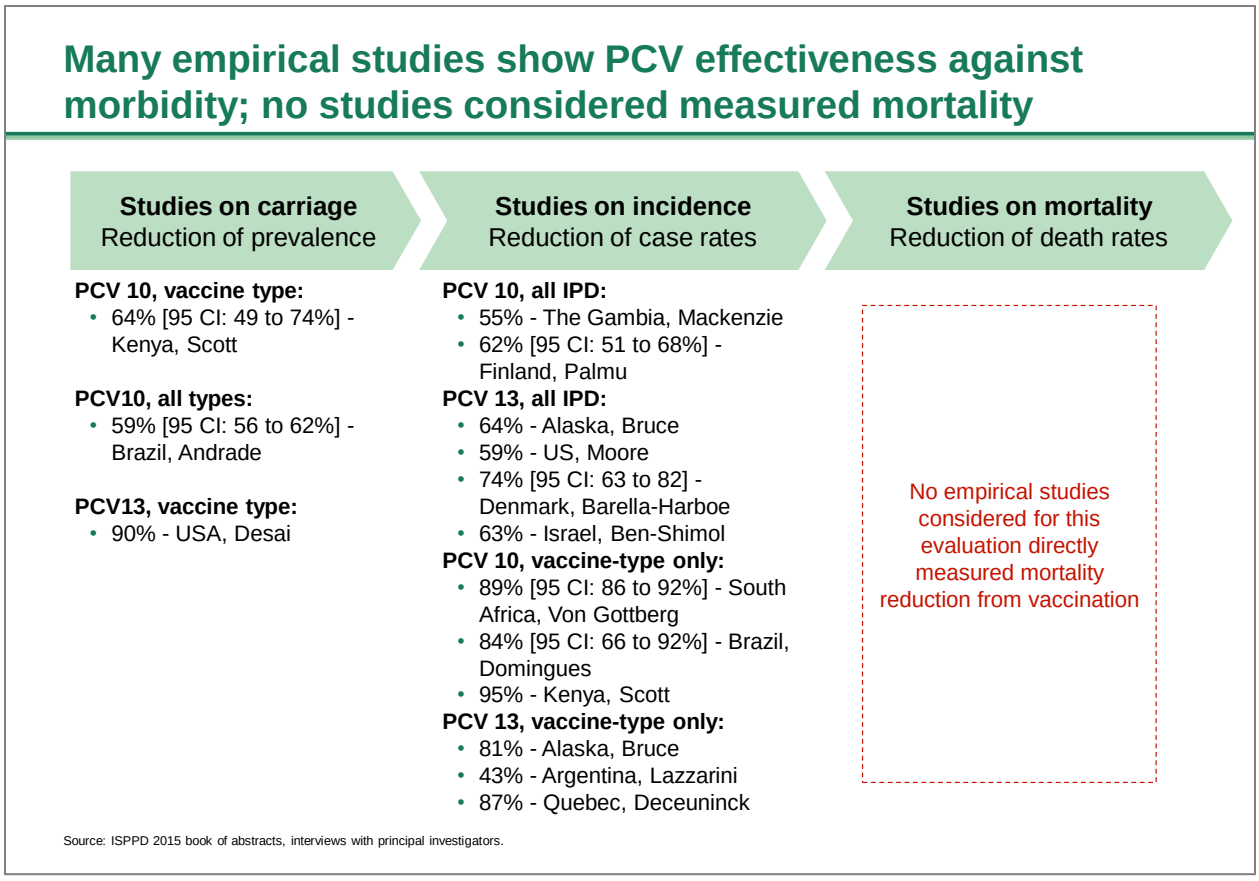

Figure 30[109,110,111,112,113,114,115,116,117,118,119]

These studies confirm that both PCV10 and PCV13 significantly reduce vaccine-type carriage rates (thereby reducing transmission) and rates of invasive pneumococcal disease (IPD). The findings of these studies are consistent with the vaccine effectiveness assumptions that will be used in the 2015 runs for both LiST and TRIVAC (58 percent against all serotype severe pneumococcal disease cases).[120,121] Note that the previous runs of LiST and TRIVAC used effectiveness against deaths, for which an empirical figure is not available.[122] In addition, there are many ongoing empirical studies and surveillance networks located in Gavi countries. As countries continue to roll out introduction and achieve more stable coverage, these studies will provide additional data that can be used for confirmation.

In this sense, local empirical studies can help confirm model inputs and are consistent, at least directionally, with model outputs. However, it is currently not possible to directly validate the model output with existing empirical studies, for two reasons.

First, there is currently no database that comprehensively tracks pneumococcal cases and deaths across all Gavi countries. The existing empirical studies use populations that are not exactly representative of the national population. The model outputs are not detailed beyond the

country level, and so it impossible to compare equal populations across empirical data and modeled data. Secondly, most empirical studies do not directly measure mortality reduction due to vaccination, as it is notoriously difficult and very costly to count childhood deaths, determine a cause of death, and then isolate the role of immunization in observed deaths averted. Generally, empirical studies that estimate deaths averted often do so indirectly, by applying fatality assumptions to observed cases averted. As a result, empirical studies that make conclusions regarding mortality often rely on the same assumptions as the academic models. To improve these assumptions, more research is needed on the fatality rates that link pneumococcal cases and deaths.[123]

In addition to providing confirmation of model inputs and assumptions, empirical studies have demonstrated the four effects cited to explain why these modeled estimates are believed to be conservative:

- **Herd effect:** Two recent studies highlight the herd effect of PCV when using the three-dose (3+0) schedule in children. One study in Australia demonstrated that this schedule in children reduced vaccine type invasive pneumococcal disease (VT-IPD) in unvaccinated adults. Unvaccinated adult VT-IPD cases decreased by 62 percent in ages 15 to 29, 43 percent in ages 30 to 49, and 36 percent in ages 50 to 64 in the first two years after vaccine introduction.[124] A second Australian study demonstrated a 35 percent reduction in both ages 15 to 49 and 50 to 64 for unvaccinated adults within the first year after introduction.[125] However, there is insufficient evidence to show that a three-dose schedule offers herd immunity against syndromic pneumonia.[126]

- **Partial vaccination impact:** Although the WHO PCV position paper recommends three primary doses (3+0), or alternatively, two primary doses plus a booster (2+1) schedule, studies have shown that one or two primary doses still offer some immune protection. Literature reviews have shown that antibody concentration is increased and nasopharyngeal carriage is decreased with both one and two doses.[127] Although PCV drop-out rates are currently unknown, drop-out between DTP1 and DTP3 was 7 percent across all 73 Gavi countries in 2014.[128] This suggests that there is a significant number of Gavi children covered with just one or two doses of PCV, which would contribute additional health impact.

- **The role of vaccination in preventing antibiotic resistance:** Pneumococcal disease is treated with penicillin and other antibiotics, whose frequent use leads to the emergence of pneumococcal strains resistant to these antibiotics. Resistant strains complicate the treatment and reduce the effectiveness of the treatment regiments. Recent studies show that routine PCV7 use decreased the incidence of IPD caused by penicillin-resistant strains by 81 percent among children <2 years, as a result of decline in non-susceptible PCV7 serotypes.[129,130]

- **Over-five deaths:** The modeled data only measures deaths averted before the age of five. This is because most pneumococcal deaths happen before the age of five (and 50 percent of under-five cases happen in the first year[131]). However, the number of childhood deaths from 5 to 19 years of age are estimated to be 21 to 33 percent the number of deaths 0 to 5 years of age.[lix] The proportion due to pneumonia, the main manifestation of pneumococcal disease, is even higher.[lx] Although the impact of vaccination on pneumococcal mortality after the age of five is not calculated, it implies that using under-five deaths to estimate the impact of PCV immunization underestimates the total childhood impact.[132,133]

[lix] Estimates of deaths occurring between 5 and 19 in 2010 range from 1.5 million to 2.3 million, which represent 21 to 33 percent of under-five deaths. See earlier Methodology section for citations.
[lx] Expert interview.

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6. Lessons Learned

6.1 Proof of concept and validation

One of the most valuable outcomes of this pilot, which may be taken for granted by 2015, is that it provided proof of concept of an advance market commitment. The pneumococcal AMC demonstrated that the international community was able to establish the legal agreements and structure necessary to support an advance market commitment, and that such a mechanism could produce many of the desired outcomes. In particular, elements such as the legally binding agreements for donors and the Target Product Profile (TPP), which set a standard for products still in development, were crucial elements of successfully turning theory into practice. Prior to this pilot, it was not guaranteed that the legal structure could be set up and executed to support the theory.[134]

The pneumococcal AMC also garnered significant interest from donors, including two countries that had not previously donated to Gavi. Many donors were attracted by the innovative nature of the pilot, as well as the market-based approach. It is likely—though hard to prove—that these characteristics resulted in more funding than would have otherwise been mobilized, both to the AMC pool for PCV as well as to Gavi itself.

And, most importantly, the AMC was proven to have the desired effect: accelerating supply of vaccines, accelerating uptake, and contributing to a large reduction in mortality and morbidity from pneumococcal disease.

6.2 Lessons learned and recommendations for future AMCs

In addition to the positive outcomes and impact achieved, this pilot yielded valuable lessons that can help shape future AMCs and other innovative financing mechanisms. While a range of topics were explored, the lessons described below are most relevant to improving outcomes and impact and most applicable across different circumstances. They build upon and complement the six lessons included in the 2013 Process and Design Evaluation.

The lessons learned identified in this evaluation are as follows:

1. Clear prioritization of outcomes drives focus of objectives and leads to greater achievement of those outcomes
2. Earlier stage products, particularly those that are technically complex, likely require a portfolio of incentive mechanisms to accelerate R&D outcomes
3. Successful engagement with the biopharmaceutical industry improves sustainability of initiatives; enabling manufacturers to shift from a CSR-based approach to a commercially viable strategy is critical
4. Complementary forces to an AMC are critical for creating the enabling environment necessary for its success

Lesson 1: Clear prioritization of outcomes drives focus of objectives and leads to greater achievement of those outcomes

Having competing objectives was a natural outcome of the AMC design process that involved multiple stakeholders and a need to balance competing donor interests. With this in mind, more explicit prioritization of the pilot objectives would have enabled focused development of critical issues and better aligned stakeholders. The stated objectives of this pilot AMC spanned the entire delivery chain, from product development to vaccine uptake, and, as a result, it would have been nearly impossible to accomplish all of the objectives with the given time and resources. In particular, the choice of a product with multiple candidates near launch shifted the emphasis away from R&D and toward supply availability and vaccine uptake. However, there were still global shortages that led to country introduction delays. A clear prioritization of the supply availability might have resulted in different implementation choices. For instance, in all three rounds of supply agreements, UNICEF opted not to award the full amount of AMC funds,[135] in hopes of incentivizing additional manufacturers to accelerate the development of vaccines and improve the likelihood of having a multi-player market with price competition.[136] However, interviews indicate that, had greater volumes been awarded to the two existing players, they may have been more aggressive with ramping up and allocating capacity thus avoiding supply shortages and further accelerating uptake.[137]

Alternatively, if having one additional manufacturer entering the market had been a clear priority, the AMC might have been structured differently. For example, the AMC could have held some portion of the AMC funds in reserve for low-cost manufacturers or created an auxiliary fund to help manufacturers overcome technical or regulatory hurdles faced during development (see Lesson 2 for further discussion). Diverting funds from current manufacturers could have potential negative short-term consequences on supply security, as suggested previously, but may have led to a lower price in the mid- to long-term if a third manufacturer was able to enter the market sooner.

More explicit prioritization would also clarify external communication and align expectations. While those close to the design process understood that the selection of PCV as the pilot product shifted focus away from R&D and toward supply availability and uptake, many other stakeholders did not share this understanding. This has been particularly evident when evaluating the “success” along Objective 1: some consider the minimal influence of the AMC on R&D timelines to be both expected and irrelevant to the AMC’s overall success, while others consider it to be disappointing. Had the AMC objectives been refined after product selection, there would be less ambiguity around the performance of the AMC.

Lesson 2: Earlier stage products, particularly those that are technically complex, likely require a portfolio of incentive mechanisms to accelerate R&D outcomes

While this pilot AMC was not a true test of early-stage R&D stimulation, as would have been the case if an earlier stage vaccine candidate like HIV or malaria had been chosen, certain lessons regarding development of early stage, technically complex products can be inferred. Namely, the difficulty of developing and scaling PCV proved to be a limiting factor in how fast companies were able to move, regardless of intent or of the power of the mechanism.

Early-stage, technically challenging products such as PCV likely require more than just pull funding to stimulate early R&D. Many suppliers, especially developing-country manufacturers, need technical support and/or direct financial support to successfully navigate development. The large existing and potential market for PCV is a pull mechanism itself, incentivizing manufacturers to continue development. This market is significantly larger than the AMC incentive, yet it still was not enough to bring a third manufacturer to market by 2015. Even with push funding from the Bill and Melinda Gates Foundation, Serum Institute of India is finding it challenging to accelerate its development timeline, highlighting the overall complexity of developing a vaccine. This is not to say that the complexity or difficulty of a product should deter investment or pull funding; rather, an AMC can be part of the solution that includes other forms of assistance.

One positive design element of the pilot AMC that aided R&D was the TPP, which set a standard for products not yet in existence. The TPP ensures appropriate serotype coverage and product presentation for the Gavi setting, which will improve the vaccine efficacy in the relevant geographies and therefore increase the deaths averted. While the TPP was not useful for GSK and Pfizer, who were already in advanced stages of development, it has clarified the path forward for manufacturers with early-stage candidates, enabling them to make the design choices most aligned with developing world needs.

Lesson 3: Successful engagement with the biopharmaceutical industry improves sustainability of initiatives; enabling manufacturers to shift from a CSR-based approach to a commercially viable strategy is critical

The AMC created a balance between manufacturer sustainability and country affordability by making the vaccine commercially viable and by developing a long term market for PCV. This balance highlights the shift in approach from a CSR model that is not long-term sustainable to creating a commercially viable market that can succeed as a long-term strategy for manufacturers and the Gavi Alliance.

The AMC designers acknowledged the need to align with manufacturer's business motivations and thus created a mechanism that works within that reality. The $1.5 billion used for top-up subsidies reduced manufacturer risk and demonstrated the high degree of Gavi and donor

commitment to the success of bringing PCV to developing countries. Vaccine industry experts validate this commitment as they see the AMC as creating a market-driven partnership between the Gavi Alliance and manufacturers that fits within a manufacturer's broader commercial strategy.[138] Having a commercially viable strategy increases the likelihood that manufacturers will continue offering PCV to countries post-AMC and post-Gavi co-financing.

In order to develop this market-driven partnership, donors, the Gavi Secretariat, AMC operational partners, and industry fundamentally changed their communication and created a platform for dialogue that can be used for future interactions. The AMC was also a chance for donors to become more skilled and knowledgeable in market shaping.[139] By building this new skill set, donors feel more empowered to make smart investments, and more confident in making innovative investments.[140] By building trust and laying this foundation, future interactions between global health partners and industry could involve both sides increasing transparency and taking greater risks leading to greater impact in Gavi countries.

For example, increased transparency with manufacturers in the assumptions and degree of confidence behind demand forecasting may enable better matching of supply and demand. If manufacturers had demand scenarios, rather than a single forecast, they would better understand the likelihood of different amounts of demand materializing and might therefore adjust the amounts of inventory they hold to better prevent supply shortages.

Involving manufacturers in the design process of the AMC could help manufacturers and the Gavi Alliance optimize the commercial strategy of an AMC. A lack of transparency probably handicapped the AMC design because both parties were dealing with imperfect information due to the market not being created yet. Both multinational and developing country manufacturers have expressed a desire to be involved in decision-making during the design phase, which could lead to better communication and transparency between manufacturers and AMC designers and optimize the value achieved by Gavi donor funds.

Lesson 4: Complementary forces to an AMC are critical for creating the enabling environment necessary for its success

While the AMC was a clear contributor to the rapid uptake of PCV as compared to other Gavi vaccines, it was part of a combination of factors that jointly addressed financial, political, and logistical barriers to adoption. In addition to the AMC, these factors included the PneumoADIP, Gavi's Accelerated Vaccine Introduction initiative, the global WHO recommendation for PCV, Gavi co-financing policy, and Gavi's operational partners. Without any one of these factors, the success would have been lower. As a result, supporting vaccine initiatives and a WHO recommendation should be considered crucial complements to an AMC or any similar financing mechanism.

The examples of Hib and rota demonstrate that without a strong WHO recommendation, even with a functioning rota ADIP and Hib Initiative, many countries are unlikely to highly prioritize a given vaccine. Initiatives such as the ADIPs are critical to establishing the clinical evidence that support a strong WHO recommendation, as well as to establishing and communicating knowledge of the disease burden in individual countries. It is the optimized timing between the PneumoADIP and the PCV WHO recommendation that increased PCV's rate of country adoption higher than observed with Hib and rota.

Gavi and Gavi's operational partners provide the facilitation and know-how to introduce new immunization programs. To help make these programs long-term sustainable for many countries, Gavi's co-financing agreements reduce the price to as low as $0.20 per dose.

The AMC seeks to guarantee supply and price for a vaccine from manufacturers. In reality, the purchase guarantee associated with the AMC contract is minimal. Country demand should be encouraged by the promise of reliable supply and affordable prices, which should in turn reassure manufacturers. Initiatives such as ADIPs provide ministries of health with the additional tools and translational research needed to shape political will, which reinforces the guarantee of demand. Reliable supply and reliable demand create a virtuous circle that benefits both countries and manufacturers.

6.3 Economic assessment

The purpose of this section is to analyze the return on donor investment in the pilot AMC. A robust set of economic and scientific studies affirm that PCV is a cost-effective vaccine, relative to other treatment and prevention options..[141,142,143,144,145,146,147] An attempted calculation of the return on the $1.5 billion invested would not produce a meaningful result given the multiple overlapping and confounding factors that influence outcomes. In theory, value for money could be qualitatively estimated by comparing the total costs associated with the AMC to the health impact that was generated by the AMC (i.e. deaths averted and DALYs saved). However, 'cost-effectiveness' as measured by deaths averted and DALYs saved is not a complete metric for capturing the value of the AMC. Rather, value for money should be considered through the broader lens of the market outcomes achieved (e.g., multiple suppliers, increased affordability, and sustainable supply), which ultimately affect future health outcomes. Through certain design elements, the AMC achieved effects on donor behavior, manufacturer behavior, and sustainability of country immunization programs that will continue to benefit the global health community and the Gavi population well into the future.

6.3.1 Costs associated with AMC

The total cost of the AMC is greater than the $1.5 billion in funds. The $1.5 billion goes to pay the top-up subsidies, but the tail price is paid through regular Gavi funds and country co-financing. The costs of designing and launching the AMC are not insignificant, as the process

spanned over five years from inception to first delivery of vaccines, and required the time of many stakeholders and external advisors. The continuing monitoring and evaluation activities of the pilot, including annual reports and evaluations, represent ongoing costs.

In addition, there are costs not directly associated with the AMC that contributed to the outcomes and impact discussed in this paper. Gavi pays out grants for vaccine introduction and health system strengthening, which have supported pneumococcal immunization programs in countries. PneumoADIP lasted six years, and was critical to establishing and communicating knowledge of the disease burden that led to a global WHO recommendation and country adoption, while Gavi's Accelerated Vaccine Introduction initiative facilitated rapid uptake. On the industry side, there is additional push funding and technical assistance given to pipeline manufacturers.

While the costs across all of these funding streams have not been totaled, Gavi and the AMC funds have already spent over $2 billion on procurement alone. Through March 2015, $851 million of the AMC funds had been spent, and Gavi had funded another $1,184 million in country co-financing.

6.3.2 Value for money

In addition to the reduction in morbidity and mortality due to pneumococcal disease, there are other sources of value for money that the AMC delivered. These include the non-health outcomes that were stated in the objectives, as well as the unintended positive results. These sources of value include, but are not limited to:

New market-based relationship with manufacturers
In total, the AMC created a new market-driven partnership between the global health community and pharmaceutical manufacturers (see Lesson 3 for more detail). By providing manufacturers with a clear business case, the AMC was able to shift manufacturers' approach to global health from a corporate social responsibility model to a market-driven model.

Through this, the AMC established a viable and earlier than expected PCV market in Gavi countries, which itself serves as a pull-mechanism for manufacturers still in R&D. The entry of more manufacturers, particularly developing country manufacturers with a lower cost base, should result in lower prices and greater supply for PCV in the future. Additionally, the experience of the AMC helped both the global health community (including donors) and biopharmaceutical manufacturers develop the skills to engage with each other on future innovative initiatives.

Sustainability of immunization programs
The AMC created supply agreements with durations of 10 years and a price per dose capped at $3.50. Manufacturers are free to extend their price agreement with countries beyond the 10 year

commitment, which both GSK and Pfizer have done.148 The longer duration of the PCV supply agreements achieved through the AMC (versus typical Gavi procurement contracts of 3-5 years) improves long-term sustainability for countries and makes it easier for these countries to commit to the AMC because they can plan ahead for that specific price. In addition, certainty on the tail price gives Gavi greater visibility into their long-term co-financing needs.

The 10-year duration of the supply agreements also helps manufacturers because they can plan their investments over a longer time horizon, which has a positive impact on vaccine availability. Demand that occurs consistently over a longer period of time helps manufacturers believe they will recover the investments for expanding capacity over a greater volume of doses.

Faster speed of country uptake

Manufacturers face risk when investing in capacity for uncertain markets. The AMC top-up structure incentivized manufacturers to ramp-up their capacity by front-loading the additional subsidy on the first 21 percent of doses procured in each supply agreement. This enabled manufacturers to recoup their investment earlier. Additionally, the tail price was set at a level to allow more than one manufacturer to participate in the AMC, thereby ensuring supply security.

By paying more upfront to reduce hurdles faced by countries and manufacturers, the AMC contributed to a faster speed of country uptake when compared to Hib and rota. Therefore, the upfront costs of the AMC can be considered a premium paid to have many more birth cohorts vaccinated than may otherwise have been. As the AMC top-up is paid out, the ongoing costs of PCV procurement will decrease, but children born in these early years could never have been vaccinated at this low cost.

Enhanced Gavi replenishment

It is well acknowledged that the AMC was an innovative mechanism and attracted more donors and funds than would be expected for a more established mechanism.[149] In addition to the AMC's funding, during fundraising for the 2010-2015 strategic period, Gavi received $600 million more in pledges than they requested.[150] Stakeholders confirmed that this was in part due to the fact that AMC: donors were committed to the success of the AMC and were enthused by the innovative work that the Gavi Alliance was doing.

Collection of tested design levers to be used in future initiatives

The theory behind the AMC has been discussed in great detail.[151] This AMC pilot tested the effectiveness of key design levers such as top-up subsidies, 10-year supply agreements, and tail price ceilings. Now that the global health community has a better understanding of what an AMC in its current form can and cannot do, certain aspects of this AMC can be combined with other mechanisms to address the specific challenge at hand.

For instance, the current format of the AMC was found to have limited impact on R&D, partly because top-up subsidies were a weak pull-mechanism for early-stage R&D. It is well recognized

that a developing country manufacturer that develops PCV could increase the long-term sustainability of the immunization program through lower prices for Gavi countries. Given this, an AMC could be combined with complementary push-mechanisms to improve R&D outcomes and optimize the health impact in future initiatives.

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7. Considerations for Future Evaluations

In conducting this evaluation, **we encountered two types of limitations** that warrant further discussion when considering future AMC evaluations.

The first, applicable to all areas of the evaluation, relates to the challenges inherent in isolating the influence of the AMC mechanism from all the other concurrent factors, such as Gavi's non-AMC financial support for countries, the context of the product and the disease, and macro global health trends. For instance, delineating outcomes achieved due to the $1.5 billion in top-up money from those achieved due to the cumulative amount Gavi has paid on standard tail price subsidy is impossible to do with certainty as decisions are made based on their joint existence. This is an inherent challenge that is very difficult to solve, because other variables cannot be controlled in an ethically sound and/or feasible way. While counterfactuals, such as the comparisons to the Hib and rota vaccines, use real-life examples to illustrate what Gavi support looks like without an AMC, there are no perfect vaccine counterfactuals. Future evaluations will likely encounter the same challenges.

The second set of limitations, specific to the overarching goal to reduce morbidity and mortality, relates to understanding the true and precise mortality and morbidity impact of immunization. Current gaps in collective knowledge on epidemiology and immunology limit confidence and precision related to impact measures; this is closely related to the finite amount of empirical evidence that can be gathered and research that can be conducted. However, surveillance mechanisms are lacking in low—income countries, for the reason that empirical studies and research are particularly hard to conduct in low-income, resource-constrained settings. Where data exists, it is often unreliable.

Progress can be reasonably achieved against this second set of limitations. We hope that our experience can inform research between now and the next evaluation, with the intent of narrowing the confidence interval around impact estimates. Actions to improve this could include and not be limited to:

Action 1: *Continue investment in empirical studies and population surveillance*

Empirical studies on pneumococcal impact will play an important role in creating a more definitive evaluation of mortality and morbidity impact. In particular, a larger evidence base is needed to improve modeling output and increase functionality of the models (e.g., ability to model serotype replacement[lxi]). While these studies may be a harder sell to some funders

[lxi] Although serotype replacement was at one point modeled in TRIVAC, it has been removed for the latest run due to insufficient evidence base and the desire to avoid false precision. LiST has never included it.

because they are research investments rather than direct disease interventions, they are crucial components to understanding the impact of an intervention and inform decision-making.

In addition to specific empirical studies, continued support for surveillance networks that build databases on coverage, morbidity, and mortality is extremely important. Surveillance systems such as the INDEPTH Network are crucial to tracking uptake and disease burden across entire populations over long periods of time, but they currently do not cover sufficient geography to track national statistics. Also, at the moment, INDEPTH uses verbal autopsy to determine cause of death, and so does not distinguish pneumococcal pneumonia or pneumococcal meningitis. Continual improvement of the cause of death determination process and geographic expansion of these networks will make the resulting data even more useful in intervention evaluation.

Given that these studies and surveillance databases produce results beneficial to parties far beyond Gavi, the funding and support required should also be broad-based. For instance, several major foundations such as the Bill and Melinda Gates Foundation, the Skoll Global Threats Fund, and the Rockefeller Foundation have investments in surveillance networks. However, how these commitments can be leveraged to support impact evaluations for global health interventions is still to be determined. In addition, many Gavi-funded studies are underway, and the Full Country Evaluations have already proven to be helpful by providing…. However, these must continue to be supported as part of a Monitoring and Evaluation program for a mechanism such as AMC, or any disease intervention in general.

Action 2: *Build uncertainty ranges and sensitivity analyses into academic models*

Until this year, Gavi's impact evaluations have utilized point estimates. However, this belies the high degree of uncertainty that exists in the academic models and their inputs. The range calculated for this evaluation, created by a low and a high estimate, is not a statistical range; rather, it represents different ways of calculating and attributing deaths averted. Uncertainty ranges and sensitivity analyses need to be applied to each of these estimates to understand the true degree and drivers of uncertainty.

Gavi and the modeling teams for LiST and TRIVAC are already working on putting in place uncertainty ranges for their respective models, which will be available later this year or next year. Maintaining these ranges in evaluations and external communications will be important to avoid false precision. False precision erases important information in making decisions about future mechanisms to invest in.

Action 3: *Validate models using sub-national data*

One important remaining gap in the use of academic impact models is the lack of validation of output with empirical data (as opposed to using empirical studies to determine input, as in Action 1). In part, this is due to the difference in scale between these approaches; empirical

studies mostly measure a relatively small population (a subset of a nation), while, to date, the models have been used to generate country-wide or global estimates, often using semi-globalized averages as input assumptions.

However, the academic models have the flexibility to be run on smaller populations in order to compare and validate against the results from empirical studies. To accomplish this, the models would need to be run on a sub-national scale, with inputs modified to match the study population (e.g., serotype prevalence, underlying disease burden, and simultaneous interventions). Modeled cases averted and, ideally, deaths averted, could then be compared to the empirical trends. This has not been done as part of this evaluation, as it requires collection of population-specific inputs (e.g., co-morbidities, baseline morbidity and mortality), but could be added to ongoing surveillance studies.

The advantage of this approach would be to confirm the structure and methodology of the models, as opposed to validation of the inputs as in Action 1. This has not been done to date because

Action 4: *Delineate drivers of differences across mortality revisions*

In our analysis, we have begun to explore the drivers of differences between mortality estimates in 2008 and current mortality estimates. However, this analysis is high level and can only quantify those changes that are due to inputs with proportional effects on the output. While a full accounting of all of the drivers of differences is not needed, it would be helpful to delineate how much of the difference is due to AMC-related factors versus unrelated factors. AMC-related factors might include changes to coverage estimates or new products with a different efficacy. Unrelated factors might include changes in underlying disease burden, changes in the structure of the academic models used to measure impact, or new information related to case fatality and epidemiology.

This evaluation has begun to perform this quantitative delineation, but the full breakdown was not performed because the estimates are adjusted, not direct, versions of the output and the numerical values of all input sources were not available. If desired, a distinct exercise could be commissioned, in close collaboration with the relevant modelers, to perform a quantitative evaluation of the actual AMC impact against the original goal, or expected impact.

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Appendix I. Interviews performed for this report

Indicator	Organization	Name
1	Canada, Department of Foreign Affairs, Trade and Development	Sara Nicholls
2	Center for Global Development	Owen Barder
3	Columbia University	Paul Wilson
4	Dalberg	Veronica Chau
5	External consultant	Lisa Lee
6	Full Country Evaluations Country Leads	Jasim Uddin (Bangladesh)
7	The Bill and Melinda Gates Foundation	Andrew Jones
8		Orin Levine
9		Amit Srivastava
10		Damian Walker
11		Greg Widmyer
12		John Yang
13	Gavi Secretariat	Matthew Blakley
14		Lauren Franzel
15		Peter Hansen
16		Hope Johnson
17		Melissa Ko
18		Ariane McCabe
19		Melissa Malhame
20		Wilson Mok
21		Aurelia Nguyen
22		Sara Sa Silva
23	GlaxoSmithKline	Eunice Miranda
24		Catherine Muller
25		John Musunga
26	Hewlett Foundation (former Center for Global Development)	Ruth Levine
27	IHME / University of Washington	Steve Lim
28	Inventprise	Subhash Kapre
29	Johns Hopkins University	Katrin Gorham
30		Audrey Mitchell
31		Kate O'Brien
32		Lois Privor-Dumm
33		Neff Walker
34	London School of Hygiene and Tropical Medicine	Andrew Clark
35		Brian Greenwood

Indicator	Organization	Name
36		Anthony Scott
37	Medical Research Council Unit	Grant MacKenzie
38	Médecins Sans Frontières	Manica Balasegaram
39		Kate Elder
40	Panacea Biotec	Rajesh Jain
41	PATH	David Fleming
42	Pfizer	Erik Bossan
43		Lindsay Diestchi
44		Susan Silbermann
45	Serum Institute of India	Suresh Jadhav
46	Tivorsan (former Wyeth)	Jim Connolly
47	UK Department for International Development	James Droop
48	UNICEF	Jesus Barral-Guerin
49		Gian Gandhi
50		David Mutuerandu
51		Ann Ottosen
52	University of Liverpool	Naor Bar-Zeev
53	University of Washington	Dean Jamison
54	World Bank	Susan McAdams
55	World Health Organization	Carsten Mantel
56		Michel Zaffran
57	Yale University	Daniel Weinberger

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Appendix II. Additional detail on manufacturers with PCV candidates

Finlay Institute: Finlay is a Cuban organization with a 7-valent PCV product. The 7 serotypes included differ from Pfizer's Prevenar 7, and provide more coverage for Gavi countries. Finlay has completed Phase I trials.[152,153] However, their strategy does not appear to include targeting Gavi markets.[154]

Minhai Biotech: Minhai is a Chinese company whose product is entering Phase I trials.

Walvax: Walvax is a Chinese company currently planning for clinical trials.

Sinovac / CanSino: Sinovac obtained permission for clinical trials in 2015, and has financial support from the PRC government.[155] CanSino has a licensing and tech transfer agreement with Sinovac.[156]

Tergene: Tergene is a new Indian biotech start-up currently in preclinical trials.[157]

Biological E Limited: Biological E is a premier Indian company currently researching a 13 valent PCV product.[158]

PnuVax: PnuVax is a Canadian company with an R&D program for PCV. PnuVax has received support from BMGF.

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Appendix III. Coverage Data by Country

Coverage data comes from WHO/UNICEF Estimates of National Immunization Coverage, as of July 2015

Country	Year of PCV Intro	Surviving Infants (in 2014)	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)
Afghanistan	2013	1,006,513	0	0	0	0	0	40
Angola	2013	1,000,589	0	0	0	0	9	61
Armenia	2014	38,999	0	0	0	0	0	0
Azerbaijan	2013	189,228	0	0	0	0	0	64
Bangladesh	2015	3,056,519	0	0	0	0	0	0
Benin	2011	356,714	0	0	36	76	69	70
Bhutan		13,173	0	0	0	0	0	0
Bolivia (Plurinational State of)	2014	242,411	0	0	0	0	0	56
Burkina Faso	2013	660,360	0	0	0	0	0	91
Burundi	2011	439,982	0	0	14	96	96	95
Cambodia	2015	360,258	0	0	0	0	0	0
Cameroon	2011	778,175	0	0	23	84	88	87
Central African Republic (the)	2011	147,865	0	0	8	47	23	47
Chad		559,110	0	0	0	0	0	0
Comoros (the)		24,653	0	0	0	0	0	0
Congo (the)	2012	156,965	0	0	0	10	69	69
Côte d'Ivoire	2014	765,870	0	0	0	0	0	2
Cuba		115,820	0	0	0	0	0	0
Democratic People's Republic of Korea (the)		351,593	0	0	0	0	0	0
Democratic Republic of the Congo (the)	2011	2,926,864	0	0	0	13	31	61
Djibouti	2012	20,832	0	0	0	0	82	78
Eritrea	2015	167,285	0	0	0	0	0	0
Ethiopia	2011	2,999,181	0	0	12	38	63	76
Gambia (the)	2009	77,677	0	99	95	98	96	96
Georgia	2014	54,402	0	0	0	0	0	0
Ghana	2012	833,268	0	0	0	43	89	98

Guinea		427,850	0	0	0	0	0	0
Guinea-Bissau	2015	60,914	0	0	0	0	0	0
Guyana	2011	14,108	0	0	50	90	96	97
Haiti		251,824	0	0	0	0	0	0
Honduras	2011	164,519	0	0	78	88	87	85
India		24,853,495	0	0	0	0	0	0
Indonesia		4,950,806	0	0	0	0	0	0
Kenya	2011	1,476,168	0	0	85	82	75	81
Kiribati	2013	3,038	0	0	0	0	40	57
Kyrgyzstan		151,664	0	0	0	0	0	0
Lao People's Democratic Republic (the)	2013	170,842	0	0	0	0	0	72
Lesotho	2015	56,985	0	0	0	0	0	0
Liberia	2014	145,339	0	0	0	0	0	45
Madagascar	2012	786,164	0	0	0	0	76	72
Malawi	2011	615,574	0	0	0	99	89	87
Mali	2011	686,016	0	0	56	74	79	84
Mauritania	2013	123,992	0	0	0	0	1	84
Mongolia		67,864	0	0	0	0	0	0
Mozambique	2013	1,003,575	0	0	0	0	45	73
Myanmar		907,582	0	0	0	0	0	0
Nepal	2015	561,482	0	0	0	0	0	0
Nicaragua	2010	120,115	0	0	61	98	98	98
Niger (the)	2014	895,074	0	0	0	0	0	13
Nigeria	2014	6,517,414	0	0	0	0	0	0
Pakistan	2012	5,047,972	0	0	0	0	66	68
Papua New Guinea	2013	202,998	0	0	0	0	0	0
Republic of Moldova (the)	2013	43,178	0	0	0	0	1	28
Rwanda	2009	345,324	0	97	97	98	99	99
Sao Tome and Principe	2012	6,077	0	0	0	0	97	95
Senegal	2013	536,128	0	0	0	0	0	81
Sierra Leone	2011	207,671	0	0	75	92	92	83
Solomon Islands	2015	16,488	0	0	0	0	0	0
Somalia		426,120	0	0	0	0	0	0

South Sudan		402,510	0	0	0	0	0	0
Sri Lanka		326,094	0	0	0	0	0	0
Sudan (the)	2013	1,238,169	0	0	0	0	30	97
Tajikistan		244,181	0	0	0	0	0	0
Timor-Leste		41,906	0	0	0	0	0	0
Togo	2014	241,420	0	0	0	0	0	34
Uganda	2013	1,533,014	0	0	0	0	0	50
Ukraine		483,218	0	0	0	0	0	0
United Republic of Tanzania	2012	1,955,487	0	0	0	0	80	93
Uzbekistan	2015	642,083	0	0	0	0	0	0
Viet Nam		1,555,547	0	0	0	0	0	0
Yemen	2011	805,102	0	0	56	82	88	88
Zambia	2013	598,458	0	0	0	0	0	77
Zimbabwe	2012	512,873	0	0	0	21	95	91

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Appendix IV. Gavi PCV Results Framework

	Input	Process	Output	Outcome	Impact
PCV programmatic results	• Cumulative number (%) of countries submitting proposals for PCV • Amount ($) of PCV Gavi top-up funds disbursed • Qualitative description and overview of BP investments specific to PCV • Is there sufficient supply available to meet UNICEF tenders?	• Cumulative number (%) of countries that have included • PCV in national cMYP, including committed country co-financing • Number of new grant applications approved/not approved/postponed • Number of doses approved/shipped • Number of active PCV grants • Number (%) of countries with • PCV registration in place at time of application to Gavi • Number (%) of countries requesting presentation switch/approved presentation switch • Number (%) of countries meeting co-financing payments for PCV	• Cumulative number (%) of countries that have introduced PCV • Cumulative number (%) of countries that have introduced PCV within a year of IRC approval • Number/% of countries experiencing delays in introduction? • Number of children vaccinated • Number (%) countries with surveillance system in place for IBD Surveillance	• PCV3 coverage across Gavi 73 countries • Number (%) of countries with >85% PCV3 coverage • Number (%) of countries with PCV3 coverage within ±5% points of DPT3 coverage within a year of introduction • Number of eligible graduated countries continuing PCV in routine immunisation schedule post-graduation • PCV3 coverage across Gavi graduated countries	• Reduction in proportion of under-5 mortality caused by pneumonia • Reduction in proportion of under-5 mortality caused by meningococcal meningitis • Reduction in under-5 mortality rate • Number of pneumococcal cases, deaths and DALYs averted by PCV vaccination
AMC specific inputs and process	• Cumulative amount ($) of AMC commitments received • Cumulative amount and % of total AMC tail-price funds disbursed • Number of PCV doses on supply agreement • Number (%) of eligible graduating and graduated countries submitting proposals to access AMC price	• Number of eligible graduating and graduated country applications for AMC price approved/ not approved/postponed • Number of manufacturers publicly registered to supply PCV under the Pneumococcal AMC • Number of manufacturers with TPP eligible vaccines licensed or expected to be licensed within 1-3 years. • Number of manufacturers that have signed binding Supply Agreements to make vaccines available to the AMC within tail-price ceiling for 10 years • Number of annual doses committed to the AMC in the biding and long-term Supply Agreements			
Cross cutting	• Vaccine effectiveness studies • Targeted assessments • Surveillance investments			• AEFI monitoring improvements • Commissioned evaluations • Full country evaluations	

[1]Pneumonia Strategy Overview [internet]. The Bill and Melinda Gates Foundation. [2015 Oct]. http://www.gatesfoundation.org/What-We-Do/Global-Health/Pneumonia
[2] Gavi Supply Agreements [internet]. Gavi The Vaccine Alliance. [2015 Oct]. Accessible at: http://www.gavi.org/funding/pneumococcal-amc/manufacturers/supply-agreements/.
[3] Gavi Secretariat, AMC for Pneumococcal Vaccines: Annual Report 1 April 2014 – 31 March 2015. Geneva: The Gavi Alliance, March 2015.
[4]Pneumococcal disease factsheet. Geneva, GAVI Alliance: 2013 June.
[5]Gavi data on vaccine introduction dates (as of October 12, 2015).
[6]EvaluatePharma database (accessed September 2015).
[7]Gavi The Vaccine Alliance. Pneumococcal Roadmap Public Summary. Geneva: Gavi The Vaccine Alliance, 2013.
[8]Gavi The Vaccine Alliance. Pneumococcal Roadmap Public Summary. Geneva: Gavi The Vaccine Alliance, 2013.
[9]Hay M, Thomas D, Craighead J, Economides C, Rosenthal J. Clinical development success rates for drugs. Nature Biotechnol. 2014 Jan: 32(1):40-51.
[10]Davis M, Butchart A, Wheeler J, Coleman M, Singer D, Freed G. Failure-to-success ratios, transition probabilities and phase lengths for prophylactic vaccines versus other pharmaceuticals in the development pipeline. Vaccine. 2011 Nov: 29(51):9414-6.
[11] Clark A, Jauregui B, Griffiths U, Janusz C Bolanos-Siera B, Hajjeh R, Andrus J, Sanderson C. TRIVAC decision - support model for evaluating the cost-effectiveness of Haemophilus influenzae type b, pneumococcal and rotavirus vaccination. Vaccine. 2013 Jul: 31 (Suppl 3): C19 – C29.
[12] Walker N, Tam Y, Friberg I. Overview of the Lives Saved Tool (LiST). BMC Public Health. 2013: 13 (Suppl 3): S1.
[13] Expert interview
[14]Clark A, Jauregui B, Griffiths U, Janusz C Bolanos-Siera B, Hajjeh R, Andrus J, Sanderson C. TRIVAC decision - support model for evaluating the cost-effectiveness of Haemophilus influenzae type b, pneumococcal and rotavirus vaccination. Vaccine. 2013 Jul: 31 (Suppl 3): C19 – C29.
[15]Walker N, Tam Y, Friberg I. Overview of the Lives Saved Tool (LiST). BMC Public Health. 2013: 13 (Suppl 3): S1.
[16] Lee L, Franzel L, Atwell J, Datta D, Friberg I, Goldie S, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccines. 2013: 31S: B61 – B72.
[17]Expert Interviews
[18]Hill K, Zimmerman L, Jamison D. Mortality risks in children aged 5 – 14 years in low-income and middle-income countries: a systemic empirical analysis. Lancet Glob Health. 2015: 3: e609-16.
[19]United Nations Inter-agency Group for Child Mortality Estimation. Levels & Trends in Child Mortality. 2015.
[20]Expert interview
[21]Expert interview
[22]Wiedenmayer K, Bosch-Capblach X, Hanlin R, Towse A, Tetteh E, Garau M. Gavi Baseline Study for pneumococcal vaccine AMC. Swiss Centre for International Health; 2010 July.
[23]Gavi Alliance. GAVI's Accelerated Vaccine Introduction Initiative [Internet]. [2009 Oct; 2015 Oct]. Available from: http://www.gavi.org/Library/Publications/GAVI-fact-sheets/Factsheet--GAVI-s-Accelerated-Vaccine-Introduction-Initiative/.
[24]Wiedenmayer K, Bosch-Capblach X, Hanlin R, Towse A, Tetteh E, Garau M. Gavi Baseline Study for pneumococcal vaccine AMC. Swiss Centre for International Health; 2010 July.
[25]Wiedenmayer K, Bosch-Capblach X, Hanlin R, Towse A, Tetteh E, Garau M. Gavi Baseline Study for pneumococcal vaccine AMC. Swiss Centre for International Health; 2010 July.
[26]Global vaccine Safety: Age of administration of rotavirus vaccines [Internet]. [2009 Aug; 2015 Oct]. Available from:

http://www.who.int/vaccine_safety/committee/topics/rotavirus/rotarix_and_rotateq/7Aug_2009_age_administration/en/.

[27] Expanded Program of Immunization Vaccine Prices for Year 2015 – Amendment I. Revolving Fund Prices [Internet]. 2015 Mar 24 [accessed 2015 Oct]. Available at: http://www.paho.org/HQ/index.php?option=com_content&view=article&id=9561%3A2014-revolving-fund-prices&catid=839%3Arevolving-fund&Itemid=40714&lang=en.

[28] AMC Vaccine Candidate Summary Table (Gavi internal memo).

[29] Gavi internal pipeline analysis from 2010. Written correspondence with Gavi Secretariat. 2015 Oct.

[30] Independent Expert Committee Recommendation for AMC Pilot (Gavi internal memo). Paris: 2006 Feb.

[31] Cernuschi T, Furrer E, McAdams S, Jones A, Fihman J, Schwalbe N. The GAVI Alliance White Paper: Pneumococcal Advance Market Commitment: Lessons Learnt on Disease and Design Choices and Processes. Geneva: The Gavi Alliance, September 2011.

[32] Expert interviews

[33] Expert interviews

[34] Expert interviews

[35] Expert interviews

[36] Expert interviews

[37] EvaluatePharma database (accessed September 2015).

[38] Expert interviews

[39] EvaluatePharma database (accessed September 2015).

[40] Expert interviews

[41] Expert interviews

[42] Expert interviews

[43] Merck Sharp & Dohme Corp. A Study to Evaluate the Safety, Tolerability and Immunogenicity of V114 in Healthy Adults and Infants (V114-005) [Internet]. ClincalTrials.gov. First Received 2015 Aug 20, last updated 2015 Oct 20 [accessed 2015 Oct 29]. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02531373?term=merck+pneumococcal+15&rank=2.

[44] Merck Sharp & Dohme Corp. A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Two Formulations of V114 in Healthy Adults 50 Years of Age or Older (V114-006) [Internet]. ClincalTrials.gov. First Received 2015 Sep 10, last updated 2015 Oct 28 [accessed on 2015 Oct 29]. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02547649.

[45] Expert interviews

[46] Expert interviews

[47] Thomson Reuters Newport Data (accessed Oct 2015).

[48] Expert interviews

[49] Medecins Sans Frontieres. The Right Shot: Extending the reach of affordable and adapted vaccines 2nd Edition [internet]. Geneva: Medecins Sans Frontieres, 2015 Jan [accessed 2015 Oct]. Available at: http://www.msfaccess.org/content/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines.

[50] Gavi Secretariat, AMC for Pneumococcal Vaccines: Annual Report 1 April 2014 – 31 March 2015. Geneva: The Gavi Alliance, March 2015.

[51] Expert interviews

[52] Expert interviews

[53] Expert interviews

[54] Expert interviews

[55] Expert interviews

[56] Expert interviews

[57] Wiedenmayer K, Bosch-Capblach X, Hanlin R, Towse A, Tetteh E, Garau M. Gavi Baseline Study for pneumococcal vaccine AMC. Swiss Centre for International Health; 2010 July.
[58] Miller G. Pfizer revels in massive Prevnar vax job [internet]. FiercePharma Manufacturing: January 23 2012 [accessed September 2015]. Available at: http://www.fiercepharmamanufacturing.com/story/pfizer-revels-massive-prevnar-vax-job/2012-01-23.
[59] Expert interviews
[60] Gavi Secretariat, AMC for Pneumococcal Vaccines: Annual Report 1 April 2014 – 31 March 2015. Geneva: The Gavi Alliance, March 2015.
[61] Gavi Secretariat, AMC for Pneumococcal Vaccines: Annual Report 1 April 2014 – 31 March 2015. Geneva: The Gavi Alliance, March 2015.
[62] Snyder C, Begor W, Berndt E. Economic Perspectives on the Advance Market Commitment for Pneumococcal Vaccines. Health Aff (Millwood). 2011 Aug: 30(8):1508-17.
[63] Snyder C, Begor W, Berndt E. Economic Perspectives on the Advance Market Commitment for Pneumococcal Vaccines. Health Aff (Millwood). 2011 Aug: 30(8):1508-17.
[64] Data on country GNI per capita and introduction dates from Vaccine Introduction Management System (as of 2015 Sep).
[65] Gavi country introduction dates for PCV (as of 2015 Oct 12).
[66] Expert interviews
[67] GSK. About us: sites [internet]. [accessed September 2015]. Available at: http://sg.gsk.com/en-sg/about-us/sites/.
[68] World Health Organization Grants Prequalification for Global Use to GSK's 10-Valent Synflorix Vaccine. Pipeline Review: November 8 2009 [accessed September 2015]. Available at: http://www.pipelinereview.com/index.php/2009110630612/Vaccines/World-Health-Organization-Grants-Prequalification-for-Global-Use-to-GSKs-10-Valent-Synflorix-Vaccine.html.
[69] GlaxoSmithKline Vaccine Manufacturing Facility, Tuas, Singapore [Internet]. Available at: http://www.pharmaceutical-technology.com/projects/gsksingapore/.
[70] GlaxoSmithKline Vaccine Manufacturing Facility, Tuas, Singapore [Internet]. Available at: http://www.pharmaceutical-technology.com/projects/gsksingapore/.
[71] Dalberg written correspondence with experts, 2012.
[72] Miller G. Pfizer revels in massive Prevnar vax job [internet]. FiercePharma Manufacturing: January 23 2012 [accessed September 2015]. Available at: http://www.fiercepharmamanufacturing.com/story/pfizer-revels-massive-prevnar-vax-job/2012-01-23.
[73] Pfizer (USA) opens new plant in Puurs (Flanders) [internet]. Belgium: Feb 11 2015 [accessed Sep 2015]. Available at: http://www.investinflanders.be/EN/news/2015/02/11/Pfizer-(USA)-opens-new-plant-in-Puurs-(Flanders)
[74] Expert interviews
[75] Expert interview
[76] Expert interview
[77] Expert interview
[78] Gavi country application information (as of 2015 Oct 12).
[79] UNICEF data on dates of supply availability by country introduction (as of 2015 Oct 12).
[80] Expert interviews.
[81] Expert interview.
[82] WHO/UNICEF Estimates of National Immunization Coverage (WUENIC), through 2014. WHO Data, statistics and graphics [internet]. July 2015 [accessed Aug 2015]. Available at: http://www.who.int/immunization/monitoring_surveillance/data/en/.
[83] Gavi country introduction dates for PCV (as of 2015 Oct 12).

[84] WHO/UNICEF Estimates of National Immunization Coverage (WUENIC), through 2014. WHO Data, statistics and graphics [internet]. July 2015 [accessed Aug 2015]. Available at: http://www.who.int/immunization/monitoring_surveillance/data/en/.
[85] Graduating countries [Internet]. Gavi The Vaccine Alliance. [accessed 2015 Oct]. Available at: http://www.gavi.org/support/apply/graduating-countries/.
[86] WHO/UNICEF Estimates of National Immunization Coverage (WUENIC), through 2014. WHO Data, statistics and graphics [internet]. July 2015 [accessed Aug 2015]. Available at: http://www.who.int/immunization/monitoring_surveillance/data/en/.
[87] Gavi country application information (as of 2015 Oct 12).
[88] Global use of rotavirus vaccines recommended [intenet]. Geneva: World Health Organization, June 2009 [accessed October 2015]. Available at: http://www.who.int/mediacentre/news/releases/2009/rotavirus_vaccines_20090605/en/
[89] The imperative for stronger vaccine supply and logistics systems, Vaccines, 2013; Health system cost of delivering routine vaccination in low- and lower-middle income countries: what is needed over the next decade?, Bulletin of the WHO, 2013.
[90] Data on country GNI per capita and introduction dates from Vaccine Introduction Management System (as of 2015 Sep).
[91]Thomson Reuters Newport Data (accessed Oct 2015).
[92] Medecins Sans Frontieres. The Right Shot: Extending the reach of affordable and adapted vaccines 2nd Edition [internet]. Geneva: Medecins Sans Frontieres, 2015 Jan [accessed 2015 Oct]. Available at: http://www.msfaccess.org/content/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines.
[93] Data on country GNI per capita and introduction dates from Vaccine Introduction Management System (as of 2015 Sep).
[94]Expanded Program of Immunization Vaccine Prices for Year 2015 – Amendment I. Revolving Fund Prices [Internet]. 2015 Mar 24 [accessed 2015 Oct]. Available at: http://www.paho.org/HQ/index.php?option=com_content&view=article&id=9561%3A2014-revolving-fund-prices&catid=839%3Arevolving-fund&Itemid=40714&lang=en.
[95] WHO/UNICEF Estimates of National Immunization Coverage (WUENIC), through 2014. WHO Data, statistics and graphics [internet]. July 2015 [accessed Aug 2015]. Available at: http://www.who.int/immunization/monitoring_surveillance/data/en/.
[96] Surviving infants from UN World Population Prospects (as of 2015).
[97] Pneumococcal disease factsheet. Geneva, GAVI Alliance: 2013 June.
[98] Gavi The Vaccine Alliance [Internet]. Geneva: Gavi The Vaccine Alliance; 1 June 2008 [October 2015]. Available from: http://www.gavi.org/Library/News/AMC-updates/Pilot-AMC-for-pneumococcal-disease/.
[99] Fleming D. Advance Market Commitment for Pneumococcal Disease: Innovative Finance for Development. Gavi Alliance & Fund Board Meetings; June 2008.
[100]Written feedback of Gavi review committee for 2015 Outcomes and Impact Evaluation. 2015 Oct.
[101] Expert interviews
[102] Written documentation and historical memos from Gavi.
[103] The State of the World's Children: 2007 [internet]. New York: United Nations Children's Fund, 2006. Available from: http://www.unicef.org/sowc07/docs/sowc07.pdf.
[104] The State of the World's Children: 2015 [internet]. New York: United Nations Children's Fund, 2014. Available from: http://www.unicef.org/publications/index_77928.html.
[105] "FAQ – impact estimates in 2016-2020" (Gavi internal memo).
[106] Gavi Strategic Demand Forecast v2, Strategic Demand Forecast v8 (accessed 2015 Sep).
[107] Gavi Strategic Demand Forecast v11 (accessed 2015 Sep), Strategic Demand Forecast v12 (accessed 2015 Nov).

[108] GAVI'S VACCINE IMPLEMENTATION TECHNICAL ASSISTANCE CONSORTIUM: Supported Special Studies: List of Related Publications and Presentations [internet]. Baltimore: Johns Hopkins School of Public Health, [2015, accessed 2015 Oct]. Available from: http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/special-studies.html.
[109] Andrade AL, Ternes YM, Vieira MA, Moreira WG, Lamaro-Cardoso J, et al. Direct effect of 10-valent conjugate pneumococcal vaccination on pneumococcal carriage in children Brazil, PLoS One. 2014 Jun 3, 9 (6): e98128.
[110] Barrella Harboe Z, Dalby T, Weinberger D, Benfield T, Molbak K, et al. Decline in incidence and mortality of invasive pneumococcal disease after introduction of 13-valent conjugate childhood vaccination, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 154.
[111] Ben-Shimol S, Greenberg D, Givon-Lavi N, and Dagan R. Serotype-specific PCV7/PCV13 effect on invasive pneumococcal disease (IPD) in children <5 years in Israel, July 2004 – June 2013, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 156.
[112] Bruce M, Singleton RS, Bulkow L, Bruden D, Rudolph K, et al. Invasive pneumococcal disease (IPD) in Alaska children: Impact of the 13-valent pneumococcal conjugate vaccine (PCV13), 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 146.
[113] Deceuninck G and De Wals P. Effectiveness of three pneumococcal conjugate vaccines (PCVs) to prevent invasive pneumococcal disease (IPD) in Quebec, Canada, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 163.
[114] Desai AP, Sharma D, Crispell EK, Baughman W, Thomas S, et al. Decline in pneumococcal nasopharyngeal carriage of vaccine serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine in children in Atlanta, Georgia, The Pediatric Infectious Disease Journal. 2015 Nov, 34 (11) 1168-74.
[115] Domingues CMAS, Verani JR, Montenegro ER, Brandileone MCC, Flannery B, et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: A matched case-control study, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 145.
[116]Lazzarini DL, Contrini MM, Glatstein E, Garnero AV, Ezcurra GC, et al. Rapid decrease of invasive pneumococcal disease after one year of the introduction of PCV13 in Argentina, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 161.
[117] Moore M, Taylor T, Pondo T, Barnes M, Petis S, et al. Impact of 13-valent pneumococcal conjugate vaccine (PCV13) against invasive pneumococcal disease (IPD) among children <5 years old in the U.S., 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 149.
[118]Palmu AA, Kilpi TM, Rinta-Kokko H, Nohynek H, Ruokokoski E, et al. Impact of 10-valent pneumococcal conjugate vaccine (PCV10) against clinical invasive pneumococcal disease (IPD) among vaccine-eligible children in Finland, 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 150.
[119] Von Gottberg A. Update from Africa. 9th International Symposium on Pneumococci and Pneumococcal Diseases. 2014 (3): 139.
[120]Expert interviews
[121]Expert interviews
[122]Lee L, Franzel L, Atwell J, Datta D, Friberg I, Goldie S, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccines. 2013: 31S: B61 – B72.
[123]Expert interviews
[124]Lehmann D, Willis J, Moore H, Giele C, Murphy D, Keil AD, et al. The changing epidemiology of invasive pneumococcal disease in aboriginal and non-aboriginal western Australians from 1997 through 2007 and emergence of nonvaccine serotypes. Clin Infect Dis. 2010 Jun: 50 (11): 1477-86.
[125]Roche PW, Krause V, Cook H, Barralet J, Coleman D, Sweeny A, et al. Invasive pneumococcal disease in Australia, 2006. Commun Dis Intell Q Rep. 2008 Mar: 32 (1): 18 – 30.

[126] Loo J, Conklin L, Fleming-Dutra K, Knoll M, Park D, Kirk J, et al. Systemic Review of the Indirect Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Pneumococcal Disease and Colonization. Pediatr Infect Dis J. 2014 Jan: 33 (Suppl 2): S161-71.
[127]Whitney C, Goldblatt D, O'Brien K. Dosing Schedules for Pneumococcal Conjugate Vaccine: Considerations for Policy Makers. Pediatr Infect Dis J. 2014 Jan: 33 (Suppl 2): S172- S181.
[128]Gavi The Vaccines Alliance. Health Systems Goals Indicators [Internet]. Geneva: Gavi The Vaccines Alliance; [2015 Jul, accessed 2015 Oct]. Available from: http://www.gavi.org/results/goal-level-indicators/health-systems-goal-indicators/.
[129]Nuorti J, Whitney C. Prevention of Pneumococcal Disease Among Infants and Children --- Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). CDC Morbidity and Mortality Weekly Report. 2010 Dec: 59(RR11);1-18.
[130]Kyaw M, Lynfield R, Schaffner W, Craig A, Hadler J, Reingold A. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med. 2006 Aug: 354(14):1455-63.
[131]Russell F, Sanderson C, Temple B, Mulholland K. Global Review of the Distribution of Pneumococcal Disease by Age and Region. World Health Organization [Internet]. 2011 Oct [accessed 2015 Oct]. Available from: http://www.who.int/immunization/sage/6_Russel_review_age_specific_epidemiology_PCV_schedules_session_nov11.pdf.
[132]Hill K, Zimmerman L, Jamison D. Mortality risks in children aged 5 – 14 years in low-income and middle-income countries: a systemic empirical analysis. Lancet Glob Health. 2015: 3: e609-16.
[133]Expert Interviews.
[134] "The Advance Market Commitment for Pneumococcal Vaccines Process and Design Evaluation", February 15, 2013, Dalberg Global Development Advisors.
[135] Advance Market Commitment for Pneumococcal Vaccines Annual Report. Secretariat of Gavi, The Vaccine Alliance, for years 2010 – 14
[136] Advance Market Commitment for Pneumococcal Vaccines Annual Report. Secretariat of Gavi, The Vaccine Alliance, for years 2010 – 14; Expert interviews
[137] Expert interviews
[138] Expert interviews
[139] Expert interview
[140] Expert interview
[141] Ayieko P, Griffiths UK, Ndiritu M, Moisi J, Mugoya IK, et al. Assessment of Health Benefits and Cost-Effectiveness of 10-Valen and 13-Valent Pneumococcal Conjugate Vaccination in Kenyan Children, PLoS One. 2013 Jun 24; 8(6): e67324.
[142] Ray GT. Pneumococcal Conjugate Vaccine: Pharmacoeconomic Analysis and the Impact of the Herd Effect, Third Regional Pneumococcal Symposium, Istanbul.
[143] Ray GT, Whitney CG, Fireman BH, Ciuryla V, and Black SB. Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects. Pediatric Infectious Disease Journal. 2006 Jun; 25(6):494-501.
[144] Sibak M, Moussa I, El-Tantawy N, Badr S, Chaudhri I, et al. Cost-effectiveness analysis of the introduction of the pneumococcal conjugate vaccine (PCV-13) in the Egyptian national immunization program, 2013. Vaccine. 2015 May 7; 33 Suppl 1:A182-91.
[145] Türel O, Kisa A, McIntosh ED, and Bakir M. Potential cost-effectiveness of pneumococcal conjugate vaccine (PCV) in Turkey, Value Health. 2013 Jul-Aug; 16(5):755-9.
[146] Urueña A, Pippo T, Betelu MS, Virgilio F, Giglio N, et al. Cost-effectiveness analysis of the 10- and 13-valent pneumococcal conjugate vaccines in Argentina. Vaccine. 2011 Jul 12; 29(31):4963-72.

[147] Wisløff T, Abrahamsen TG, Bergsaker MA, Løvoll Ø, Møller P, et al. Cost effectiveness of adding 7-valent pneumococcal conjugate (PCV-7) vaccine to the Norwegian childhood vaccination program. Vaccine. 2006 Jul 17; 24(29-30):5690-9.
[148] GSK and Pfizer extend vaccine access programme. 2013 Jul 30 [internet], [accessed 2015 Oct]. Available at: http://www.pmlive.com/pharma_news/gsk_and_pfizer_extend_vaccine_access_programme_493311
[149] Expert interviews
[150] http://blogs.nature.com/news/2011/06/gavi_alliance_vastly_exceeds_u_1.html
[151] Berndt ER, Glennerster R, Kremer MR, Lee J, Levine R, et al. Advance market commitments for vaccines against neglected diseases: estimating cost and effectiveness, Health Economics. 2007 May, 16(5): 491-511.
[152] Expert Interviews
[153] Dotres C, Puga R, Ricardo Y, Brono C, Paredes B, Echemendia V, et al. Safety and preliminary immunogenicity of Cuban pneumococcal conjugate vaccine candidate in healthy children: A randomized phase I clinical trial. Vaccine. 2014 Sep: 32(41):5266-5270.
[154] Expert interview
[155] US SEC Form 20F for Sinovac Biotech LTD. for fiscal year ending 2014 Dec 31 [internet]. [accessed 2015 Sep]. Available at: http://www.sinovac.com/file/File/1436664659.pdf.
[156] US SEC Form 20F for Sinovac Biotech LTD. for fiscal year ending 2010 Dec 31 [internet]. [accessed 2015 Sep]. Available at: http://www.sinovac.com/file/File/financialreports/2010_20-F.pdf.
[157] Somasekhar M. Tergene Biotech develops vaccine to combat pneumonia [internet]. Hyderabad: Business Line, July 16 2015 [accessed Sep 2015]. Available at: http://www.thehindubusinessline.com/companies/tergene-biotech-develops-vaccine-to-combat-pneumonia/article7429987.ece.
[158] Biological E Limited. Research Pipeline [internet]. Biological E: 2014 [accessed Sep 2015]. Available at: http://www.biologicale.com/research_pipline.html