ADVANCE MARKET COMMITMENT FOR PNEUMOCOCCAL VACCINES

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PREPARED BY THE AMC SECRETARIAT OF GAVI, THE VACCINE ALLIANCE

Gavi
The Vaccine Alliance

AMC ADVANCE MARKET COMMITMENTS for vaccines

Contents

Abbreviations

AMC	Advance Market Commitment
AMP	Agence de Médicine Préventive
CDC	US Centers for Disease Control and Prevention
DTP	Diphtheria, tetanus, pertussis vaccine
EPI	Expanded Programme on Immunization
FCE	Full country evaluations
FOC	Firm order commitment
Gavi	Gavi, the Vaccine Alliance
Gavi Secretariat	Secretariat of Gavi, the Vaccine Alliance
IAC	Independent Assessment Committee
IPD	Invasive pneumococcal disease
IRC	Independent Review Committee
M&E	Monitoring & evaluation
PEF	Partners' engagement framework
PCV	Pneumococcal conjugate vaccine
PROWG	Pneumococcal & Rotavirus Operational Working Group
PSA	Provisional supply agreement
PSF	Product summary file
RFP	Request for Proposals
SD	Supply Division (UNICEF)
SDF	Strategic demand forecast
SDS	Strategic demand scenarios
TPP	Target product profile
UNICEF	United Nations Children's Fund
VI-TAC	Vaccine Implementation Technical Advisory Consortium
WHO	World Health Organization
WUENIC	WHO/UNICEF estimates of national immunization coverage

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Executive summary

The purpose of this report is to provide an update on Advance Market Commitment (AMC) implementation activities, including supply and procurement, country demand, monitoring and evaluation, media and communications and financial reporting. This report is the ninth pneumococcal AMC Annual Report[i] and covers the period from **1 January to 31 December 2017**. It is the third AMC Annual Report in which the reporting cycle is aligned with the calendar year. The aim of this change is to increase efficiencies and create alignment with other annual reporting requirements for the Gavi pneumococcal vaccine programme and the AMC Secretariat.

Supply and demand

The pilot AMC for pneumococcal vaccines is now in its ninth year of implementation and significant progress continues to be made.

A total of 156 million doses of pneumococcal conjugate vaccine (PCV) were procured through the AMC in 2017, a 5% decrease from 2016 (164 million doses)[ii]. The decrease was caused by doses being procured from volumes in later years to meet India's demand; these doses were subsequently delivered in 2017[iii]. With the current six supply agreements, the total contracted supply amount through 2024 amounts to 1.46 billion doses. Out of the US$ 1.5 billion AMC funds, the two suppliers that have prequalified PCV have been allocated US$ 1.095 billion of the funds. Twenty-seven percent of the AMC funds remain available.

In terms of country demand, 81% of AMC-eligible countries (59 out of 73) have been approved to introduce the AMC-eligible pneumococcal vaccines to date. As of 31 December 2017, 58 countries have introduced these life-saving vaccines, including one, India, during this reporting period (1 January to 31 December 2017). The remaining country that has been approved for Gavi support, Haiti, is expected to introduce the vaccine in the coming eighteen months.

Based on the Base Demand Forecast v14.0, which was approved during the 2016 procurement cycle, the Gavi Secretariat, in consultation with UNICEF Supply Division (SD), decided to issue a fourth call for supply offers for the procurement of pneumococcal vaccines. The decision to conduct a tender in 2017 was made by Alliance partners based on the AMC Terms and Conditions, Gavi's strategic demand scenarios v2017Q1 and the outcomes of the latest rounds of applications in 2017 for vaccine support to the Gavi Secretariat.

Monitoring and evaluation

AMC progress continues against selected indicators as shown in Table 1. It is estimated that more than 109 million children were immunised with AMC-supported pneumococcal vaccines between programme start and the end of December 2016. By the end of 2017, this figure is projected to have reached more

[i] Previous AMC Annual Reports can be found on the AMC website: http://www.gavi.org/library/gavi-documents/amc/

[ii] Total procured doses from the supply agreements which include countries that have access to AMC prices, in addition to Gavi-funded doses.

[iii] This did not re-occur in December 2017 for delivery in 2018

than 149 million (actual 2017 data will become available in July/August 2018). The continued scale-up of PCV is forecasted to result in approximately 655,000[iv] prevented deaths by 2020.

Table 1. Selected non-confidential indicators for AMC progress tracking (calendar year view)

	2009	2010	2011	2012	2013	2014	2015	2016	2017
Objective 1: To accelerate the development of pneumococcal vaccines that meet developing country needs.									
Cumulative number of AMC eligible target produce profile (TPP) vaccines	0	2	2	2	2	2	2	2	2
Cumulative number of AMC-registered manufacturers who have made their registration public	0	4	4	4	4	4	4	4	4
Objective 2: To bring forward the availability of effective pneumococcal vaccines for developing countries.									
Annual number of doses of TPP vaccine procured under AMC by year (in millions)	0	7	36	58	58	100	133	164	156
Objective 3: To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers.									
Cumulative number of countries that have applied for Gavi support for PCV	21	21	49	52	59	59	59	60	60
Cumulative number of AMC-eligible/Gavi-supported countries that have been approved	3	17	37	46	51	55	58	59	59
Cumulative number of AMC-eligible/Gavi-supported countries introducing TPP vaccines	0[v]	1[vi]	16	24	38	46	54	57	58
Coverage of PCV in AMC-eligible/Gavi-supported countries*	0%	1%	5%	9%	19%	28%	35%	41%	n/a**
Cumulative number of children vaccinated with Gavi support (in millions)	-	0.5	4	10	26	48	76	109	n/a**

Source: Gavi Secretariat

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

*** WUENIC coverage data and WHO-reported number of immunised for 2017 will be available in July 2018*

PCV coverage performance at the country level continues to be tracked, using WHO/UNICEF estimates of national immunization coverage (WUENIC) data, which are published annually in July for the previous year. Information to date shows that countries continue to successfully introduce PCV into their routine systems, with PCV third-dose (PCV3) coverage tracking well against the third-dose coverage of diphtheria-tetanus-pertussis vaccine (DTP3) by the second year of implementation, at 91%, except in a small subset of countries.

[iv] *While programmatically there was little change in the number of children vaccinated remaining on target and the effectiveness of the vaccine, the impact of the vaccine is revised downward predominantly due to new information on the vaccine preventable burden of disease and slower roll out of the vaccine among high burden populations. The reduction in deaths averted from the previous estimate is mostly driven by revised coverage estimates that were lower than expected for some large Gavi countries, most notably Nigeria These modelled forecasts use the WHO established Child Health Epidemiology Reference Group (CHERG) estimates of causes of child mortality as an input to the models. In the latest version of these estimates pneumococcal related mortality was revised down. Hence the burden preventable by the vaccines was also revised down and this is reflected in the lower impact estimates.*

[v] *Two countries introduced PCV in 2009, but with a vaccine that was not TPP compliant. They have since switched to a TPP vaccine in 2011.*

[vi] *Same as above.*

As part of the AMC monitoring and evaluation framework, and as recommended by the Gavi Evaluation Advisory Committee and agreed by the AMC stakeholders, the first AMC outcomes and impact evaluation took place in 2015. The final report was published in early 2016[vii].

The Gavi Evaluation Advisory Committee (EAC) approved a two-year continuation (2017–2019) of the full country evaluation project. This includes targeted priorities by country in Mozambique, Zambia and Uganda, including country-specific evaluation questions proposed by national stakeholders.

Gavi continues to fund a number of special studies demonstrating the effectiveness and impact of PCV to help facilitate evidence-based decision making in support of the introduction and continued implementation of pneumococcal vaccines in developing countries through the AMC.

Media and communication activities

Increasing AMC visibility through traditional, online and social media remains an important goal for Gavi's communications team. This multi-platform approach continues as 58 countries have now introduced pneumococcal vaccines into their national immunisation schedule.

Financial activities

From 1 January to 31 December 2017, US$ 556 million was disbursed to UNICEF for the purchase of pneumococcal vaccines. Of this amount, US$ 37 million was from the AMC funds to pay for the AMC-funded portion of the vaccine purchase. The remaining US$ 519 million was allocated from general Gavi funds to pay for the tail price portion of the vaccine purchase and related fulfilment costs[viii].

Challenges and priorities ahead

With 59 AMC-eligible countries approved for PCV and 58 already having introduced it since the first introduction in 2010, the priorities moving forward will focus on supporting the remaining future introductions in countries that have been approved, as well as supporting countries that have not yet applied to access pneumococcal vaccines through the AMC. For countries that have introduced, the priorities remain to sustain PCV implementation and improve coverage, support product switches and measure the impact of PCV, especially as countries start to transition out of Gavi support. Reducing the price of pneumococcal vaccines and ensuring a proper balance between supply and demand remain key priorities, in addition to strategic discussions on PCV catch-up vaccination.

[vii] *Access the full report at http://www.gavi.org/results/evaluations/pneumococcal-amc-outcomes-and-impact-evaluation/*

[viii] *Fulfilment costs are the extra costs incurred in supplying vaccines (estimated at US$ 0.08 per dose during the 2016-2020 period), in addition to the cost of the vaccine itself. These costs typically include the cost of syringes, safety boxes and freight.*

Background

Advance Market Commitments (AMC) for vaccines aim to encourage the development and production of affordable vaccines tailored to the needs of developing countries. In June 2009, the Governments of Italy, the United Kingdom, Canada, the Russian Federation, Norway and the Bill & Melinda Gates Foundation, collectively pledged a total of US$ 1.5 billion to fund a pilot AMC against pneumococcal disease.

The overarching goal of the pilot AMC is to reduce morbidity and mortality from pneumococcal disease, preventing an estimated seven million childhood deaths by 2030. The objectives of the pneumococcal AMC are:

1. **to accelerate the development of pneumococcal vaccines** that meet developing country needs (e.g. in terms of serotype composition and vaccine presentation) as specified in the target product profile (TPP);
2. **to bring forward the availability of effective pneumococcal vaccines** for developing countries by guaranteeing the initial purchase price for a limited quantity of new vaccines that represents value for money and incentivises manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand;
3. **to accelerate vaccine uptake** by ensuring predictable vaccine pricing for countries and manufacturers, through binding commitments by participating companies to supply vaccines at low, long-term and sustainable prices; and
4. **to test the effectiveness of the AMC mechanism** as an incentive for needed vaccines and to learn lessons for possible future AMCs.

Following the initiation of the pneumococcal AMC in 2009, the first vaccines became available for procurement under the AMC terms and conditions, and the first roll-out occurred in Nicaragua in December 2010. To date, 81% of 73 AMC-eligible countries have submitted applications to Gavi for financial support and been approved for pneumococcal vaccine introduction.

The purpose of this report is to provide an update on AMC implementation activities, including supply and procurement, country demand, monitoring and evaluation, media and communications and financial reporting. This report is the ninth pneumococcal AMC Annual Report[ix] and covers the period from **1 January to 31 December 2017**. It is the third AMC Annual Report in which the reporting cycle is aligned with the calendar year; the aim of this change is to increase efficiencies and create alignment with other annual reporting requirements for the Gavi pneumococcal vaccine programme and the AMC Secretariat.

The report was developed by the AMC Secretariat at Gavi, in collaboration with the World Bank and UNICEF Supply Division (SD). For more information about the AMC Secretariat, please refer to Annex 1.

[ix] *Previous AMC Annual Reports can be found on the AMC website: http://www.gavi.org/library/gavi-documents/amc/*

1. Supply and procurement update

1.1 WHO recommendation and AMC-eligible pneumococcal vaccines

WHO recommends the inclusion of pneumococcal vaccines be given priority in childhood immunisation programmes worldwide, especially in countries with an under-five mortality rate above 50 per 1,000 live births[1]. For administration to infants, three primary doses (3p+0 schedule) or, as an alternative, two primary doses plus a booster (2p+1 schedule) are recommended. Primary vaccination can be initiated as early as at six weeks. Gavi currently supports PCV for administration in infant routine immunisation programmes.

WHO also states that catch-up vaccination can be conducted as part of a pneumococcal vaccine introduction to accelerate herd protection and thereby increase the impact of PCV on disease burden and carriage[2]. The SAGE Working Group on PCV reviewed the effectiveness of catch-up vaccination leading to an updated WHO recommendation in October 2017, which states that '"*Catch-up vaccination as part of PCV introduction will accelerate both direct and indirect protection and therefore accelerate PCV impact on disease, particularly in case of high VT carriage prevalence and disease burden in children aged **1 to 5 years old**",* thus expanding the age range of the target population recommended for catch-up vaccination.

Furthermore, the revised recommendation provides more guidance on the dose schedule: "*Catch-up vaccination with PCV can be done with 1 dose of vaccine for those initiating vaccine at age 24 months and older. For those who are 12-23 months at the time of first vaccination some programs have used 2 PCV doses separated by at least 8 weeks, and others have used 1 dose. For those initiating vaccination at age 6 months or under, a 3 dose regimen should be offered. For infants aged 7-11 months, some programmes have used 2 doses, and others have used 3 doses. If there is limited availability or capacity for catch-up immunization, the youngest children should be prioritized to receive catch-up doses of PCV because of the higher pneumococcal disease risk."*[x]

Gavi will review a proposal to support PCV catch-up vaccination for those countries that have yet to introduce. In the near future, the expectation is that Haiti, Guinea, the Democratic People's Republic of Korea and Tajikistan will be among the next Gavi countries to introduce PCV, and the first to potentially benefit from a change in programmatic support. This proposal will be discussed by the Policy and Programme Committee (PPC) in 2018.

As of 31 December 2017, there are currently two pneumococcal conjugate vaccines (PCV) available for procurement under the AMC. These two vaccines meet the criteria for TPP, which describe the minimum characteristics required for a pneumococcal vaccine to be eligible for AMC financing. No additional manufacturers are expected to have WHO-prequalified vaccines before 2019/2020.

1.2 Pneumococcal conjugate vaccine, 10-valent

The 10-valent PCV (PCV10) is a liquid vaccine originally available in a 2-dose vial without preservative, produced by GlaxoSmithKline. It was launched in Europe in 2009, obtained WHO prequalification on 12 March 2010 and was deemed AMC-eligible on 16 April 2010 by the AMC Independent Assessment Committee (IAC).

[x] http://www.who.int/immunization/sage/meetings/2017/october/4_PCV_WG_MERGED_Evidence_to_Rec__SEPT_26.pdf?ua=1 page 62

GlaxoSmithKline (GSK) recently developed a 4-dose vial presentation of PCV10[3], which includes a preservative and was prequalified by WHO on the 16th October 2017. It was deemed AMC-eligible on the 17th October 2017 by the AMC IAC. The 4-dose vial presentation is replacing the 2 dose vial, and thus, all countries that are currently using PCV10 2-dose vial will need to switch to PCV10 4-dose vial or another product of their preference. PCV10 2-dose will continue to be available for countries until PCV10 4-dose vial has acquired local registration.

1.3 Pneumococcal conjugate vaccine, 13-valent

The 13-valent PCV (PCV13) is a liquid vaccine in a single-dose vial, produced by Pfizer Inc. It obtained WHO prequalification on 22 August 2010 and was deemed AMC-eligible by the AMC IAC on 23 August 2010.

In addition to the above single-dose vial, Pfizer has developed a 4-dose vial presentation of PCV13, which also includes preservative and with a Phase 3 safety, tolerability and immunogenicity study completed in 2015[4]. The multidose vial presentation obtained WHO prequalification on 14 July 2016 and it was deemed AMC-eligible on 9 August 2016. The PCV13 single-dose vial presentation remains available after the PCV13 4-dose vial presentation has been prequalified by WHO.

1.4 Supply offers and agreements

There have been three completed calls for supply offers for supply of PCVs under the AMC to date. The fourth and last calls for supply offers was published on 6 June 2017 and the process was still ongoing as of 31 December 2017. A summary of the first, second and third AMC supply agreements can be found in Annex 2. A summary of the supply commitments as of 31 December 2017 is shown in Table 2 below.

Table 2. Status of overall supply commitments, as of 31 December 2017

Manufacturer	Date of signature (week of)	Annual supply commitment (doses)	Tail price	Supply start date	AMC Funds allocated
GSK	23 March 2010	30 million	US$ 3.50; reduced to US$ 3.05 from 2017*	2012	US$ 225 million
Pfizer Inc.	23 March 2010	30 million	US$ 3.50; reduced to US$ 3.40 mid 2013; US$ 3.30 from 2014; US$ 3.05 from 2017** and $2.95 from 2018***	2013	US$ 225 million
GSK	12 Dec 2011	18 million	US$3.50; reduced to US$ 3.05 from 2017	2014	US$ 135 million
Pfizer Inc.	12 Dec 2011	18 million	US$ 3.50; reduced to US$ 3.40 mid 2013; US$ 3.30 from 2014;US$ 3.05	2014	US$ 135 million

			from 2017** and $2.95 from 2018***		
GSK	22 July 2013	24 million	US$ 3.40; reduced to US$ 3.05 from 2017	2015	US$ 180 million
Pfizer Inc.	22 July 2013	26 million	US$ 3.40 in 2013; US$ 3.30 from 2014; US$ 3.05 from 2017** and $2.95 from 2018***	2016	US$ 195 million

**Reduced tail price as announced on March 2016*

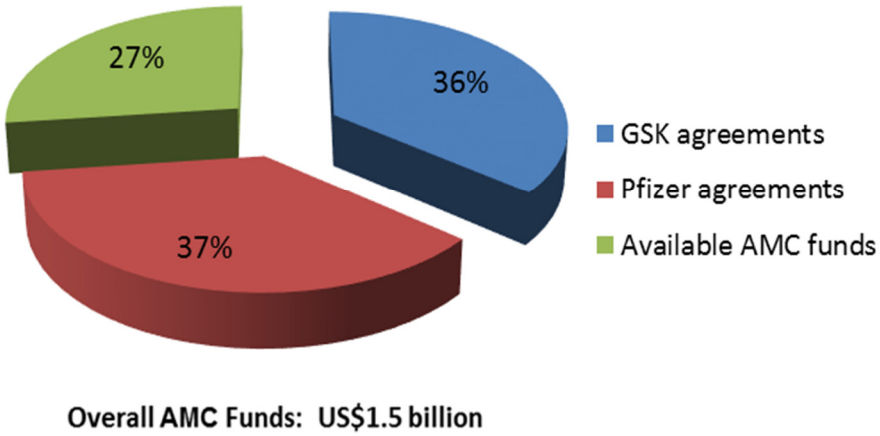
***Reduced tail price for MDV as announced in January 2017; tail price for SDV remains unchanged at US$ 3.30*

**** Reduced tail price for MDV as announced in January 2018; tail price for SDV remains unchanged at US$ 3.30*

The first price reduction achieved under the third supply agreements and the second tail price reduction from 2017 will likely contribute to a total savings of US$ 185 million and US$ 285 million respectively over the lifetime of the agreements. The recent price reduction by Pfizer from US$ 3.05 to US$ 2.95 will contribute additional savings of USD 52.79 million over the duration of the existing three supply agreements and the AMC-4 supply agreement.

The allocation of AMC funds is summarised in Figure 1.

Figure 1. Allocation of AMC funds



Based on the Base Demand Forecast v14.0, which was approved during the 2016 procurement cycle, the Gavi Secretariat, in consultation with UNICEF SD, decided to issue a fourth call for supply offers for the procurement of pneumococcal vaccines.

1.5 Doses contracted to date

The number of doses on contract has increased since the 2013 supply agreements were signed, as additional doses were brought forward during the capacity development period in order to meet demand. Table 3 summarises the total contracted supply, as of 31 December 2017.

Table 3. Total annual contracted supply, as of 31 December 2017 (in millions*)

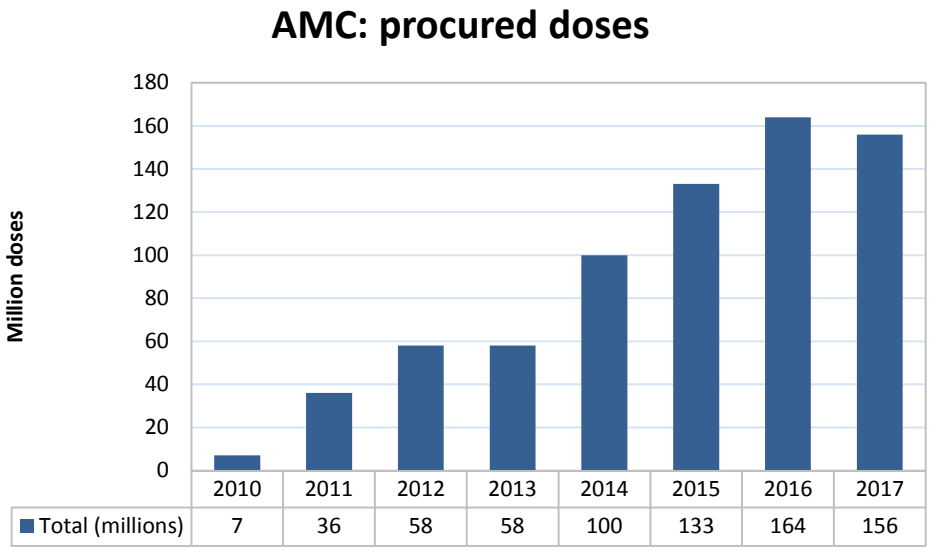
Year	2010	2011	2012	2013	2014	2015	2016	2017	2018-2020	2021	2022	2023	2024	TOTAL
Doses contracted in 2010	5.5	28.9	54.0	53.5	45.9	40.6	57.7	60.0	60.0	54.9	19.0			**600.0**
Doses contracted in 2011			13.0	11.7	33.8	35.1	31.9	36.0	36.0	36.0	36.0	18.5		**360.0**
Doses contracted in 2013				3.0	9.0	43.8	44.6	80.3	50.0	50.0	50.0	57.9	11.4	**500.0**
Grand Total	**5.5**	**28.9**	**67.0**	**68.2**	**88.8**	**119.5**	**134.2**	**176.3**	**146.0**	**140.9**	**105.0**	**76.4**	**11.4**	**1,460.0**

Source: UNICEF Supply Division
** Contracts are amended annually based on actual supply and demand to ensure that the total quantity on the supply agreements remain unchanged. Note: some numbers may appear not to add due to rounding.*

1.6 Doses procured between 2010 and 2017

A total of 156 million pneumococcal vaccine doses were procured in 2017. The total number of doses procured and delivered from 2010 to 31 December 2017 is summarised in Figure 2 below:

Figure 2. Pneumococcal vaccine: procured volumes 2010-2017 (in millions of doses)



Source: UNICEF Supply Division. Please note that the figure above indicates the number of doses placed on purchase orders during the respective years, including for delivery in a subsequent year.

It should be noted that special measures were undertaken with both suppliers in 2012 to ensure production at maximum capacity level in order to secure additional supply availability for 2013, when demand was projected to outpace supply. This resulted in early procurement of approximately 10 million additional doses in 2012 instead of in 2013. These doses were delivered during the first half of 2013 to minimise delays in country introductions. Some supply constraints remained nonetheless. In 2016, 8.9

million additional doses were procured by pulling volumes from later years, which were initially carried over from previous years, to meet India's demand; these doses were delivered in 2017. There were no India purchase orders (POs) issued in 2017 for delivery in 2018. This explains the decline in total volumes in comparison with the previous year.

1.7 Strategic demand forecasts

Strategic demand forecasts for pneumococcal vaccine have evolved over time, with important changes in the forecasted demand. In early versions of the forecasts, revisions to assumptions about eligibility for Gavi support and country interest in the vaccine were key drivers of changing projections. However, for the last several forecasts the long-term view of demand has become relatively stable between forecasts. Nevertheless, projections for the period through 2020 have been revised substantially. The relative variability during this period reflects the uncertainty on the introduction plans for a few large countries, in particular India and Indonesia.

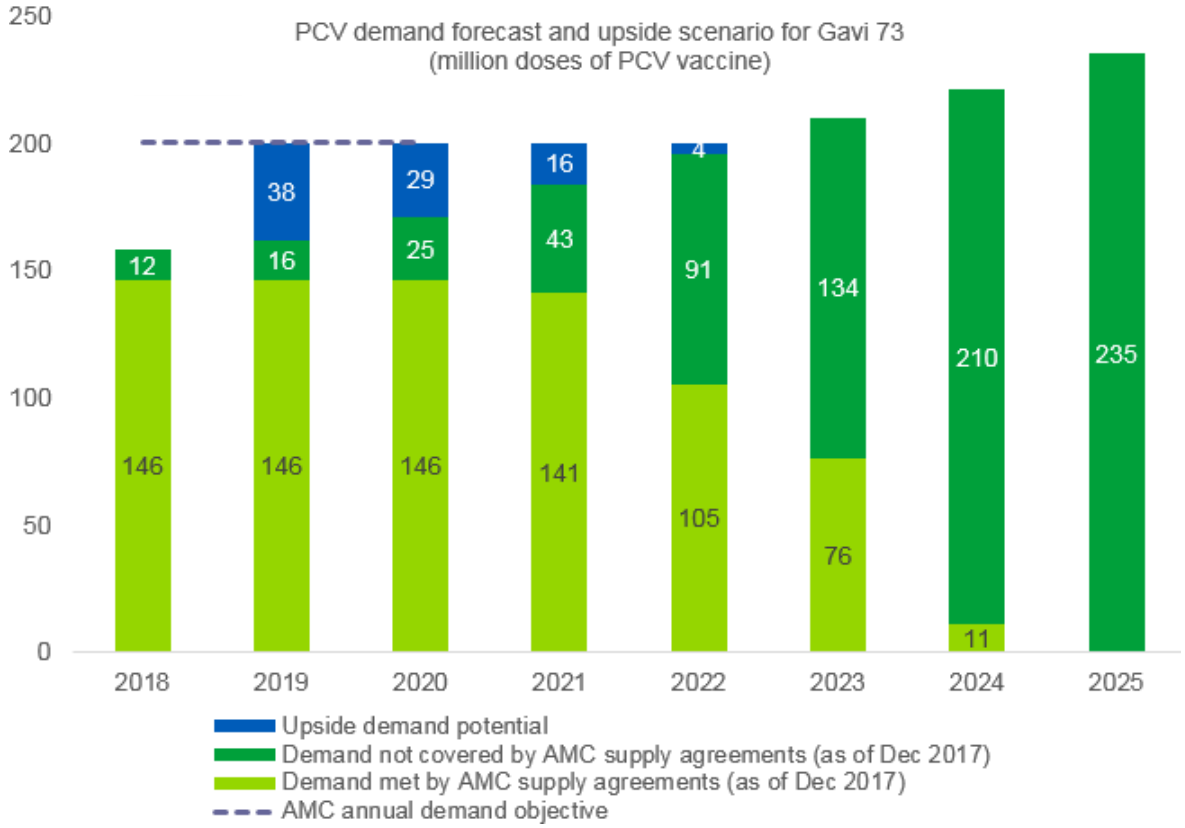
The following demand forecasts were developed, published and/or analysed in the reporting period:

- Base Demand Forecast v14.0 was completed in October 2016 and included in the previous AMC Annual report. It was published on the Gavi website in early 2017[5]. Subsequently Gavi published PCV Strategic Demand Scenarios (SDS) in Q1 2017. This forecast represents the expected future demand through the AMC and UNICEF SD based on the financial forecasts of Gavi and is enhanced to represent AMC demand. The Gavi Secretariat and UNICEF completed an assessment of the need for the issuance of the next call for supply offers based on SDS v2017Q1 and concluded that a call for supply offers was needed[xi].
- Demand forecasting for Gavi's v15.0 operational and financial forecast was completed in late 2017. This update includes several improvements to the forecasting approach. For example, the projection of needs for ongoing programmes was driven by individual country analysis and triangulation of multiple data sources. The volumes associated with the v15.0 financial forecast were published on Gavi's website in December 2017.

The latest demand forecast is shown in Figure 3 below. The upside demand potential represents potential demand factors that may result in the full allocation of 200 million annual doses before 2020.

[xi] *https://www.unicef.org/supply/files/UNICEF_and_Gavi_Decision_PCV_Tenders_April_2017Final.pdf*

Figure 3. Demand forecast[xii]



1.8 Availability of pneumococcal vaccines

In 2017, demand for PCV continued to increase. In 2017 UNICEF and Gavi decided to issue another call for offers. In anticipation of the finalisation of the fourth call for supply offers, UNICEF and Gavi agreed to manage the timing of supply of contracted doses by managing carry-over doses and ”pulling forward” doses from the end of 10-year AMC supply agreements that had already been signed until additional supply agreements could be executed.

In Q1 2017, Gavi finalised an updated supply and procurement roadmap for pneumococcal vaccines. It found that the global supply of pneumococcal vaccines is expected to exceed the demand of 73 Gavi-supported countries in the 2017-2026 period. However, there will be limited buffer capacity in the short term as India introduces Gavi-financed PCV in five states in the 2017-2019 period, prior to pipeline manufacturers entering the market. After 2020, limited buffer capacity is expected to continue as current AMC supply contracts tail off and pipeline manufacturers ramp up supply.

In 2017 GSK’s new 4-dose vial presentation of their PCV10 vaccine obtained WHO prequalification and was deemed AMC-eligible by the IAC on 17 October 2017.

As of January 2018, the price of Pfizer’s PCV13 4-dose vial available to Gavi-supported countries was reduced from US$ 3.05to US$ 2.95 per dose. A future price reduction to US$ 2.90 per dose for PCV13

[xii] *Forecasted demand in Figure 3 is limited to the 73 AMC-eligible countries.*

4-dose vial is possible in 2019, provided that the total volume of doses procured through the AMC for all countries reaches specific levels in 2018. PCV pricing will remain a focus of the Alliance's future efforts.

Several uncertainties have the potential to impact supply and demand over the next 10 years. These include:

- PCV introduction timelines and scale-up plans of large countries eligible to access pneumococcal vaccines at the price available through the AMC, such as Indonesia and India.
- The potential expansion of Gavi support to align to the recently revised WHO recommendation for PCV vaccination and include support for catch-up vaccination at introduction for countries launching PCV routine immunisation programmes in 2018 or later (see also section 1.1).
- The market entry of pipeline manufacturers and their achievement of production capacity targets.
- The potential for countries to change their presentation preference.

An action plan was agreed by Gavi stakeholders and focuses on:

- mitigating potential supply risks;
- supporting pipeline manufacturers to bring vaccines to market to ensure competitive market dynamics and sufficient buffer capacity;
- maintaining market health by ensuring country presentation preferences are grounded in an evidence base and a consideration of supply availability and price; and
- driving continued price reductions.

Additional detail can be found in the public summary of the pneumococcal vaccine roadmap, available on the Gavi website.

1.9 AMC-registered manufacturers

Following the signature of AMC legal agreements on 12 June 2009, manufacturers can enter into an AMC registered manufacturers' agreement with Gavi, the Vaccine Alliance and the World Bank. As part of the registration agreement, manufacturers formally agree to the AMC terms and conditions; accept to provide an annual update on expected timing for application for AMC Eligibility and for WHO prequalification; and recognise the role of the IAC in the determination of AMC eligibility. As described in the AMC procedures memorandum, manufacturers interested in participating in the AMC must submit an AMC-registered manufacturer application package to the AMC Secretariat. This registration does not imply any commitment from manufacturers to participate in the AMC. It is, however, a prerequisite for taking part in UNICEF's calls for supply offers.

Details about the registered manufacturers are confidential unless a firm agrees to have its registration made public. The list of AMC-registered manufacturers who have made their registration public is as follows[6]:

- GSK Biologicals (Belgium)
- Panacea Biotec Ltd. (India)
- Pfizer Inc. (United States of America)
- Serum Institute of India (India)

To date, only two of these manufacturers are producing WHO prequalified and AMC-eligible pneumococcal vaccines, while the rest are not expected to have WHO prequalified vaccines before 2019/2020. Gavi continues to actively monitor the pipeline development for other manufacturers.

2. Country demand and introductions overview

2.1 Gavi-supported countries approved for the introduction of PCV

As of 31 December 2017, 59 of the 73 AMC-eligible countries (81 %) have applied and been approved for support for pneumococcal vaccines.

No new countries applied for PCV support through the AMC in 2017. Further information on non-supported countries is provided in Section 2.5 below.

	Eligible to apply according to DTP3 coverage (>70%)	Not eligible to apply according to DTP3 coverage (<70%)
Eligible to apply for full support	Comoros, Democratic People's Republic of Korea and Tajikistan	Chad, Guinea[xiii], Somalia and South Sudan

2.2 Introduction of PCV in countries transitioned from Gavi support

In June 2010, the Gavi Board approved that all Gavi-eligible countries (as per the 2003 definition) continue to have access to pneumococcal vaccines under the terms and conditions of the AMC. As a result of this Board decision, fully self-financing[xiv] countries that have not yet been approved to receive Gavi support for pneumococcal vaccine are able to apply for and introduce this vaccine under the terms and conditions of the AMC. To do so, they need to have achieved DTP3 coverage at or above 70% according to the latest WHO/UNICEF estimates, commit to procure through UNICEF, and self-finance the tail price component of the AMC price from the outset. Fully self-financing countries that have not yet applied and are eligible to do so are listed below.

	Eligible to apply according to DTP3 coverage (>70%)	Not eligible to apply according to DTP3 coverage (<70%)
Eligible to apply for AMC price (Fully self-financing)	Bhutan, Cuba[xv], India[xvi], Indonesia, Sri Lanka, Timor-Leste and Vietnam	Ukraine

2.3 Pneumococcal vaccine introductions

As of 31 December 2017, 58 countries have introduced pneumococcal vaccines supported by the AMC. All the introductions that have taken place to date are outlined in Table 4 below.

Of the 58 countries with Gavi-supported pneumococcal vaccine programmes, 13 countries are using PCV10, while the remaining 45 countries are using PCV13. As of 2017, Mozambique and Myanmar

[xiii] *Guinea, although it does not currently meet the requirement of 70% DTP3 coverage, is planning to introduce PCV in 2018 through the country engagement framework process. The country will need to meet the 70% DTP3 coverage requirement ahead of the introduction.*

[xiv] *As per previous Gavi graduation terminology, graduating (accelerated transition) and graduated (fully self-financing) countries.*

[xv] *Cuba is planning to introduce PCV7, hence it will not be able to access AMC products/prices.*

[xvi] *India is in accelerated transition but can apply for the AMC tail price for the non-Gavi supported portion of PCV vaccines.*

requested a switch in PCV product (from PCV10 to PCV13) and are expected to switch in 2018; while two other countries (Armenia and Azerbaijan) successfully switched products in the second half of 2016.

Table 4. Pneumococcal vaccine introductions to date

Year	Country	Product	Status	Cumulative No.
2009	Gambia	PCV7 (donation)	Switched to PCV13 in 2011	1
	Rwanda	PCV7 (donation)	Switched to PCV13 in 2011	2
2010	Nicaragua	PCV13	Introduced in December	3
2011	Guyana	PCV13	Introduced in January	4
	Yemen	PCV13	Introduced in January	5
	Kenya	PCV10	Introduced in January	6
	Sierra Leone	PCV13	Introduced in January	7
	Mali	PCV13	Introduced in March	8
	Congo, DR	PCV13	Introduced in April (phased intro.)	9
	Honduras	PCV13	Introduced in April	10
	Central African Republic	PCV13	Introduced in July	11
	Benin	PCV13	Introduced in July	12
	Cameroon	PCV13	Introduced in July	13
	Burundi	PCV13	Introduced in September	14
	Ethiopia	PCV10	Introduced in October	15
	Malawi	PCV13	Introduced in November	16
2012	Ghana	PCV13	Introduced in April* (joint intro. with rotavirus vaccine)	17
	Zimbabwe	PCV13	Introduced in June*	18
	Pakistan	PCV10	Introduced in October (phased intro.)	19
	Congo Rep	PCV13	Introduced in October	20
	Madagascar	PCV10	Introduced in November	21
	Sao Tome and Principe	PCV13	Introduced in November	22
	Djibouti	PCV13	Introduced in December	23
	Tanzania	PCV13	Introduced in December* (joint intro. with rotavirus vaccine)	24
2013	Mozambique	PCV10	Introduced in April	25
	Uganda	PCV10	Introduced in April (phased intro.)	26
	Kiribati	PCV13	Introduced in May	27
	Angola	PCV13	Introduced in June	28
	Zambia	PCV10	Introduced in July (joint intro. with measles second dose)	29
	Sudan North	PCV13	Introduced in August	30
	Moldova	PCV13	Introduced in October	31
	Lao PDR	PCV13	Introduced in October	32
	Burkina Faso	PCV13	Introduced in October (joint intro. with rotavirus vaccine)	33
	Senegal	PCV13	Introduced in November	34

	Mauritania	PCV13	Introduced in November	35
	Papua New Guinea	PCV13	Introduced in November	36
	Afghanistan	PCV13	Introduced in December	37
	Azerbaijan	PCV10	Introduced in December. Switched to PCV13 in 2016	38
2014	Liberia	PCV13	Introduced in January	39
	Bolivia	PCV13	Introduced in January	40
	Togo	PCV13	Introduced in June (joint intro. with rotavirus vaccine)	41
	Niger	PCV13	Introduced in August (joint intro. with rotavirus vaccine)	42
	Armenia	PCV10	Introduced in September. Switched to PCV13 in 2016	43
	Côte d'Ivoire	PCV13	Introduced in September	44
	Georgia	PCV10	Introduced in November	45
	Nigeria	PCV10	Introduced in December (phased intro.)	46
2015	Cambodia	PCV13	Introduced in January	47
	Nepal	PCV10	Introduced in January	48
	Solomon Islands	PCV13	Introduced in February	49
	Bangladesh	PCV10	Introduced in March (joint intro. with IPV)	50
	Guinea Bissau	PCV13	Introduced in June	51
	Lesotho	PCV13	Introduced in July	52
	Eritrea	PCV13	Introduced in August	53
	Uzbekistan	PCV13	Introduced in November	54
2016	Kyrgyzstan	PCV13	Introduced in March	55
	Mongolia	PCV13	Introduced in June (2 districts)	56
	Myanmar	PCV10	Introduced in July	57
2017	India	PCV13	Introduced in May (phased intro.)	58

** Ceremonial launch; National introduction in the month following*

In 2015, an updated analysis to identify the common hurdles faced by countries at the time of introduction was carried out, in order to continue to gather lessons learned on PCV programme implementation. The analysis covered 56 out of the 58 countries[xvii] that had been approved for support at the time. Given the low number of introductions in 2016 and 2017, this analysis was not updated, and it will be revised once considered relevant. As highlighted previously, the global supply constraints in the earlier years of the programme created uncertainty for countries and impaired adequate planning, which led to further delays. Training and cold chain readiness remain the key bottlenecks, as well as the availability of funds (either due to delays in disbursement from Gavi to countries and/or to funding flow issues within the country as a result of decentralisation, for example) and competing priorities at country level, such as multiple concurrent vaccine introductions and campaigns. As highlighted in Section 2.6 below, Gavi continues to strengthen its resource allocation and coordination mechanisms to ensure that these key cross-cutting bottlenecks are addressed in future introductions.

[xvii] *The two countries that originally introduced with donations were excluded from the analysis.*

2.4 Future pneumococcal vaccine introductions

One Gavi-supported country, Haiti, which has already been approved for pneumococcal vaccine support through the AMC, is expected to introduce the vaccine in 2018.

Table 5. Future planned pneumococcal vaccine introductions

Year	Country	Product	Status	Cumulative No.
2018	Haiti	PCV13	Planned for Q4	59

2.5 Future pneumococcal vaccine applications

Out of the 73 AMC-eligible countries, only 14 (19%) have yet to be approved to access pneumococcal vaccines through the AMC. Although a subset of these countries have expressed strong interest in introducing the vaccine in the near future, only three are eligible to apply to access Gavi support in 2018 based on eligibility and on DTP3 coverage levels, which must be higher than 70% (based on the latest WHO/UNICEF estimates of national immunisation coverage) as per Gavi application guidelines. These are Comoros, the Democratic People's Republic of Korea and Tajikistan.

Six countries that have already transitioned from Gavi support are still eligible to access pneumococcal vaccines through the AMC based on their DTP3 coverage, but will need to fully fund the vaccine from the programme outset. These are Bhutan, Cuba, Indonesia, Sri Lanka, Timor-Leste and Vietnam. The remaining countries, Chad, Guinea, Somalia, Ukraine and South Sudan, are currently ineligible due to their DTP3 coverage being below 70%. Gavi will continue to support health system and routine immunisation strengthening in these countries to ensure adequate readiness to introduce PCV and other vaccines in the future.

There will be three rounds for vaccine support applications in 2018 during which countries can apply for PCV support.

In addition to the vaccine support application rounds, there is a new process through which countries can access Gavi support: the country engagement framework (CEF). This is a tailored approach, aligned with a country's strategic multi-year plan. CEF brings together all types of Gavi support into a single portfolio view for the upcoming 3-5 year period. Countries are moving towards the CEF process in stages. Guinea and Comoros have initiated the CEF process and have indicated their interest in introducing PCV.

2.6 Coordination and support for pneumococcal vaccine introductions and implementation

With the introduction of the partners' engagement framework (PEF) for the 2016-2020 strategic period, Gavi continues to strengthen its coordination mechanisms with partners to ensure that technical assistance to countries can be delivered more efficiently and effectively. The new PEF structure, split between foundational support, targeted country assistance and strategic focus areas, ensures that Alliance resources, including technical assistance, are delivered more efficiently and effectively to address key bottlenecks at the country level.

At the global level, the Pneumococcal and Rotavirus Operational Working Group (PROWG) was established in 2011 with the aim of facilitating effective partner coordination, including country communication and operational decision-making. The PROWG has been instrumental in creating

favourable conditions for Gavi-supported countries to successfully apply, introduce and sustain use of pneumococcal and rotavirus vaccines as per Gavi's mission and the AMC goals and objectives.

The PROWG members represent WHO, UNICEF SD, UNICEF Programme Division, PATH, Johns Hopkins University (JHU), Clinton Health Access Initiative (CHAI) and the Gavi Secretariat. The working group meets periodically by teleconference to discuss the following key topics, among others:

- monitoring the progress of implementation, such as reports of faster (or slower) uptake of the vaccine post-launch;
- in close collaboration with countries and regional offices, determining technical assistance needs and mobilise relevant resources to ensure successful application, programme planning and implementation;
- monitoring and supporting country application development, including development of introduction plans;
- monitoring preparedness issues and implementation milestones for successful launch and sustained use of the vaccines; and
- gathering lessons learned and analysing experiences to optimise and improve future introductions.

A list of current PROWG members is provided in Annex 3.

At the country level, programmatic challenges post-introduction are being gathered through post introduction evaluations (PIEs), which are evaluations of the overall impact of the introduction of a new vaccine(s) on a country's national immunisation programme. PIEs are conducted as standalone assessments or as part of comprehensive reviews of the Expanded Programme on Immunization (EPI). During 2016, five countries[xviii] conducted a PIE for PCV. A PIE focuses on a range of programmatic aspects, such as pre-introduction planning, vaccine storage and wastage, logistics of administering the vaccine, and community receptiveness. It is used to rapidly identify problem areas needing correction within the immunisation programme, either pre-existing or resulting from the introduction of a new vaccine, and provide valuable lessons for future vaccine introductions. The PIEs carried out to date have identified that PCV introduction is generally successful and high coverage is reached within a short period, due to high demand. Some of the issues identified include cold chain and vaccine management, training and reporting and monitoring. The PEF aims to resolve these issues through targeted country assistance, in particular. The Gavi full country evaluations have also provided relevant lessons learnt regarding routine introductions of PCV[xix].

2.7 Global Action Plan for the prevention and control of Pneumonia and Diarrhoea (GAPPD)

In 2013, WHO/UNICEF published the integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD)[7]. GAPPD proposes a cohesive approach to ending preventable pneumonia and diarrhoea deaths and provides a roadmap for national governments and their partners to plan and implement integrated approaches for the prevention and control of pneumonia and diarrhoea. It brings together critical services and interventions, including immunisation, to create healthy

[xviii] *Burkina Faso, Cote d'Ivoire, Eritrea, Kyrgyzstan and Nigeria*

[xix] *See Section 4.3 for more information.*

environments, promotes practices known to protect children from disease and ensures that every child has access to proven and appropriate preventive and treatment measures.

Gavi works within this broader context, supporting the advancement of GAPPD and funding pilot projects with this objective until 2015. As pneumococcal vaccines are introduced, and their coverage approaches that of DTP3 immunisation, this presents a unique opportunity to strengthen the integration of service deliveries and help improve the coverage of other important interventions. Since 2014, Gavi also requires countries to describe in their PCV applications the status of implementation of other complementary interventions for disease prevention and control, and how they could leverage the opportunity of new vaccine introduction to strengthen an integrated approach. This was not designed to raise the requirements for proposal approval, but rather as an opportunity to prompt countries' consideration and planning of comprehensive disease prevention and control at the time of proposal development.

On World Pneumonia Day 2016, the WHO department of Maternal Child and Adolescent Health (MCA) launched a Monitoring and Visualization Tool for GAPPD[xx]. This tool allows users to review progress against the Sustainable Development Goal (SDG) 3 and GAPPD target towards ending preventable under-five deaths from pneumonia and diarrhoea by 2030. The data is classified on 24 key indicators related to the protection, prevention and treatment of diarrhoea and pneumonia in children under five years of age and two indicators on mortality due to the two diseases. The tool permits access to country-specific profiles for 136 countries, and thus facilitates the review specific coverage and health impact indicators that will be useful to avert childhood diarrhoea and pneumonia deaths.

[xx] http://www.who.int/maternal_child_adolescent/epidemiology/gappd-monitoring/en/

3. AMC Independent Assessment Committee

The IAC serves a number of key functions. Most importantly, it has the mandate to review and approve the TPP and thereby the minimum technical requirements that candidate products must meet to be eligible for AMC funding[xxi]. In addition, the IAC establishes when and if an adjustment of the preset long-term price of vaccines is necessary. During the current reporting period, IAC members met once (in October 2017) to review GSK's application for AMC eligibility of the PCV10 4-dose vial presentation, in addition to being called upon to approve the AMC Annual Report.

The IAC currently comprises nine members representing expertise in: public health, health economics, vaccine business development, vaccine industry economics, contract law, public-private finance and clinical performance and delivery systems. A list of IAC members can be found in Annex 4.

As expressed in the IAC Charter and Bylaws, the initial term of up to six years of IAC members is subject to reappointment and may only be renewed once. Hence the membership of three IAC members will be revised in 2017-18 and the IAC Selection and Oversight Panel will appoint new members.

[xxi] *Also see section 3.2 of the 2010 AMC Annual Report, http://www.gavi.org/funding/pneumococcal-amc/*

4. Monitoring and evaluation

In 2007 the United Kingdom's Department for International Development in conjunction with the Canadian International Development Agency commissioned a monitoring and evaluability assessment study on behalf of the AMC for Pneumococcal Vaccines Donor Committee. The study proposed a monitoring and evaluation framework including four key components:

- annual monitoring to be implemented by the AMC Secretariat;
- a baseline study to establish the context (industry and country situation) at the beginning of the intervention and to develop proposed counterfactuals (two counterfactuals were proposed to estimate what would happen if no AMC were to be implemented and to measure incremental impact of the AMC initiative on the vaccine market and pneumococcal disease and mortality);
- An independent process and design evaluation to assess the AMC implementation process and the efficiency and effectiveness of the AMC design; and
- impact evaluations every four years from entry into the first AMC supply agreement to assess the achievements of the AMC and the association (and to the extent possible, causality) between the AMC intervention and observed outcomes.

Annual monitoring is carried out by the AMC Secretariat and an Annual Report has been published on the AMC website each year since 2010. The baseline study was completed in 2010 and is available on the AMC website. The AMC process and design evaluation was carried out in 2012. Upon recommendation of the Gavi Evaluation Advisory Committee and following consultations with AMC stakeholders in 2013, the first impact evaluation of the AMC was completed in 2015 instead of in 2014 (see 4.2 below).

4.1 Programme performance reporting

A comprehensive PCV results framework is currently being used for regular monitoring of the Gavi pneumococcal vaccine programme and the AMC. At the end of 2015, additional indicators were added to reflect the Gavi's new 2016-2020 strategy.

Pneumococcal vaccine coverage in Gavi-supported countries continues to be closely monitored. In 2016, weighted PCV3 coverage in the original 73 Gavi-supported countries was 41%, based on the WUENIC data published in July 2017[8] – a 6 percentage point increase in relation to 2015. In the subset of Gavi-supported countries that introduced the vaccine prior to 2016 (54), average PCV3 coverage has reached 72%. Among countries that introduced prior to 2014 (46), average PCV3 coverage has reached 70%. Gavi's 2016-2020 strategy does not define targets for PCV coverage, but instead includes a composite indicator tracking overall coverage of all vaccines in Gavi's portfolio. Actual 2017 data will become available in July 2018 and reported in the next AMC Annual Report.

Figure 4 shows PCV3 coverage in 2016 (WUENIC July 2017 data). For the same group of countries, DTP3 coverage was 76%, demonstrating that most countries continue to successfully introduce PCV into their routine systems. 47 countries have more than 90% PCV3 coverage as a percentage of DTP3[xxii]. One country (Papua New Guinea) has less than 50% of PCV3 coverage as a percentage of DTP3

[xxii] *This analysis excludes mid-2016 introductions and phased introductions.*

coverage; the situation in this country is being closely monitored and bottlenecks are being addressed through Alliance support.

A few countries had chosen to move the PCV third dose administration to a later visit (e.g. Nepal, 9 months[xxiii], with measles first dose; Bangladesh, 18 weeks, visit for PCV only; Moldova, 12 months). In Bangladesh, coverage for PCV3 reached a 1:1 ratio with DTP3 by the end of 2016; a decision from the National Committee for Immunization Practices (NCIP) in January 2017 moved the PCV third dose administration to 14 weeks. In the case of Nepal, the change is not in line with WHO recommendations, which recommend at least 8 weeks between first and second dose in the 2p+1 schedule. Immunogenicity studies are currently being carried out in Nepal to ensure that the change to a novel schedule does not affect the immunogenicity of PCV.

Figure 4. 2016 PCV3 coverage across Gavi-supported countries

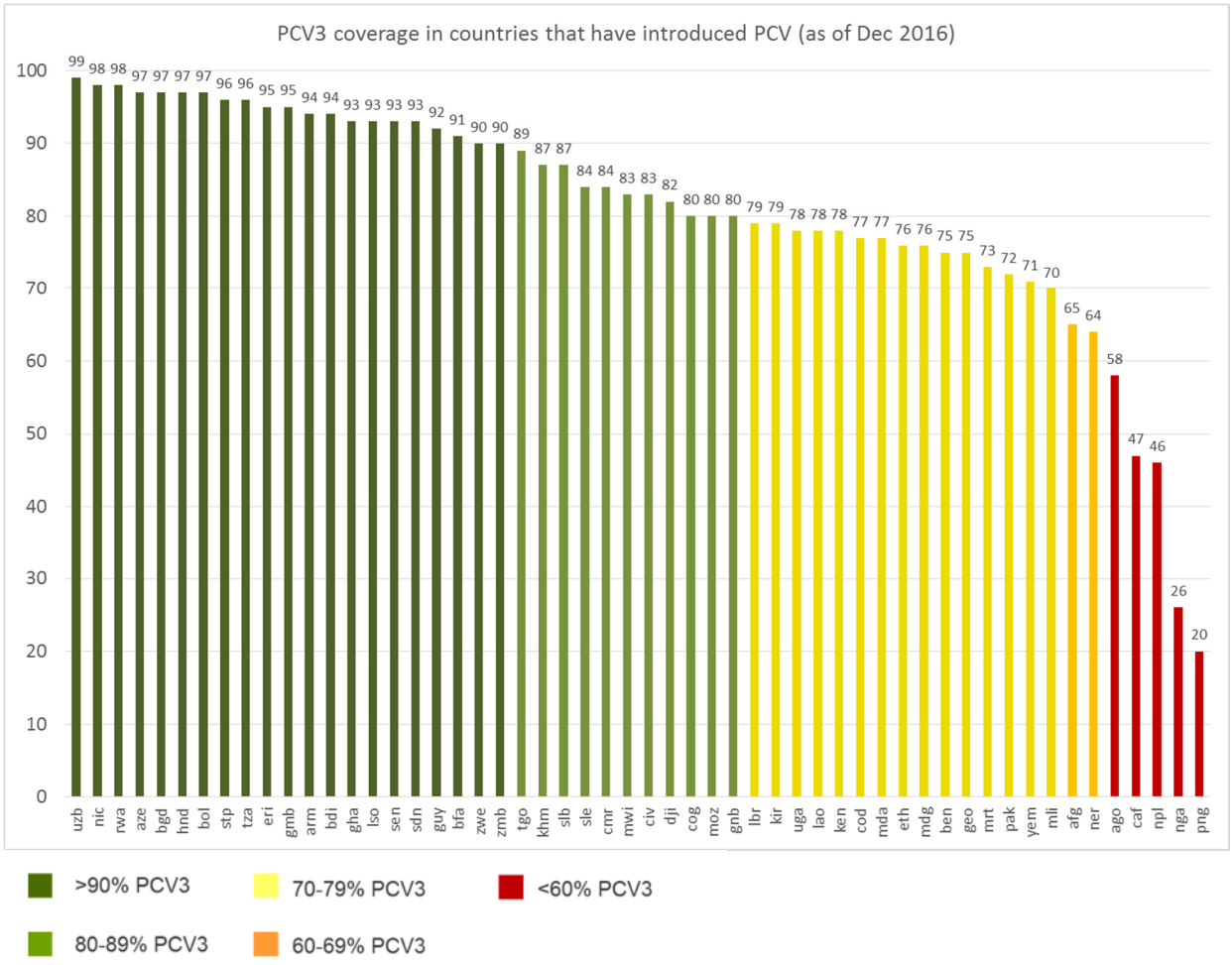
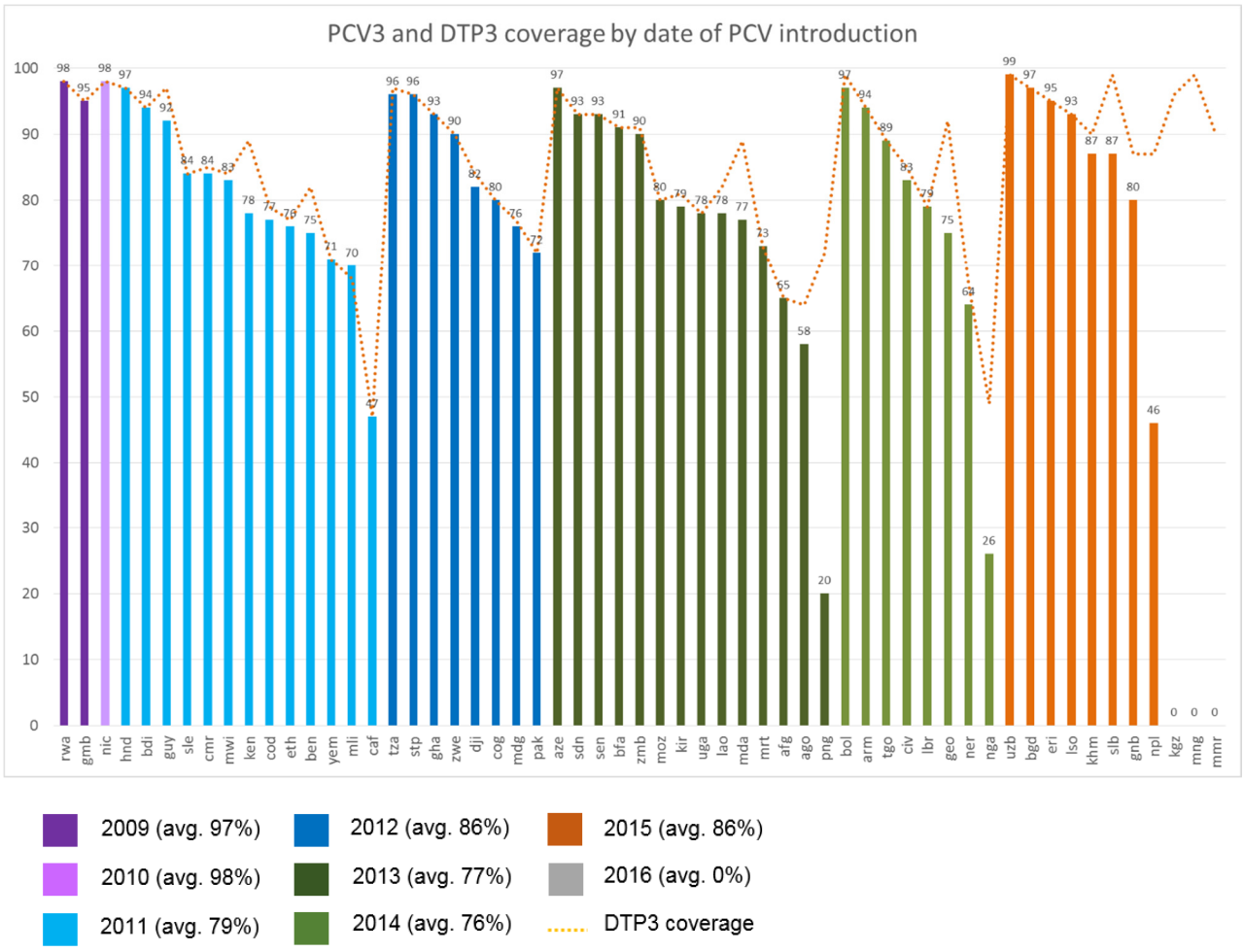


Figure 5 shows PCV3 coverage in 2016 (WUENIC July 2017 data) according to the date of PCV introduction in routine immunisation, versus the 2016 DTP3 coverage (WUENIC July 2017 data). Countries that introduced in 2015 and 2016 might not have had sufficient time to ensure routinisation of the third dose of PCV prior to the data collection. From countries that introduced in 2014 and prior, Papua

[xxiii] *Nepal has currently a 2+1 schedule (6 weeks, 10 weeks and a booster at 9 months).*

New Guinea and Nigeria stand out with a gap of 52 and 23 percentage points, respectively, between PCV3 and DTP3. In Papua New Guinea, this difference is due to a phased roll-out that concluded in 2016 as well as vaccine management issues.

Figure 5. PCV and DTP third dose coverage by date of PCV introduction



4.2 AMC Outcomes and Impact Evaluation

In 2015, and as per the AMC monitoring and evaluation framework, the Gavi Secretariat commissioned The Boston Consulting Group (BCG) for an outcomes and impact evaluation, in order 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. The evaluation also captures lessons learned in the pilot and recommendations for future impact evaluations of the AMC.

The request for proposals (RFP) for the evaluation was published in March 2015. AMC stakeholders and partners were widely consulted on the evaluation questions, design options and other methodological matters. The RFP was also reviewed and approved by Gavi's EAC. Proposals were submitted through an open and competitive bidding process and then judged by an independent selection committee. The committee recommended the selection of BCG. After the review of the draft report by the AMC stakeholders, the final report was published on the Gavi website in early 2016[9]. The Gavi Secretariat has prepared a management response to the findings and recommendations, which is publicly available with

the report on the Gavi website. The Gavi evaluation advisory committee (EAC) also submitted an independent assessment of the quality and usefulness of the report.

The evaluation validated that the pilot pneumococcal AMC contributed towards reducing morbidity and mortality from pneumococcal disease, accelerating vaccine supply availability (as per the second objective of the AMC) and uptake (as per the third objective of the AMC) in Gavi-supported countries, as well as supporting reduction in morbidity and mortality from pneumococcal disease, with 3 million under-five deaths estimated to be averted by 2030[xxiv]. Although the AMC has not succeeded in accelerating the development timelines for additional manufacturers, as per the first objective of the AMC, it 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.

4.3 Full country evaluations

In 2013, Gavi launched a set of evaluations with the aim of understanding and quantifying the barriers to and drivers of immunisation program improvement, with emphasis on the contribution of Gavi, in four countries. There are four countries taking part in the full country evaluations (FCE) project: Bangladesh, Mozambique, Uganda and Zambia. Local research institutions in all FCE countries are partnering with the Institute of Health Metrics and Evaluation (IHME) and PATH to collect information, data and evidence to help improve immunisation programmes. The introduction and implementation of PCV in the routine immunisation programme (routinisation) in these four countries were evaluated as part of this project. The original FCE project contract ended in December 2016.

Based on multiple stakeholder consultations at the country and global level, the Gavi EAC agreed on a two-year continuation (2017 - 2019) of the FCE project, with targeted priorities by country in Mozambique, Zambia and Uganda including country-specific evaluation questions proposed by national stakeholders. The FCE second phase will continue with the prospective approach to ensure the timely dissemination of emerging findings, allowing for the opportunity to inform implementation processes on a timely basis.

In previous Gavi FCE reports (2013, 2014 and 2015) the introduction process and routinization of PCV in Mozambique, Uganda and Zambia and the joint introduction of PCV with IPV in Bangladesh were evaluated (Table 8). The 2016 report presents the continued monitoring of the routinization of PCV in all four countries, and presents findings of the impact of the PCV introduction on pneumococcal disease burden, based on studies in Mozambique and Bangladesh.

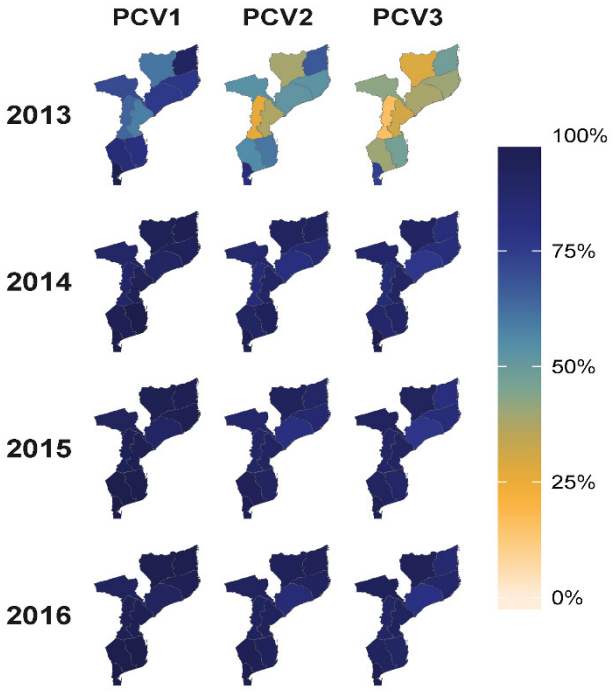
[xxiv] *These estimates are a result of an external evaluation and not Gavi targets.*

Table 6: Timeline of PCV vaccine introductions in Gavi FCE countries (2013-2016)

	Bangladesh	Mozambique	Uganda	Zambia
2013		PCV introduction (April 2013)	PCV introduction in one district (April 2013)	PCV introduction (July 2013)
2014		PCV routinisation	PCV national rollout and routinisation	PCV routinisation
2015	PCV introduction (March 2015)	PCV routinisation	PCV routinisation	PCV routinisation
2016	PCV and IPV routinisation	PCV routinisation	PCV routinisation	PCV routinisation

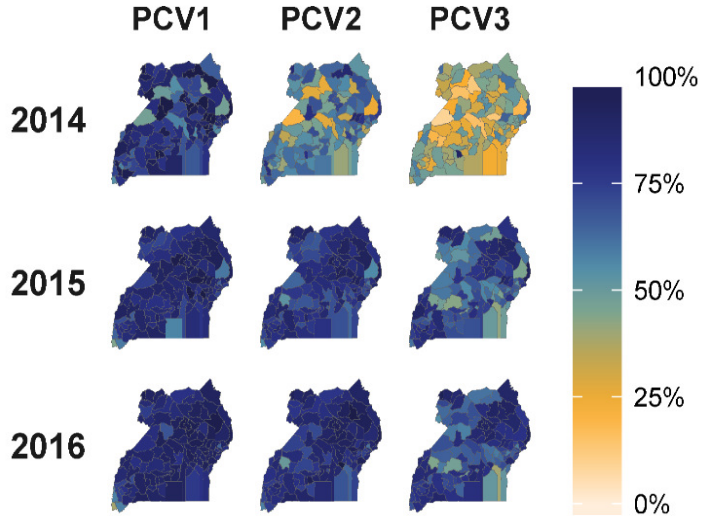
Evaluation findings indicated Gavi FCE countries in 2016 have experienced variable success in routinising PCV as shown in coverage maps below. PCV was introduced in Bangladesh in March 2015 and based on a review of EPI health management information system (HMIS) data, is well routinised; EPI HMIS data of January-October 2016 showed that PCV third-dose coverage is 93%, compared to 97% for the third dose of pentavalent.

Figure 6. Map of PCV coverage in Mozambique



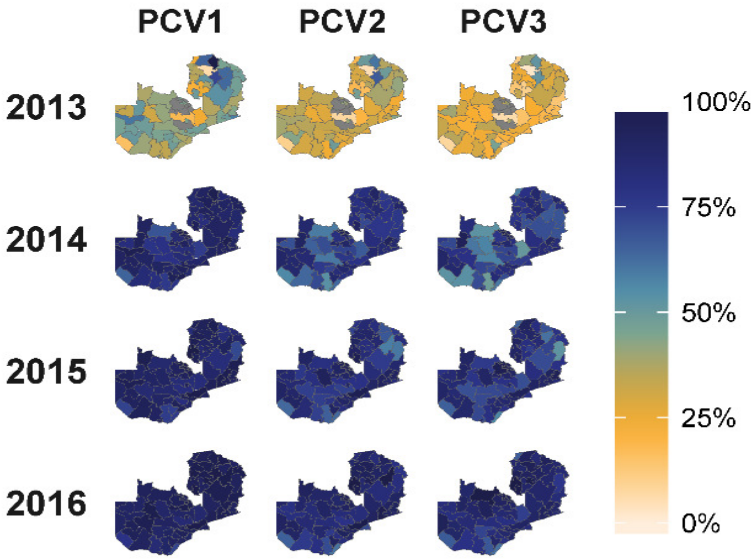
In Mozambique, PCV was introduced in April 2013 and was quickly integrated into the routine EPI, as demonstrated by the coverage maps in Figure 6.

Figure 7. Map of PCV coverage in Uganda



In Uganda, PCV was nationally rolled out in 2014. Challenges in routinisation in 2014 and 2015 were driven by vaccine stock-outs and were covered in detail in the 2015 report. The PCV/pentavalent ratio improved tremendously in 2015 and 2016. This improvement coincided with strategic interventions by Uganda's National EPI (UNEPI) and partners including scale-up of the Reach Every District micro-planning strategy and training of health workers on data quality improvement by Data Improvement Teams throughout the country. In 2016, the evaluation findings suggest that the discrepancy in delivery between PCV and pentavalent vaccines may be due to reporting issues at the facility level with pentavalent vaccine being better recorded as it is a performance indicator for facilities in Uganda. This potential root cause highlights data quality issues in administrative and HMIS data and suggests that a population-based coverage survey or data quality audit would be necessary to confirm the discrepancy between PCV and pentavalent vaccine delivery in Uganda. Based on subnational data collection, no stock-outs of PCV were observed in facilities visited in 2016.

Figure 8. Map of PCV coverage in Zambia



In Zambia, where PCV was introduced in 2013, two factors may account for the reported undercoverage of PCV: supply-side challenges causing stock-outs and data quality issues. Although procurement and distribution of vaccines appear to be the main challenges around routinisation, there is a need for further research in this area and the FCE team will continue assessing it.

As part of the FCE, pneumococcal vaccine impact was assessed in two countries: Mozambique and Bangladesh. This assessment included pre- and post-introduction nasopharyngeal carriage surveys, case-control studies and time series analyses of surveillance data on invasive pneumococcal disease (IPD) and X-ray-confirmed pneumonia.

In Mozambique, evidence from vaccine effectiveness studies suggests that the introduction of PCV in 2013 has reduced nasopharyngeal carriage of vaccine-type pneumococcus and reduced the incidence of vaccine-type invasive pneumococcal disease (IPD) and pneumonia.

More specifically, the nasopharyngeal carriage study aimed to estimate the effects of PCV10 introduction on pneumococcal nasopharyngeal carriage among HIV-infected and HIV-uninfected children. The study involved carriage surveys pre- (October 2012–March 2013) and post- (first round October 2014–April 2015; second round October 2015–May 2016) PCV introduction. Based on this study, a direct effect of the vaccine on PCV10 serotype-specific (VT) pneumococcal carriage was observed at the first round (within 18 months) and second round (within 30 months) after PCV introduction.

- A 44% (95% CI 33, 59) reduction in vaccine serotype (VTS) pneumococcal carriage was observed in HIV-uninfected children receiving three doses and 70% reduction (95% CI: 57-78) was observed at the second round.
- A 60% (95% CI 25, 95) reduction in VTS pneumococcal carriage was observed in HIV-infected children receiving three doses at the first round and no additional decline was observed at the second round.
- There was also an early signal of an indirect effect among HIV-infected children, with a 31% reduction (95% CI: 11, 46) among HIV-infected children receiving no PCV doses
- As expected, there was also an increase in pneumococcal carriage of non-PCV10 VTS, including serotypes in PCV13 (i.e., 19A).

Findings from the pneumococcal impact study in Bangladesh suggest some reductions in both the overall transmission of pneumococci and serotypes included in the vaccine (VTS) as measured through population-based nasopharyngeal carriage surveys pre- and post-vaccine introduction. During the pre-vaccine period (before March 2015), a total of 1901 specimens were collected and processed among different age groups. In the post vaccine period, a total of 2060 specimens were collected. There were observed reductions in vaccine-type pneumococcal carriage among children who were age-eligible for PCV of approximately 25% but no change among age-ineligible children. There were increases in non-vaccine serotypes of 17%–20% among age-eligible children.

The reduction in carriage in Mozambique has been accompanied by a reduction in vaccine-type IPD. Based on a Bayesian regression discontinuity design of surveillance data from the Manhiça Demographic Surveillance System (DSS), it was estimated that a significant reduction in vaccine-type IPD of 94% (95% UI: 65.8, 99; Figure 9). There was also a significant reduction in X-ray-confirmed pneumonia (85%, 95% UI: 64.3, 93.7; Figure 10). There was a nonsignificant change in non-vaccine-type IPD (16.3%, 95% UI: -55.4, 203.4; Figure 11).

Figure 9: Reduction in vaccine-type IPD over time in Manhiça DSS

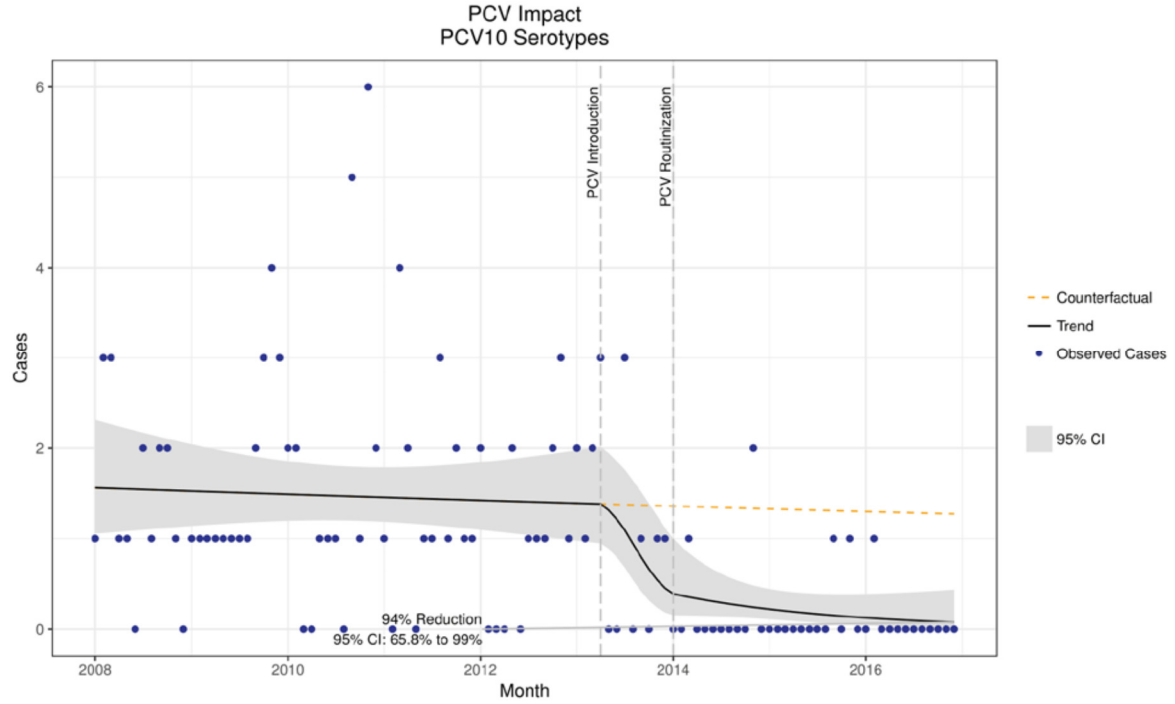


Figure 10: Reduction in X-ray confirmed pneumonia over time in Manhiça DSS

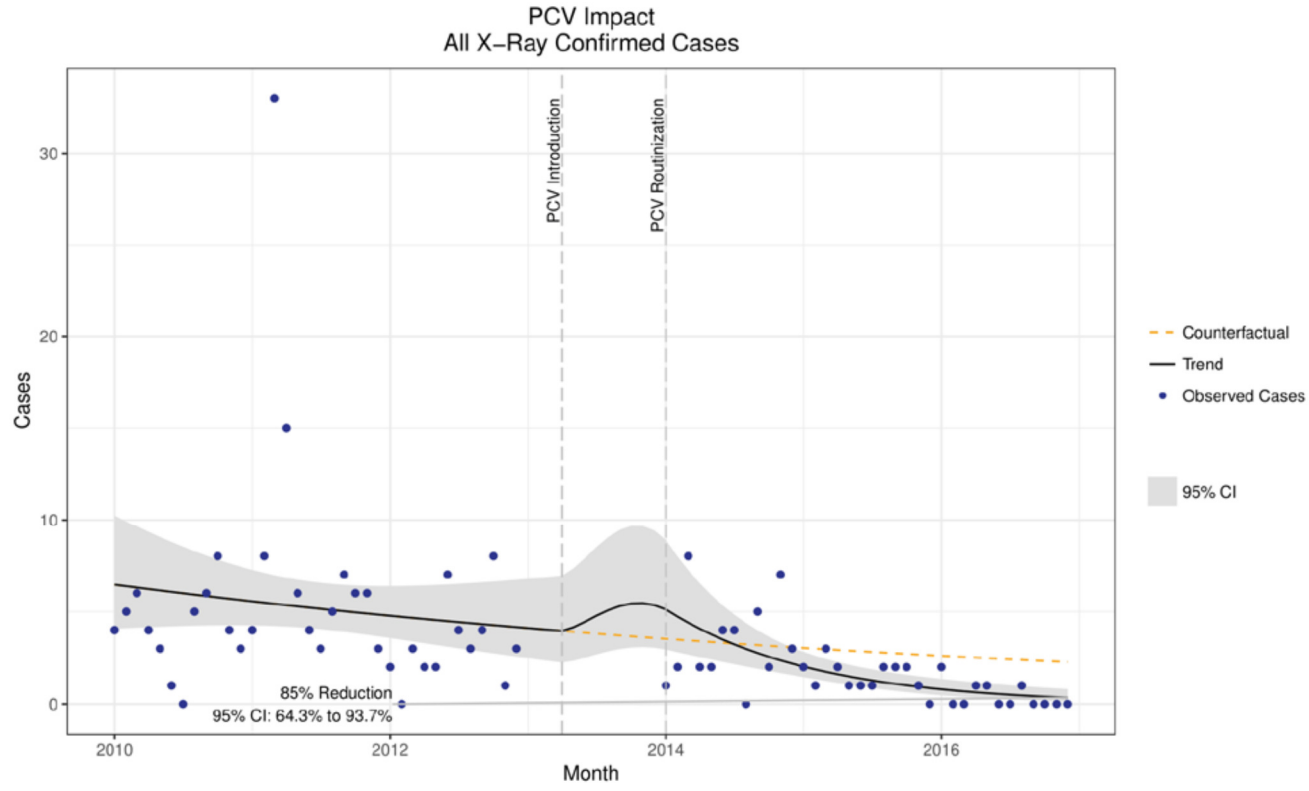
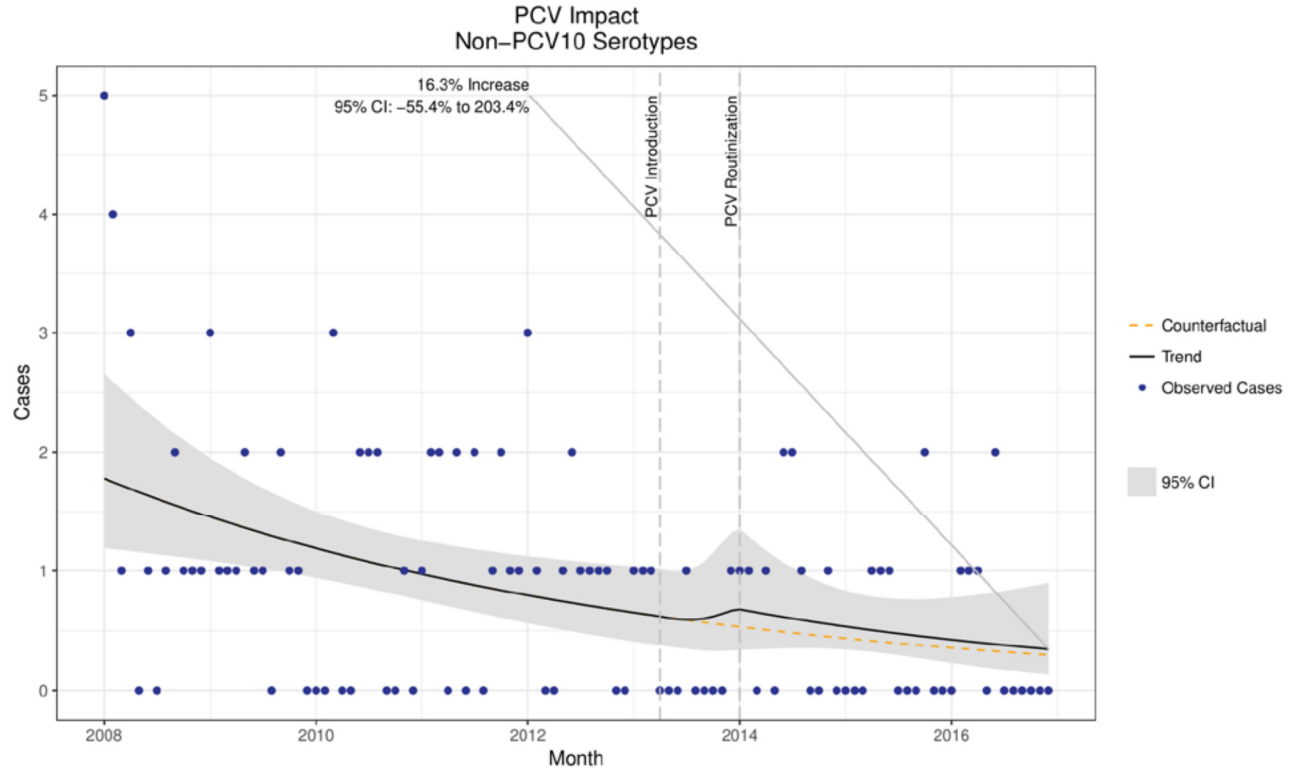


Figure 11: Change in non-vaccine-type IPD over time in Manhiça DSS



The high effectiveness noted in the vaccine effectiveness studies on vaccine-type pneumococcal disease is consistent with the high coverage of the vaccine achieved in Manhiça district (small-area estimates of vaccine indicate that coverage of three-dose PCV in Manhiça district was 89.3%, 95% UI: 85.1, 93.4 in 2016). The high coverage was the result of the rapid routinisation of PCV nationwide, which has been maintained to the present date (see Finding 1 in the 2016 FCE cross-country report for further details). This provides evidence that the high coverage of PCV nationally in Mozambique (88.0%, 95% UI: 86.0, 90.1 in 2016) has led to considerable reductions in vaccine-type pneumococcal disease. Given the similar results seen in reducing pneumococcal disease in other studies in Africa and elsewhere, scale-up of PCV has also likely led to reductions in pneumococcal disease in the other three FCE countries. These findings also highlight the missed opportunities for health impact due to suboptimal coverage of these vaccines, particularly at the subnational level (Figure 6 – 8).

The 2016 report includes a number of key recommendations for the Alliance and for the four FCE countries. As in previous years, the four countries and Alliance partners will continue to implement the key evaluation recommendations in order to address PCV-related implementation bottlenecks and improve programme performance.

The final report is available on the Gavi website, along with an Alliance management response (document jointly developed by Gavi Secretariat and Alliance partners to provide contextual information on ongoing efforts and future actions identified to address the key findings and recommendations), in line with previous annual reports[10].

4.4 Estimates of the impact of pneumococcal vaccination

In 2011, a multidisciplinary group with expertise in mathematical modelling was established by Gavi and the Bill & Melinda Gates Foundation to estimate the impact of vaccination in 73 Gavi-supported countries.

In January 2016 this was formalised into a modelling consortium, the "Vaccine Impact Modelling Consortium", which is managed by a secretariat based at Imperial College London. The consortium aims to foster a community that will continue to increase the quality and robustness of vaccine impact estimates. The consortium continues to base their approach on the methodologies adopted previously by Gavi and the Bill & Melinda Gates Foundation.

Based on current projections (Operational forecast version 15 (OPv15) and WUENIC 2017) completed in late 2017, PCV use is expected to avert approximately 655,000 future deaths among children in Gavi-supported countries by 2020.

4.5 Other special studies on PCV impact

In addition to support for surveillance, Gavi funds a number of special studies to help facilitate evidence-based decision-making for vaccine introduction and impact monitoring to support sustained implementation of pneumococcal vaccines in developing countries. Studies will assess the impact of PCV on health and economic outcomes and monitor potential changes in pneumococcal serotype epidemiology. The status of the historical and ongoing studies and key findings are provided in Annex 5.

The earliest assessments in Gavi countries were supported under the Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) and Vaccine Implementation Technical Assistance Consortium (VI-TAC) grant. These included pneumococcal vaccine effectiveness and impact studies in Kenya and South Africa and economic impact evaluations of pneumococcal vaccines in Ghana and The Gambia, concluded in 2015. The PCV impact study in Kenya will continue through 2018 to monitor potential changes in the epidemiology of pneumococcal disease, including serotype epidemiology.

These Gavi-funded special studies yielded important findings that continue to develop the PCV evidence landscape and to inform policies. Health economic analyses from The Gambia have demonstrated that PCV is likely to be both cost-effective and cost-saving, and to reduce the substantial economic burden borne by families of children with disease. Evidence is also being collected on some novel PCV dosing schedules (for example in Nepal, mentioned in Section 4.1) to determine the most effective schedules to reduce pneumococcal disease burden. In addition to a comprehensive dosing landscape analysis (published in 2014[xxv]) and peer-reviewed publications on vaccine impact in The Gambia, in 2014 the Kenya and South Africa effectiveness studies produced several key publications highlighting their results. This included herd protection with reductions in transmission of the disease by reducing nasopharyngeal colonisation of vaccine-serotype strains in both vaccinated and unvaccinated individuals as well as reductions in antibiotic-resistant strains of the disease in very young children. Overall, findings illustrate PCV effectiveness against vaccine-specific serotypes as well as protection against PD among children for vaccine and non-vaccine serotypes. Results from South Africa have shown that routine use of PCV is effective against presumed bacterial pneumonia at a magnitude similar to that measured in randomised controlled trials. More recently, results from The Gambia indicate that cases of childhood invasive forms of pneumococcal disease are reduced by more than half with the introduction of PCV.

In June 2013, Gavi issued a RFP for the "Evaluation of PCV Effectiveness in Asia" to assess the impact of PCV among Gavi-supported countries in Asia that had introduced the vaccine at an early stage. On

[xxv] http://journals.lww.com/pidj/toc/2014/01002

the recommendation of an adjudication committee, Gavi commissioned three service providers (Aga Khan University, Murdoch Children's Research Institute and Oxford University) to conduct PCV impact studies in Pakistan, Nepal and Lao People's Democratic Republic. These studies are assessing a range of outcomes, including disease effects (e.g. IPD, hospitalised pneumonia and serotype-specific disease impact), effects on agent transmission (nasopharyngeal carriage), antibiotic resistance, economic benefits and long-term sequelae. Data collection for these studies began in late 2013 and early 2014 and final results are anticipated in 2016-2018. A fourth study, to assess the impact of phased PCV introduction on the incidence of radiological pneumonia in Mongolia, has been commissioned. The collection of pre-introduction data began in 2015. Final results are anticipated in 2018 due to a delayed timeline for vaccine use in the study setting.

Gavi contracted the US Centers for Disease Control and Prevention (CDC) to assist Burkina Faso in assessing the impact of PCV introduction on pneumococcal meningitis and potential changes in circulating strains. Final results are anticipated in 2018.

As mentioned previously, pneumococcal vaccine effectiveness and impact studies were conducted in Bangladesh and Mozambique as part of the FCE work, which ended in 2016. This included population-based assessment of changes in agent transmission and impact of PCV on IPD and X-ray confirmed pneumonia in Mozambique. Gavi is currently in contact with researchers at multiple sites to discuss continuation of high-performing study sites to evaluate the long-term impact of PCV. These assessments in selected epidemiologic settings will help to further assess the impact of vaccination on disease burden and serotype epidemiology.

5. Media and communications

Increasing the visibility of the pneumococcal AMC through traditional and new media, including social media, remains an important goal for Gavi's communications team.

5.1 Communications overview 2017

On World Pneumonia Day 2017, Gavi secured coverage in media outlets worldwide, highlighting the critical impact of the AMC on the numbers of lives saved and children immunised. The AMC was promoted through a dedicated feature story on gavi.org as well as on Twitter, Facebook and vaccineswork.org. The AMC was also highlighted in both the printed and online versions of Gavi's Annual Progress Report.

In his end-of-year letter, produced by Gavi's content team, in December 2017 Gavi's CEO underlined that, thanks to the AMC, 109 million children in Gavi-supported countries had been protected against the most common cause of pneumonia – corresponding to half a million prevented deaths.

The Gavi media team also issued a press release announcing the introduction of PCV into India's routine immunisation programme, securing positive coverage in The Hindu, Indian Express, Economic Times and Times of India – the world's highest circulation English language newspaper.

Gavi continued to highlight and explain the AMC in relevant communications materials throughout 2017. In addition to sharing updated material, Gavi ensured that appropriate speaking points were incorporated into the speeches of Alliance spokespeople at vaccine launch ceremonies and other events.

5.2 Communications outlook for 2018

2018 will be particularly important to Gavi, with the Gavi mid-term review (MTR) meeting taking place at the end of the year. The MTR gives Alliance partners – particularly donors – a chance to take stock of Gavi's performance half-way through the current strategy period (2016–2020). The meeting will be an important opportunity to showcase the AMC, and Gavi will integrate AMC messaging into all relevant communication materials and seek to profile the AMC mechanism to media.

5.3 Donor and stakeholder communication

Continuing in 2017, additional efforts were made to provide regular updates to AMC stakeholders, through AMC stakeholder calls and an annual AMC stakeholder meeting. These provided opportunities to exchange information and obtain input from stakeholders on key issues. Topics included consultation on AMC scenarios, strategic demand forecasts and implications, changes in the AMC supply landscape, progress on AMC targets and supply and implementation of vaccines.

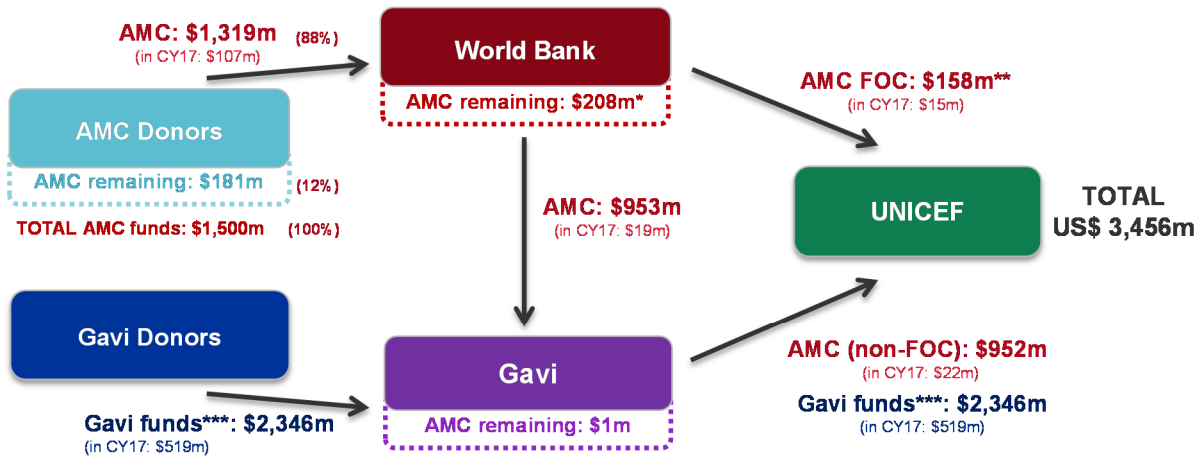
6. Financial activities

The financial structure of the AMC remains unchanged from previous years. It is composed of the six AMC donors (the Bill & Melinda Gates Foundation, Canada, Italy, Norway, the Russian Federation and the United Kingdom), the World Bank, Gavi, UNICEF, Gavi-supported countries and eligible vaccine manufacturers.[xxvi]

In summary, the process works as follows: the AMC donors, who have entered into grant agreements totalling US$ 1.5 billion, make annual payments to the World Bank. In turn, the World Bank holds the funds in trust for Gavi on behalf of the donors and confirms quarterly to Gavi the amounts being held for the AMC. To access these funds, Gavi submits a quarterly funding request to the World Bank for vaccine purchase payments in the upcoming quarter. The request is based on the most recent demand forecast and on the quarterly cash management plan submitted by UNICEF to Gavi.

Prior to procuring vaccines from AMC-eligible vaccine manufacturers, UNICEF sends a cash disbursement request for the necessary AMC and Gavi funds. Upon receipt of this request, Gavi transfers the requested funds into a Gavi-held procurement bank account. The funds can only be withdrawn from the account by UNICEF. Gavi-supported countries are obliged to co-finance the pneumococcal vaccine in accordance with Gavi's standard co-financing policy. Countries make their co-finance payments directly to UNICEF.

Figure 12. Summary of AMC financial process flow and funds disbursed (inception to 31 December 2017)



'CY17': Calendar Year 2017
** Includes US$ 26.9m of Canadian Initial Funds, not yet available for disbursement*
*** US$ 15m in CY17 was initially disbursed directly to Gavi who subsequently transferred it to the UNICEF FOC account (refer to text in Annual Report for further details)*
**** Allocated from general funds to pay for tail price portion of vaccine & related fulfilment costs*

Source: Gavi Secretariat. Note: some numbers may appear not to add due to rounding.

Details are provided in sections 6.1 - 6.3 below.

[xxvi] *Refer to AMC Annual Report 12 June 2009-31 March 2010 page 28-29 for the detailed description of the financial structure.*

6.1 Donor funds – inflow to the World Bank

The six donors are categorised into two groups. The first, known as "fixed-schedule donors" (the Bill & Melinda Gates Foundation, Italy and the Russian Federation) make annual payments to the World Bank in accordance with predetermined payment schedules set out in the individual grant agreements. The second, known as "on-demand donors" (Canada, Norway and the United Kingdom), make payments in response to requests from the World Bank based on forecasts received from Gavi to meet specific funding needs. The three fixed-schedule donors have together pledged a total of US$ 765 million to the AMC. The three on-demand donors have pledged US$ 735 million (see Table 7). These pledges combined bring the total available AMC funds to US$ 1,500 million, funds that are dedicated solely to the procurement of the pneumococcal vaccine.

6.2 Donor contribution receipts

As of 31 December 2017, the World Bank had received a total of US$ 1,319 million from AMC donors (see Table 7 below). The Bill & Melinda Gates Foundation, the Government of Canada and the Norwegian Ministry of Foreign Affairs have all paid the total amounts that they had committed to pay under their respective grant agreements.

Table 7. Grant receipts from AMC donors, as of 31 December 2017 (in US$ millions)

	Contribution Amount	Paid-in Amount	Remaining Balance
Fixed Schedule Donors			
Bill & Melinda Gates Foundation	50	50	-
Italy	635	534	101
Russia	80	64	16
sub-total:	**765**	**648**	**117**
On Demand Donors			
Canada	200	200	-
Norway	50	50	-
UK	485	422	63
sub-total:	**735**	**672**	**63**
Total	**1,500**	**1,319**	**181**

Source: The World Bank

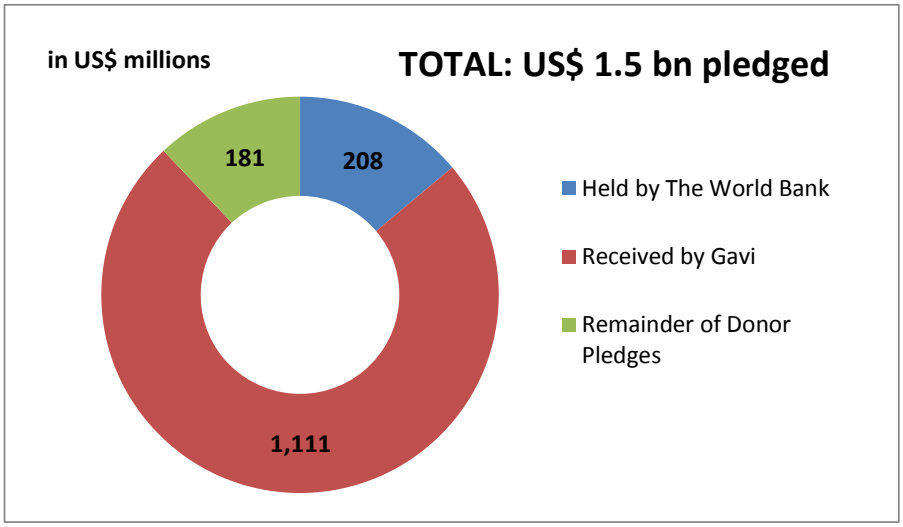
The World Bank has recorded the AMC donor funds in its financial statements as designated assets, with a corresponding liability to provide the funds to Gavi for the purchase of pneumococcal vaccines subject to the terms and conditions of the AMC. To enhance the predictability of AMC funding, the World Bank committed to transfer funds to meet the AMC-funded portion of the vaccine price, upon request from Gavi in accordance with the AMC terms and conditions and with the schedule of donor payments, whether or not donors actually pay on schedule or default. The World Bank also provides financial management and administrative services with respect to donor contributions and AMC disbursements[xxvii].

[xxvii] As agreed between stakeholders, from 2016 onwards any shortfall in investment income to cover these administrative fees, beyond the amount provided by the UK per its AMC grant agreement, will be covered by Gavi

6.3 AMC donor funds – inflow to Gavi

As of 31 December 2017, the World Bank had disbursed US$ 1,111 million (US$ 953 million to Gavi and US$ 158 million to the UNICEF procurement account relating to the firm order commitments (FOC). Of the US$ 1,111 million, US$ 35 million[xxviii] was disbursed during 2017, all of which was disbursed to Gavi. This leaves a balance of US$ 208 million held by the World Bank, of which US$ 181 million is available for immediate disbursement to Gavi (see Figures 12 and 13).

Figure 13. Status of AMC donor funds, as of 31 December 2017 (in US$ millions)



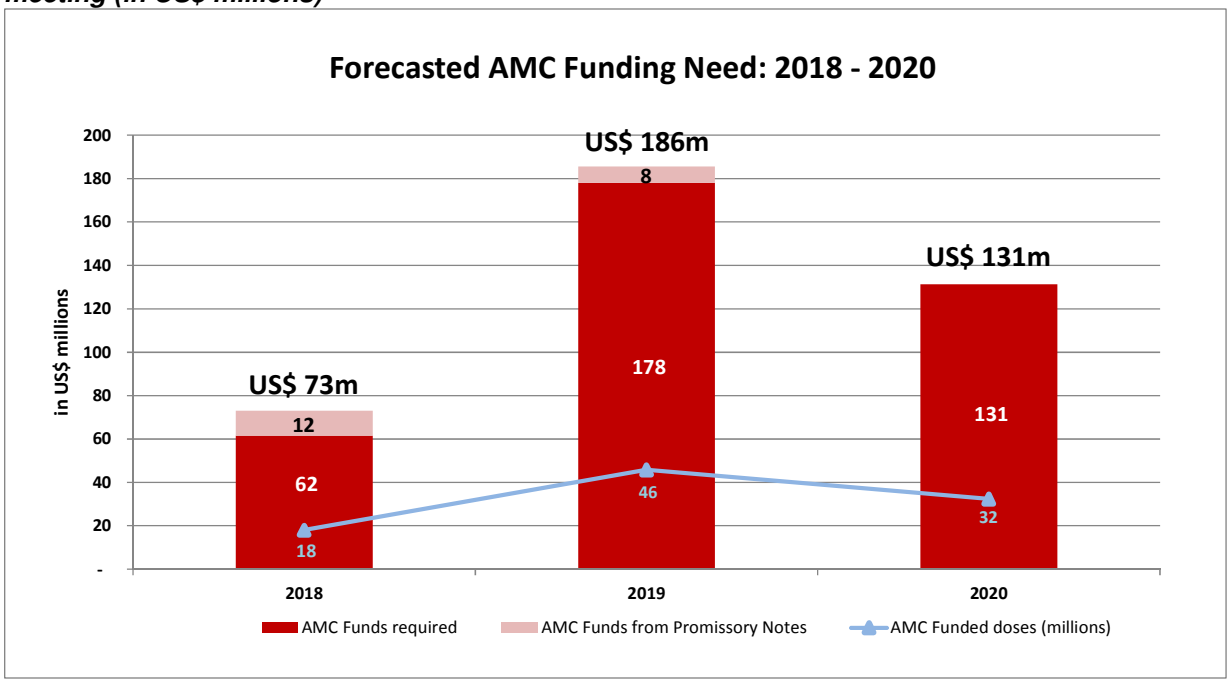
Source: Gavi Secretariat

As part of the reporting process, Gavi regularly submits a semi-annual estimate (SAE) to the World Bank, which provides forecasted demand for pneumococcal vaccine doses and corresponding AMC funding on a rolling three-year basis. Gavi submitted one SAE in June 2017 with forecasted cost for the 2017-2019 time period.

At the November 2017 Gavi Board meeting, the financial forecast presented included approximately US$ 390 million of AMC funds required for the period of 2018-20. This equates to approximately 100 million doses of the pneumococcal vaccine. During post-Board discussions with AMC donors and the World Bank, the AMC Secretariat highlighted the dependencies underpinning key forecast assumptions regarding PCV demand and AMC supply. As such, an updated AMC financial forecast will be prepared in March 2018 to reflect the best known information at this point and this updated forecast will be submitted as part of the Semi-Annual Estimate process.

[xxviii] *This amount includes US$ 15 million for the 2018 portion of the AMC FOC requirement under the pending new supply agreement (s) (to be signed in Q1 2018). Given the required sequencing of FOC payments prior to supply agreement signature, Gavi requested the IBRD to transfer these AMC funds via the regular Quarterly Funding Request process and subsequently transferred the funds directly into the FOC account.*

Figure 14. Latest forecast of AMC funds needed, as presented at the November 2017 Gavi Board meeting (in US$ millions)



Source: Gavi Secretariat Nov-17 Board Forecast. Note: cash flow basis; some numbers may appear not to add due to rounding.

6.4 UNICEF procurement: outflow of AMC donor funds

During 2017, US$ 556 million was disbursed to UNICEF for the purchase of pneumococcal vaccines. Of this amount, US$ 37 million pertains to the AMC-funded portion of the vaccine purchase[xxviii]. The remaining US$ 519 million was allocated from general Gavi funds to pay for the tail price portion of the vaccine purchase and related fulfilment costs[xxix]. Total funds include the transfers relating to the AMC-funded portion of the minimum purchase obligation, also known as the FOC, on a pending supply agreement amounting to US$ 15 million (see Figures 12 and 15).

Six supply agreements have been signed under the AMC programme as of 31 December 2017 (a pending agreement following the fourth call for supply offers is expected to be signed during Q1 2018). As of 31 December 2017, AMC funding allocated under all six existing agreements was fully disbursed, and US$ 15 million for the pending agreement was also disbursed. The remainder of AMC funding allocated under this fourth call is expected be disbursed during 2018–2020.

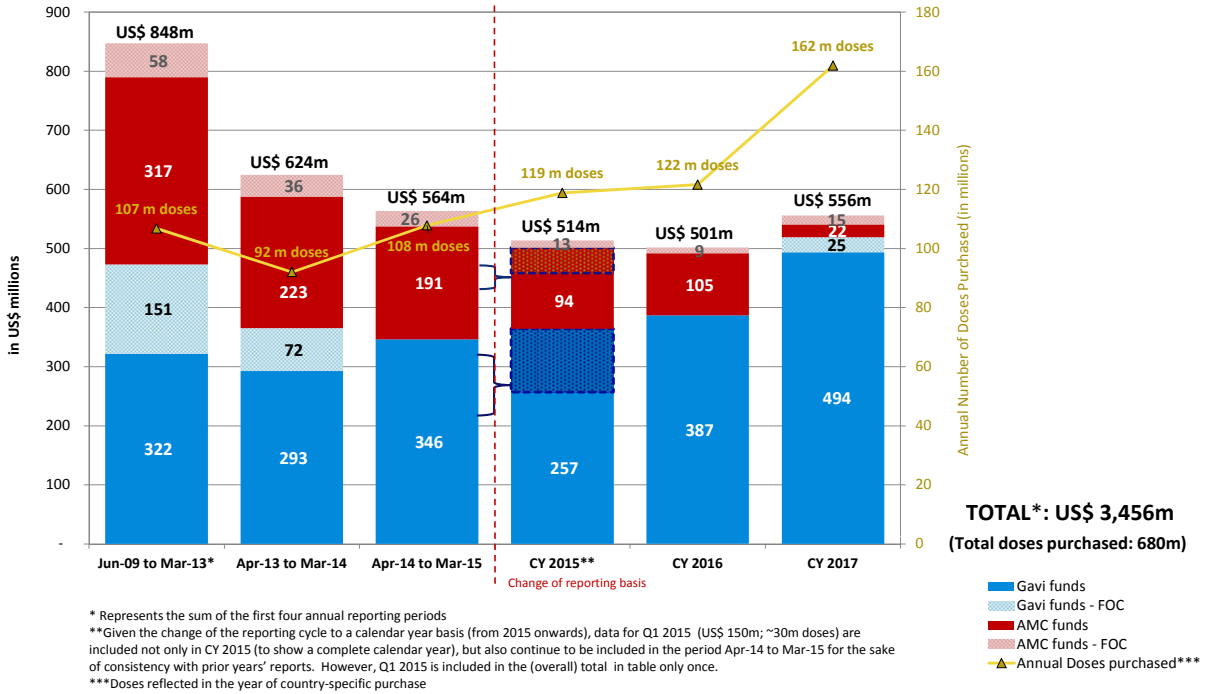
In total, as of 31 December 2017 US$ 406 million has been transferred to Gavi's "UNICEF procurement account" regarding the FOCs for the six existing signed (and one pending) supply agreements. Of this amount, US$ 248 million represents the Gavi-funded portion of the FOCs, while US$ 158 million represents the AMC-funded portion of the FOCs. Of the US$ 406 million transferred, US$ 365 million (approximately 90%) has been utilised. This represents the draw-down of already transferred FOC funds relating to all supply agreements.

[xxix] *Fulfilment costs are the extra costs incurred in supplying vaccines (estimated at US$ 0.08 per dose during the 2016-2020 period), in addition to the cost of the vaccine itself. These costs typically include the cost of syringes, safety boxes and freight.*

Figure 15. Total cash disbursements to Gavi's "UNICEF procurement account" (from inception to 31 December 2017, in US$ millions)

in US$ millions

Funding Source	Jun-09 to Mar-13	Apr-13 to Mar-14	Apr-14 to Mar-15	CY 2015** Q1	CY 2015** Q2 - Q4	CY 2015** Total	CY 2016	CY 2017	TOTAL	of which: AMC / Gavi	of which: FOC	of which: Non-FOC
AMC Funds - FOC	58	36	26		13	13	9	15	158	1,110	158	
AMC Funds	317	223	191	43	94	137	105	22	952			952
Gavi Funds - FOC	151	72	-	-	-	-	-	25	248	2,346	248	
Gavi Funds	322	293	346	107	257	364	387	494	2,098			2,098
TOTAL:	848	624	564	150	364	514	501	556	3,456		406	3,050



* Represents the sum of the first four annual reporting periods
**Given the change of the reporting cycle to a calendar year basis (from 2015 onwards), data for Q1 2015 (US$ 150m; ~30m doses) are included not only in CY 2015 (to show a complete calendar year), but also continue to be included in the period Apr-14 to Mar-15 for the sake of consistency with prior years' reports. However, Q1 2015 is included in the (overall) total in table only once.
***Doses reflected in the year of country-specific purchase

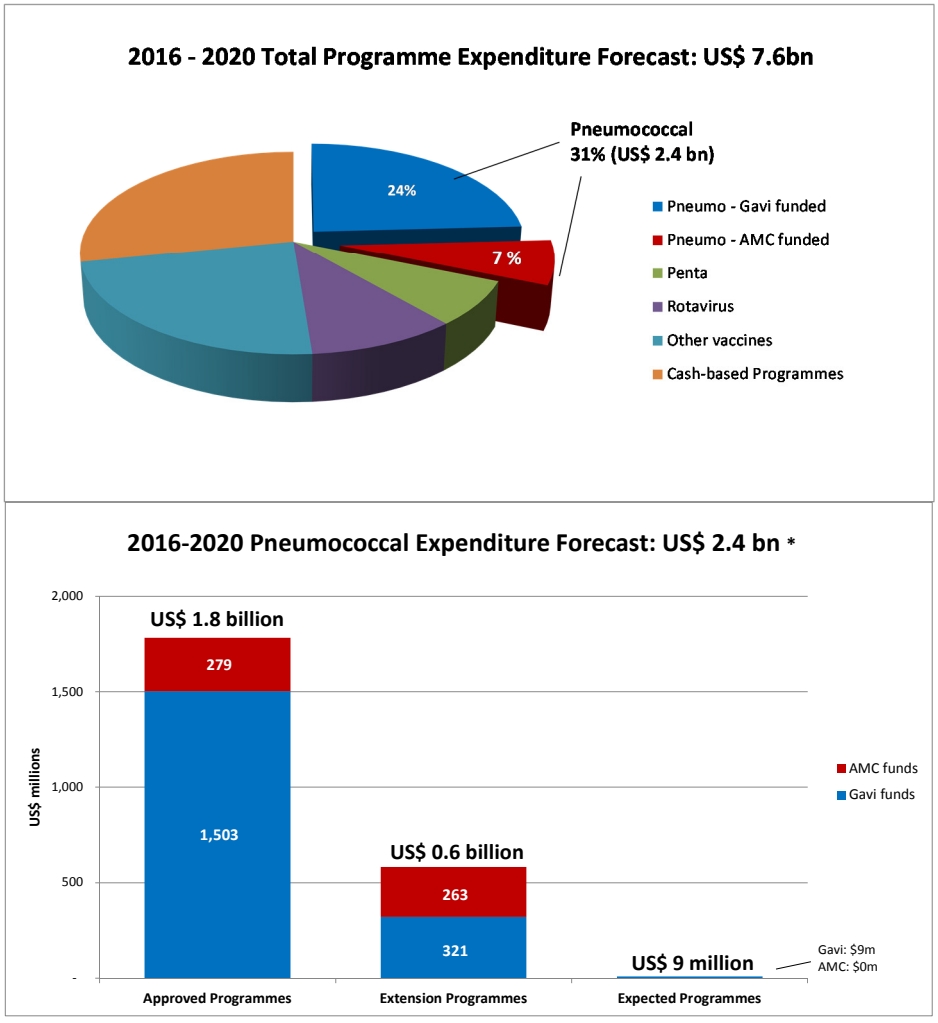
Source: Gavi Secretariat. Note: For the latest four reporting periods (April 14–March 15, CY 2015, CY 2016 and CY 2017) the total numbers of doses have increased from the previous reporting periods while the overall amounts paid have decreased. This is due to a higher proportion of doses being procured under the Gavi-funded tail price only. Some numbers may appear not to add due to rounding.

6.5 The AMC and Gavi's long term financial forecast

At the November 2017 Gavi Board meeting, an update of Gavi's long-term financial forecast was presented[xxx]. Total programme expenditures are projected at US$ 7.6 billion for the 2016-2020 period, of which pneumococcal vaccine expenditures are anticipated to amount to US$ 2.4 billion, representing approximately 31% of total programmatic expenditures (see Figure 16).

For the 2018 and 2019 programmatic years, 49 countries had been approved to receive financial support for the procurement of the pneumococcal vaccine. The 2018 commitments amount to US$ 488 million, while 2019 commitments amount to US$ 349 million. The commitments are included as part of the total 2016-2020 expenditure forecast, presented in Figure 16 below.

Figure 16. AMC within total Gavi forecasted expenditure 2016-2020



Source: Gavi Secretariat

** Approved programmes are those approved by the Gavi Board. Extension programmes are forecasted continuations of those programmes, subject to future approval. Expected programmes are defined as those that are forecasted based on Operational Forecast v15.0 and the latest supplier assumptions.*

[xxx] *November 2017 Board paper entitled "Board-2017-Mtg-3-Doc 05 Financial update including forecast"*

Challenges and future priorities

The implementation of the pilot pneumococcal AMC has been very successful to date, with high demand and uptake at country level. Some challenges remain nonetheless: there has been a decrease in new country demand in the past 24 months; despite high vaccination coverage overall. A small subset of countries are facing PCV coverage challenges; and countries are starting to transition out of Gavi support and will start to fully self-finance the PCV programme. Moving forward, key priorities include supporting the remaining two countries that have been approved for but not yet introduced pneumococcal vaccine, and strengthening health systems and decision-making processes in those that have not yet applied to access PCV through the AMC. For countries that have already introduced the vaccine, the priorities remain to sustain PCV implementation and improve coverage. As countries start to transition out of Gavi support, measuring impact continues to be key, as is reducing the price of pneumococcal vaccines. Ensuring proper balance of supply and demand also remains a key priority.

Supporting country introductions and product switches

The Alliance is focusing its efforts on ensuring that the remaining approved countries are ready to introduce pneumococcal vaccines in the 2018-19 period, and that technical assistance is provided where appropriate to ensure high quality of implementation. Alliance partners continue to closely monitor country introduction status and coordinate technical assistance activities, with the aim of identifying and resolving issues with the support of partners at the country level. Lessons drawn from these contexts can inform future pneumococcal vaccine introductions, as well as the roll-out of other vaccines.

For countries that have already introduced and are aiming to switch to a different product, Gavi and its partners will continue to monitor and support the operational and strategic aspects of the switches. In doing so, they will pay particular attention to the programmatic challenges and encourage an informed and evidence-based switch request from countries.

Strengthening health systems and routine immunisation

Supporting the application, introduction and implementation of pneumococcal vaccines in the AMC-eligible countries that have not yet applied also remains a key priority, particularly with regard to the seven countries that remain Gavi eligible. Four of the seven countries are not eligible to apply due to the >70% DTP3 coverage eligibility criterion. In these countries, the current focus of the Alliance is on strengthening the routine immunisation system in the short term. This will help ensure that the vaccine can be introduced as soon as possible to address the high pneumococcal disease burden.

Sustaining implementation and ensuring high coverage

The Gavi-wide efforts on strengthening of health systems and routine immunisation are also key to addressing the challenges that some of the AMC-eligible countries are facing with PCV implementation. In addition, PCV implementation will continue to be closely monitored to identify issues in coverage performance in specific countries and/or settings. Efforts will also be made to better leverage PCV implementation towards improving coverage and equity of other vaccines, given the high demand for this vaccine at country level.

Ensuring sustainability for transitioning and transitioned countries

So far, the AMC procurement mechanism has achieved a ”tail-price” reduction of, at most, 14% compared with the initial ”tail-price” cap of US$ 3.50/dose. The current vaccine price may still be challenging for sustainable pneumococcal vaccination, especially as countries start to transition out of Gavi support. As outlined in the

pneumococcal vaccine supply and procurement roadmap, a key priority objective is to significantly reduce the weighted average price of the "tail price" in the short to medium term (2015–2020). Sustainability is also being addressed through Gavi's 2016-2020 strategy and PEF, particularly through the strategic focus areas for sustainability and political will.

Demonstrating the impact of PCV is also key to ensuring sustainability of pneumococcal vaccine programmes after transition. The Alliance's focus on gathering evidence on vaccine effectiveness and impact will continue going forward through Gavi-supported special studies. An AMC outcomes and impact evaluation to assess the achievements of the AMC pilot took place in 2015 and was published in early 2016.

Managing supply and demand

Thanks to the AMC, manufacturers have entered into 10+ year supply agreements, which is unique for a Gavi-supported vaccine. This provided assurance that manufacturers would invest in scaling up production capacity and that supply would be available to meet long-term demand from countries. While the scaling up of supply has so far been managed with limited interruptions by suppliers and flexibility to supply quantities across years, the coming years will require scaling up of production capacity in order to meet additional country demand. This will demonstrate the ability of the limited supplier base to continue to meet the requirements. As current demand exceeds 150 million doses annually, the limited supply base remains a risk to implementation. The Gavi Secretariat will continue to work closely with UNICEF's Supply Division to monitor the supply situation and manage the balance between supply and demand.

Conclusion

Country demand for pneumococcal vaccines has been unprecedented, with close to 81% of the 73 AMC-eligible countries already approved for support and 58 country introductions completed as of 31 December 2017. Third-dose PCV coverage increased by 6 percentage points from 2015 to 2016, reaching 41% in 2016. Based on current projections through 2020, PCV use will avert an estimated 655,000 future deaths among children vaccinated in Gavi countries.

Despite this unparalleled success, as countries enter the pathway to transition out of Gavi support, programme sustainability becomes an area of increased focus for the Alliance. Gavi will continue to support this transition pathway in order to ensure that the PCV programme, as well as other vaccine programmes, are programmatically and financially sustained in future years.

Annex 1 – Membership of the AMC Secretariat in 2017

Team	Staff member
Vaccine Implementation	**Veronica Denti** Senior Programme Manager
Resource Mobilisation	**Sebastian Meaney** Head, UK Strategy, Resource Mobilisation
Finance	**Minzi Lam Meier** Head, Financial Forecasting & AMC **Eric Godfrey** Senior Manager, Financial Forecasting & AMC
Monitoring & Evaluation	**Hope Johnson** Head, Outcomes & Impact
Public Policy Engagement	**Susan Brown** Director
Communications	**Frédérique Tissandier** Head, Global and Country Media
Market Shaping	**Edward Baker** Senior Specialist, Strategy Development & Tenders **Anna Osborne** Senior Manager, Strategy Development & Tenders
Legal	**Helene Gaudin de Villaine** Associate Legal Counsel

Source: Gavi Secretariat, as of 31 December 2017

Annex 2 – Summary of previous call for offers

First AMC supply agreements

The first procurement cycle for the supply of pneumococcal vaccines under the AMC was initiated with the issuance of a Call for Supply Offers on 4 September 2009. UNICEF SD received four offers in response to this first call. In March 2010, UNICEF SD entered into Provisional Supply Agreements (PSA) with two manufacturers – GlaxoSmithKline Biologicals (GSK) and Pfizer Inc. – the only companies whose Product Summary File (PSF) had been accepted by WHO for prequalification review. Each manufacturer committed to supply 30 million doses annually, with GSK starting in January 2012 and Pfizer Inc. in January 2013, and continuing for 10 years. Consequently, 15% of AMC funds were allocated to each manufacturer under this procurement round.

In addition to the above-mentioned PSAs, GSK and Pfizer agreed to provide in total 7.2 million, 24.2 million and 20 million doses in 2010, 2011 and 2012, as part of the AMC Capacity Development Period3F[xxxi] Both suppliers have subsequently communicated the ability to increase such early supplies, should there be demand and based on demand, quantities on contracts have been increased by 7.8 million doses in 2011 and 4 million doses in 2012. The total quantities on these contracts with each supplier remain 300 million doses each, only the distribution over the years has changed.

Both GSK and Pfizer's products received WHO prequalification in 2010 and were deemed AMC Eligible by the AMC Independent Assessment Committee (IAC) respectively on 16 April 2010 and 23 August 2010. This was communicated to suppliers with a copy to UNICEF on 6 May 2010 and on 23 August 2010. As a result the PSAs automatically turned into effective Supply Agreements, allowing the procurement of those two vaccines.

Second AMC supply agreements

Following the publication of SDF v3.0 in March 2011, Gavi, in consultation with UNICEF, decided to issue a new Call for Supply Offers for the procurement of pneumococcal vaccines that was published on 8 April 2011 with a maximum target of 74 million doses by 2016. UNICEF SD received four offers by 6 May 2011.

In the week starting 12 December 2011, UNICEF as procurement agency on behalf of Gavi confirmed the entry into new supply agreements with GSK and Pfizer Inc. Per the timeline set out in the AMC legal agreements, the supply agreements should have been finalised by 9 September 2011. However, UNICEF SD and Gavi agreed to delay the procurement timeline in order to be able to take into account any new demand recommended for approval by the IRC following the May 2011 round in the award recommendations.

Both GSK and Pfizer Inc. will start supplying 18 million doses annually (Annual Supply Commitment) from 2014 for a period of 10 years, up to a maximum of 180 million doses. The tail price for this agreement is US$ 3.50. Consequently 9% of the AMC funds are allocated to each of the two manufacturers under this agreement according to the AMC terms and conditions. The total doses awarded to GSK and Pfizer Inc. under both supply agreements amounts to 48 million annually.

[xxxi]The capacity development period is defined as the period during which suppliers develop dedicated manufacturing capacity to serve Gavi-eligible countries under their respective Supply Agreements.

As part of the supply agreements, manufacturers have agreed to provide in total 30 million doses in 2012 and 2013 as part of the AMC Capacity Development Period.

UNICEF opted not to award the full quantities of the Gavi Strategic Demand Forecast for 2016 in response to this second tender. 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. It should be noted, however, that 100% of the quantities offered for supply in 2012-2013 in response to tenders have been contracted. Furthermore, UNICEF considered that the unexpected ramp up of demand led to a faster than expected commitment of the AMC funding and that it would be prudent to pause to allow for a discussion with AMC stakeholders before proceeding to commit more than 50% of AMC funding at this early stage.

Fifty-two percent of the AMC funds corresponding to US$ 780 million remained unallocated following the completion of the second Call for Offers and will be available for successive rounds of calls for offers.

Third AMC supply agreements

Following the publication of the third Call for Supply Offers on 27 August 2012, Gavi announced two new supply agreements for the supply of pneumococcal conjugate vaccines under the Advance Market Commitment (AMC). These new supply agreements include the first decrease to the AMC Tail Price as well as additional short term supply to support the accelerated introduction in a number of countries.

On 24 July 2013, UNICEF, in its capacity as Gavi's procurement agency, confirmed its entry into new supply agreements with GlaxoSmithKline Biologicals (GSK) and Pfizer Inc.

GSK will start supplying 24 million doses annually (Annual Supply Commitment) from 2015 for a period of 10 years. Consequently 12% of the AMC funds are allocated to this manufacturer under this agreement according to the AMC terms and conditions. The tail price for this agreement is US$ 3.40 from 2013 and US$ 3.05 from 2017. The total doses awarded to GSK under its three supply agreements amounts to 720 million.

Pfizer will start supplying 26 million doses annually (Annual Supply Commitment) from 2016 for a period of 10 years. Consequently 13% of the AMC funds are allocated to this manufacturer under this agreement according to the AMC terms and conditions. The Tail Price for this agreement is US$ 3.40 in 2013; US$ 3.30 from 2014; US$3.05 from 2017 for the multi-dose vial only and US$2.95 for the multi-dose vial only from 2018 onwards. The total doses awarded to Pfizer under its three supply agreements amounts to 740 million.

In addition, Pfizer has agreed that the reduced Tail Prices outlined above can be applied to all doses remaining to be procured under its first and second supply agreements. To access Pfizer's reduced Tail Price, Gavi has provided a financial guarantee for the Tail Price component, equivalent to 80% of the total contracted quantities in the period between 2013 and 2015. The standard AMC commitments of 20%, 15% and 10% in the first three years of each supply agreement will be counted towards the financial guarantee. It has also been agreed to accelerate the procurement of doses at US$ 7.00 under the new supply agreement to ensure that all doses at that price will have been procured before 2016.

As part of these supply agreements, GSK and Pfizer Inc. have agreed to provide a total of 42 million doses during the AMC capacity development period.

UNICEF has opted not to award the full quantities of the Gavi Strategic Demand Forecast for 2017 in response to this third tender and has only awarded quantities to meet the approved demand. Quantities have been reserved for award at a later point in time 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 of accessing lower tail prices through future offers.

27% of the AMC funds corresponding to US$ 405 million remain unallocated and will be available for later calls for offers.

Annex 3 – Membership of the PROWG in 2017

The Pneumococcal & Rotavirus Operational Working Group (PROWG) is a sub-team of the Vaccine Implementation Management Team. Members are as follows:

Organisation	Members
Gavi Secretariat	**Veronica Denti (August 2016 – present)** Senior Programme Manager, Vaccine Implementation, Country Programmes **Melissa Ko** (March 2015 – July 2016) Senior Programme Manager, Vaccine Implementation, Country Programmes **Cassandra Quintanilla** (November 2016 – July 2017) Vaccine Programme Manager, Vaccine Implementation, Country Programmes **Sara Sá Silva** (January – November 2016) Vaccine Programme Manager, Vaccine Implementation, Country Programmes **Mugen Ujiie** (November 2016 – April 2017) Senior Programme Manager, Vaccine Implementation, Country Programmes
PATH	**Allison Clifford** Senior Communications Officer, Vaccine Development
JHU	**Julie Buss Younkin** Scientific Communications Manager, International Vaccine Access Center **Molly Sauer** Deputy Director, Policy, Advocacy & Communications, International Vaccine Access Center
UNICEF Programme Division	**Richard Duncan** Senior Immunisation Specialist, Health Section **Ben Hickler** Communication for Development (C4D) Specialist, Routine Immunisation and New Vaccines, Health Section
UNICEF Supply Division	**David K. Mutuerandu** Contracts Manager – PCV, Rotavirus **Abraham Kofi Ntow** Contract Specialist – PCV

	Gideon Chelule Contracts Manager – Rotavirus vaccine
WHO	**Adam Cohen** Immunization, Vaccines and Biologicals, IVB/EPI **Hemanthi Dassanayake-Nicolas** Technical Officer, Strategic Information Group, EPI **Ikechukwu Udo Ogbuanu** Medical Officer, New Vaccines, EPI
CHAI (new in 2017)	**Yann LeTallec** Director Global Vaccine **Julia Roper** Associate, New Vaccine Introductions (PCV & Rotavirus lead)

Source: PROWG Terms of Reference, as of 31 December 2017

Annex 4 – Membership of the Independent Assessment Committee in 2017

George Amofah
Part-time Lecturer, School of Public Health, University of Ghana, Legon; Retired Deputy Director General, Ghana Health Service

Claire Broome (Chairperson)
Adjunct Professor Division of Global Health, Rollins School of Public Health Emory University Atlanta, Georgia, USA

Arthur Elliott
Senior Program Manager, Vaccines and Anti-Viral Agents, US Department of Health and Human Services, USA

Bernard Fanget
CEO, Bernard Fanget Consulting; and VP R&D and Pharmaceutical Development, Neovacs, France

Shahnaaz Kassam Sharif
Chief Medical Specialist, Senior Deputy Director Medical Services, Head of Preventive and Promotive Health Services, Ministry of Health, Kenya

Mary Kitambi
Public Health Specialist, Ministry of Health and Social Welfare Tanzania

Soonman Kwon (Vice Chairperson)*
Director, Brain Korea Centre for Aging and Health Policy, South Korea
*resigned in October 2017

Halvor Sommerfelt
Professor of Epidemiology, Centre for International Health, and Director, Centre for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, and Senior Consultant, Norwegian Institute of Public Health, Norway

Vitaly Zverev
Director, I.I. Mechnikov Institute of Vaccine Sera under the RAMS, Russia

Source: Gavi Secretariat, as of 31 December 2017

Annex 5 – Summary of Gavi investments in surveillance PCV special studies

Gavi invests annually approximately US$ 15-22 million in surveillance and targeted assessments across the vaccine portfolio to inform evidence-based decision making, document programme outcomes and impact and generate learning to inform programme improvements from a subset of settings predominantly through primary data collection. The table below summarises recent Gavi commissioned investments in surveillance and targeted assessments for PCV.

Study	Status of Activities	Key findings
A. Surveillance		
WHO Coordinated global surveillance networks for Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) **Hib Initiative supported IB-VPD surveillance in India and Pakistan**	Ongoing Completed	With guidance from an informal Technical Advisory Group (ITAG) and external partners, WHO continues to support countries in improved surveillance data quality, analysis and interpretation and enhanced country ownership and transition of surveillance to support country monitoring of burden of disease, short- and long-term impact of new vaccine introductions (e.g., Hib, PCV, Meningococcal A), and leveraging the surveillance platform to monitor other vaccine-preventable diseases (e.g., typhoid).
B. VI-TAC Special Studies		
1. Grant A-4: January 2009 - September 2013		
Landscape analysis of PCV dosing (analysis updated in 2016-2017 with funding by the BMGF: PCV Review of Impact Evidence (PRIME)	Analysis of dosing studies published through 2014 is complete. Nine-paper supplement published in the January 2014 issue of Pediatric Infectious Diseases Journal (PIDJ). Presentations given at ISPPD 2012. Leveraged for updated systematic review on PCV impact to inform PCV Product Assessment and review of evidence by SAGE to be presented at October 2017 for revisions of position paper as appropriate.	The available literature shows that each of three schedules (3+1, 3+0 and 2+1) all showed significant reductions in pneumococcal disease (IPD and/or pneumonia), and many programs also used catch-up campaigns. Choice of schedule should balance practical considerations and epidemiology, but achieving high coverage should be a primary goal to ensure herd protection. Varying study designs and epidemiologic settings made direct comparison of impact between schedules difficult. The landscape analysis of PCV dosing was leveraged and updated through support from the BMGF and from Gavi to inform the PCV Product Assessment. The report is a summary document to inform Gavi decisions on product switch requests and initiate country-level guidance on PCV product choice.
Effectiveness of PCV7 against IPD (South Africa)	Evaluation of impact of PCV7 is complete.	Even in a setting of routine use and with high pneumococcal transmission, PCV delivered on a novel 2+1 schedule is highly effective for HIV-

Study	Status of Activities	Key findings
	Publication in Vaccine in 2012 discussed effects of study on changes to PCV dosing schedule made by South African NAGI. Presentations given at ISPPD 2012 and 2014. Publication in PIDJ on risk factors for IPD among children in South Africa. Publication in CID in 2014 on effectiveness of PCV in this case-control study. Publication in PIDJ in 2015 on risk factors for IPD.	uninfected children (VE 74%), but insufficient among HIV-infected children (VE -12%). This may indicate the benefit of a booster dose for HIV+ children on this schedule. In addition, the study identified risk factors for IPD in HIV-uninfected children include underlying medical conditions, upper respiratory infections, day-care attendance, HIV exposure and siblings under 5 years of age.
Effectiveness of PCV7 against presumed bacterial pneumonia (PBP) (South Africa)	This case-control study measuring PCV effectiveness in HIV-infected and HIV-uninfected children is complete and published. This was the first published study on the impact of PCV on pneumonia in conditions of routine use in Africa. Poster displayed at ISPPD 2014. Publication in Thorax in 2015 showed effectiveness of PCV at preventing PBP in HIV-uninfected children.	In the matched case-control study, PCV7 was 39.2% effective (95% CI: 8.46-59.6%) in preventing Probable Bacterial Pneumonia (defined as consolidation on chest X-ray) in children 3 months to 2 years of age (those who had received two primary doses plus a booster), under conditions of routine use and using a hospital control group for comparison. There was vaccine efficacy of 20.1% when including children beginning after the first dose of PCV. Importantly, these effectiveness estimates were similar to those found in the more controlled environment of randomized trials.
Pneumo/Rota time series (South Africa)	Data collection is complete; the initial work was continued in subsequent grant portfolios – see grant A-11 below. Time series analysis of PCV impact manuscript has been submitted for publication and is under consideration	The impact of simultaneous introduction of PCV and rotavirus vaccine can inform other countries with high burden of pneumonia and diarrhoea, who are looking to adhere to the recent GAPPD recommendations. Among HIV (-) children under 5 years of age, PCV13 use was associated with reductions in all cause pneumonia of 27%-39% by year following introduction. This translated to 7-9 prevented hospitalization for every 1,000 children vaccinated.
PCV/Hib conjugate vaccine impact manual	The PCV/Hib impact manual has been completed and published on the WHO website for download. A presentation on the manual was made at NUVI meeting in May 2012.	The manual organises information on designing and conducting impact studies in one place for vaccine decision-makers and implementers in countries considering adoption or having recently adopted either Hib of PCVs. The manual includes

Study	Status of Activities	Key findings
		guidance for study design and tools to assist with study protocols.
Economic impact of PCV (The Gambia)	Assessment of the economic impact of The Gambia's introduction of PCV is complete. Poster displayed at ISPPD 2014. Manuscript describing the cost of pentavalent and pneumococcal conjugate vaccine delivery in the Gambia before and after introduction published in April 2014 in Vaccine. The results for this Gambian pneumococcal economic impact study have been published in 2016 in Cost Effectiveness and Resource Allocation.	The total incremental cost for transition to pentavalent and introduction of PCV together in The Gambia in 2009 amounted to $1,616,943 or $24.22 per fully-immunised child, over 85% of which was the cost of vaccine. Savings from the switch from tetravalent to pentavalent vaccine slightly offset the large additional cost of introducing PCV. The Gambian gov't assumed 16% of the added systems costs of the two vaccine schedule changes, while donor agencies contributed the remainder – Gavi (52%), UNICEF (31%), WHO (1%, plus significant staff time contributed for training). The economic burden results show average of pneumococcal disease in The Gambia is substantial, with costs of more than a US$100 for an admitted case. The health system meets 50% to 80% of these costs. Although fewer costs were passed onto caregivers compared to Kenya and Pakistan, out-of-pocket costs were one to ten times the average daily household expenditure (US$5-9). Provider costs per patient for treating a case of pneumococcal disease (including outpatient pneumonia, inpatient pneumonia, pneumococcal sepsis and meningitis) were substantial, (ranged from $58-13024), respectively, while the average out- of- pocket costs per patient were $2-606-34, respectively. The Out-of-pocket costs economic burden increased to $15-170 when family members' time loss from work was taken into account, and increased by another $650 if burial costs are included. Because of the large number of pneumonia cases, the economic burden due to outpatient pneumonia was >5 times that of meningitis and for inpatient pneumonia it was 10 times greater.
2. Grant A-11: September 2012 – December 2015		
PCV10 Impact (Kenya)	This is a continuation from the PneumoADIP PCV impact evaluation in Kenya.	Substantial reductions in the incidence of vaccine-type invasive pneumococcal diseases (IPD) among children less than five years of age have

Study	Status of Activities	Key findings
	Results were presented at ISPPD-9 in March 2014 and at ISPPD-10 in June 2016. Manuscript on impact of PCV10 on NP-carriage of S. pneumoniae and non-typeable H. influenzae was published in Lancet Global Health in June 2014. Multiple additional publications are expected, including analyses on PCV impact on pneumonia and IPD and indirect effects. The pneumococcal disease surveillance system is also used to monitor Hib invasive disease. A publication in Lancet Global Health in 2016 shows results from 15 years of surveillance following Hib introduction.	been shown since PCV10 was introduced in 2011. Between 2013 and 2016 there have cumulatively been only 4 cases of VT IPD in children under 5 years in the Kilifi Health and Demographic Surveillance System compared with annual cases counts of 15-40 cases per year prior to vaccine. The nasopharyngeal carriage study has shown that introduction of PCV10 in a developing country setting with a catch-up campaign has led to a two-thirds reduction in prevalence of vaccine-serotype pneumococci carried in both children targeted for vaccination and in older people who were not vaccinated. Over the past 13 years, hospitalizations for clinical pneumonia declined progressively but fell abruptly by 27% in association with PCV10 introduction. The incidence of x-ray confirmed pneumonia fell by 48%. Vaccine effectiveness of Hib vaccine during 15 years of use was 93% in children younger than 13 years of age (using a 3-dose schedule without a booster)
PCV13 Effectiveness (South Africa)	This study is a continuation of the VI-TAC Special Study in South Africa PCV7 evaluation (Grant A-4). The continuation extends the effectiveness analysis through the switch to PCV13, which has replaced PCV7. The data on PCV13 effectiveness against IPD are published in Lancet Global Health in 2017.	Effectiveness of PCV13 against vaccine-type disease among HIV-uninfected children was 85% and 91% in HIV-infected children. The effectiveness against the 6 serotypes not in PCV7 was 92% (95% CI: 40, 99) among HIV-negative children. The PCV13 vaccine effectiveness for PCV7 serotypes among malnourished children who were HIV-negative was 90%.
C. PneumoADIP Special Studies		
1. Grant: March 2004 - December 2013		
PCV Impact in Kenya	Rolled over to VI-TAC. (see above)	
PCV Impact in The Gambia	Rolled over to VI-TAC in part (for economic analyses); additional continuation funding provided by BMGF. This is a continuation of the Gambia PCV7 Impact study and is now evaluating the impact of PCV13.	The incidence of vaccine type IPD decreased 82% in children 2–23 months of age after vaccine introduction; incidence of all IPD decreased by 55% in the 2–23 month age group. This was due to an 82% (64%–91%) reduction of serotypes covered by PCV13.

Study	Status of Activities	Key findings
	The results on IPD were published in 2016 in Lancet Infect Diseases. Pneumonia impact data has been analyzed and a manuscript has been submitted to Lancet Infectious Diseases	PCV13 had a moderate impact on radiological pneumonia (23% decline after introduction) in children aged 2-11 months. The vaccine substantially reduced the severest forms of disease - pneumococcal and hypoxic pneumonia by 58% and 57%, respectively. After vaccine introduction there was a modest, non-significant increase in pneumonia due to non-PCV13 serotypes, indicating little to no serotype replacement.
Cost-effectiveness of PCV catch-up (Kenya)	Analysis of the impact and cost-effectiveness of PCV catch-up among under-one year olds, under-two year olds (current WHO recommendations), and under 5 year olds, in Gavi-eligible countries is complete but as yet unpublished. A manuscript describing challenges to constructing a model that assesses the impact of CE of PCV catch-up campaigns is being prepared.	Preliminary results from the disease transmission model found that catch-up campaigns not only lead to more rapid reduction in the IPD burden but also increases efficiency of the vaccine schedule in the first years after vaccination through rapid establishment of herd protection. Any catch-up campaign in the first years after introduction, particularly among under two and five year olds, is likely to prevent a high number of IPD cases for comparatively fewer extra vaccine doses than routine immunisation. Under 1 year old catch up campaigns achieve additional direct benefits but fewer indirect benefits. Critical review of the relevant literature on cost-effectiveness of PCV catch-up campaigns among under one year olds in low resource settings. The review places important emphasis on the economic literature of cost-effectiveness analyses of catch-up immunization programs and other alternative immunization approaches that have been implemented in low resource countries over the past 10 years. The paper sets the agenda for future work by identifying gaps and pitfalls of previously research in this area. It draws conclusions on the usefulness of cost-effectiveness of PCV catch-up campaigns evidence for model development, how much of the data for modelling are covered (and to what extent), and what may be missing; information still needed.
Economic value of vaccination in India	The overarching goal of this analysis was to look at the potential health impact and costs averted through immunisation with three	By introducing and scaling up coverage of Hib, PCV and RV, India could save over US$ 1 billion each year in economic benefits and avert more than 90,000 needless child deaths each year.

Study	Status of Activities	Key findings
	vaccines—Hib, PCV, RV vaccines. The project aimed to generate new evidence on the health and economic benefits of these vaccines at the national level and in four states in India (Bihar, Delhi, Maharashtra, and Tamil Nadu). The analysis generated new evidence in 3 categories: (i) death and cases averted; (ii) disease costs averted; and (iii) productivity loss averted. Presentation at ISPPD-9 in March 2014. All activities for this project have been completed and a publication is expected in 2018.	An estimated US$ 1 billion or 88% of the total amount of cost savings would be attributable to lost productivity due to premature pneumococcal death. Another US$ 112.8 million, or 10% of the total cost would be due to costs related to loss of productivity due to disability as a result of these diseases. Treatment costs of Hib, pneumococcal and rotavirus gastroenteritis, would account for 8.4 million (US$ 4-12million) or <1% of the total costs of these diseases. Finally, caretaker productivity loss from seeking care would represent US$ 1.5 million (US$ 1-4.9 million).
D. Other Gavi Targeted Assessments		
1. PCV Effectiveness in Asia		
Impact of PCV-10 on IPD in Lower Sindh, Pakistan (Aga Khan University)	Case-control study estimating impact of PCV on IPD: data collection is complete Cost-of-illness assessed in the same cases: data collection is complete Nasopharyngeal carriage surveys conducted to assess impact of PCV on vaccine-type carriage: data collection is complete The final round of a vaccine coverage survey is being analysed to assess impact of quality control improvement measures on PCV immunization rates. Data analysis for all studies is being finalized, with publications expected in 2018. PCV impact assessments were considerably affected by low vaccine coverage (<40% fully immunized) in the study areas.	Estimated efficacy of PCV10 against vaccine type IPD was 73% with at least one dose of vaccine, 79% for at least two doses and 82% for all three doses. While these results are not statistically significant due to lower than anticipated proportion of IPD that was vaccine-type, they suggest that a large impact may be expected when higher coverage is achieved. The average cost of illness for pneumococcal meningitis at $340 per patient per episode was much higher than that for pneumonia at $160; however, with a GNI per capita of less than $6,000, both syndromes represent significant costs to the health system and households. While direct costs were substantial ($288 for meningitis and $130 for pneumonia per episode of illness), indirect costs in the form of productivity losses were the second largest component of the economic burden at $52 for meningitis and $30 for pneumonia. After the implementation of new quality improvement measures to improve vaccination rates in low coverage areas during the rollout of PCV, coverage increased only marginally (e.g., Penta3 increased from 22% to 39%) and

Study	Status of Activities	Key findings
		remained low (<40% fully immunized) through the duration of the study. Vaccine-type colonization steadily decreased in vaccine-age-eligible children after PCV introduction in the rural site and was ~50% lower 3 years after introduction compared to pre-PCV levels. But at the urban site, the evidence of a decline was less clear: colonization decreased from pre-PCV to year 3 post-PCV by only 25% and in year 2 of the PCV program the vaccine-type colonization rate was higher than in the pre-PCV period. These findings in the urban site are suggestive of low vaccine coverage, as was observed in the coverage surveys.
Impact of PCV on disease, nasopharyngeal carriage, and health economics in Nepal (Oxford University)	Enrolment continues in surveillance-based studies evaluating invasive bacterial disease and pneumonia, along with studies examining PCV impact on nasopharyngeal carriage in hospitalized pneumonia cases and healthy children. An immunogenicity trial compared two dosing schedules (6+10 weeks+9 month booster vs. 6+14 weeks+9 month booster): Publication is expected in 2018. An analysis of PCV10 impact on hospitalized pneumonia and meningitis using administrative data began in 2015. The data will be available for pre/post analysis in 2018. A health economic impact study (with cost of illness and catastrophic expenditures analyses) has completed data collection and analysis is ongoing. Publication is expected in 2018.	In children under 2 with pneumonia carrying a vaccine-type, there has been a statistically significant 50% relative reduction since vaccine introduction in 2015. In urban-dwelling healthy children aged 6–24 months, there has been a significant 40% relative reduction, despite only half of community children enrolled in the study receiving PCV10 (a large proportion were too old for the routine schedule). In the rural setting, there was also a significant decrease in the proportion of children carrying a PCV10 serotype. These reductions are expected to increase as the proportion vaccinated grows among children under 5. In the immunogenicity trial, the novel 6+10 schedule was inferior to the recommended 6+14 schedule for some serotypes as measured by average antibody concentration and proportion of children reaching the antibody concentration that correlates with efficacy. But differences observed after the primary series are not likely to be clinically important, especially because differences are substantially diminished after the booster dose. Results suggest the accelerated schedule may be used by programs if the standard schedule cannot be implemented. Retrospective administrative data on hospitalizations from the pre-vaccine period (2012-2015) have been collected from 4 hospitals.

Study	Status of Activities	Key findings
		Preliminary analysis of data from Patan Hospital, where data on all hospital admissions was collected, shows that before vaccine introduction, pneumonia, meningitis and sepsis accounted for a significant number of childhood admission. Data for the post-introduction period will continue being collected through Q4 2017, allowing for pre/post analysis in 2018. In the cost of illness study, the average cost per episode ranged from $160 for pneumonia to $370 for meningitis, which translates to 25-50% of the median per capita annual income of $670. Using the conventional threshold of 40% of the household's annual capacity to pay, a single case of hospitalized pneumonia was considered catastrophic for about 10% of households studied, and for over 80% of households in the poorest income quintile. The proportion in the poorest quintile was nearly 95% after adjusting for differences in disposable income between wealthy and poor households. The cost of hospitalized pneumococcal disease per 100,00 children 1-59m ranged from $73,000 to $156,000. About a third of costs were incurred prior to hospitalization. Primary caregivers lost 11 days of wages for pneumonia and meningitis and 17 days for sepsis.
Impact of PCV introduction on hospitalised pneumonia, IPD and nasopharyngeal carriage in Lao PDR (Murdoch Children's Institute)	Pre- and post-PCV13 introduction carriage surveys are complete and lab testing and data analysis are ongoing. Surveillance for IPD is ongoing. Pre-PCV retrospective review of administrative hospital pneumonia data is complete and post-PCV review and analysis are ongoing, with results anticipated by early 2018.	Preliminary pre-introduction results show 33% of children 12-23mo and 6% of infants 5-8 weeks carry vaccine-type pneumococci in the nasopharynx. Over 80% of pneumococci detected contained antibiotic resistant genes. PCV significantly decreased vaccine-type carriage in children 12-23 months by 42%. There was no significant decrease in unimmunized infants (5-8 week olds) 3 years after PCV introduction, suggesting no meaningful indirect effects yet. Final IPD surveillance and retrospective pneumonia review results are anticipated by early 2018.
Impact of PCV on hospitalized pneumonia and nasopharyngeal carriage in Mongolia	Enrolment of hospitalized pneumonia cases continues, with approximately 7,000 chest x-rays collected since 2015. PCV was introduced in June 2016 and	Preliminary analysis of hospitalized pneumonia cases with radiographs suggests pre-introduction approximately 19% have for primary endpoint pneumonia (PEP; which is associated with bacterial disease). The majority (76%) of

Study	Status of Activities	Key findings
(Murdoch Children's Institute)	preliminary impact results will be available in 2018. Carriage results are available for a selection of hospitalized pneumonia cases pre-introduction; testing the remaining pre-introduction and post-introduction specimens is ongoing. One each pre- and post-PCV community carriage surveys have been successfully completed; testing and analysis of post-PCV specimens is ongoing and is expected to be complete in mid-2018. One additional post-vaccine carriage survey will be performed in 2018, with overall results available in early 2019.	pneumococci present in the nasopharynx in children hospitalized with pneumonia belonged to PCV13 serotypes. Enrolment and assessment of films post-introduction continues and preliminary pre-post analysis will be possible by early 2018. Preliminary analyses of pre-introduction carriage in pneumonia cases found the majority (76%) of pneumococci present in the nasopharynx of children hospitalized with severe pneumonia or PEP belonged to PCV13 serotypes; almost a third carried a vaccine type. No difference was noted in carriage proportions between children <1 year and 1-4 years of age. Preliminary analysis of the pre-introduction carriage survey among healthy children and infants found 61% aged 12-23 months were carrying a pneumococcus, of which 43% were vaccine-type. Almost a third of infants acquired pneumococcus in their first 8 weeks of life. Factors associated with increased risk of carriage included use of coal/wood for fuel and income below the minimum living standard. Lan testing of the 2017 post-introduction survey is underway.
2. US Centers for Disease Control and Prevention (2013-2016)		
Evaluating the impact of PCV in Burkina Faso	Evaluation of the impact of PCV on meningitis using data from national surveillance is continuing through 2017 (4 years post introduction). Evaluation of the impact of PCV on carriage in all ages is ongoing; post-PCV data collection is complete and lab testing and analysis is underway. Analysis of baseline (pre-introduction) meningitis surveillance was published in PLoS ONE in 2016. Analysis of pre- vs 2 years post-introduction data is complete and a manuscript has been submitted; publication is expected in 2018.	Two years post-PCV, the incidence of PCV13-type meningitis significantly decreased among vaccine-age-eligible children, by 76% in <1 year olds and by 58% in 1-4 year olds. VT meningitis in all ages (including adults) decreased by 23%, but incidence of serotype 1 (which is associated with outbreaks and did not show efficacy in the PCV licensure trials) did not decrease. Incidence of non-PCV13 serotypes also decreased by 47%, suggesting some of the decline in VT might be due to temporal trends. Among children aged <1 year, serotypes 12F/12A/12B/44/46 (17%), 1 (12%), and 5 (10%) predominated.
3. Full Country Evaluations (2013-2016)		
3.1 Evaluating the impact of PCV on nasopharyngeal carriage, IPD and x-ray	Vaccine effectiveness studies will potentially continue in 2017.	Evidence from vaccine effectiveness studies suggests that the introduction of PCV in 2013, which was rapidly routinised in the country, has reduced nasopharyngeal carriage of vaccine-type

Study	Status of Activities	Key findings
confirmed pneumonia in Mozambique		pneumococcus and reduced the incidence of vaccine-type invasive pneumococcal disease (IPD) and pneumonia. The nasopharyngeal carriage study aimed to estimate the effects of PCV10 introduction on pneumococcal nasopharyngeal carriage (i.e. vaccine preventable disease transmission) among HIV-infected and HIV-uninfected children. The study involved carriage surveys pre- (October 2012–March 2013) and post- (first round October 2014–April 2015; second round October 2015–May 2016) PCV introduction. Based on this study, a direct effect of the vaccine on PCV10 serotype-specific (VT) pneumococcal carriage was observed at the first round (within 18 months) after PCV introduction. • A 41% (95% CI 6–69) reduction in VT pneumococcal carriage was observed in HIV-uninfected children receiving three doses. • A 61% (95% CI 9–82) reduction in VT pneumococcal carriage was observed in HIV-infected children receiving three doses. • As expected, there was also an increase in pneumococcal carriage of non-PCV10 VT, including serotypes in PCV13 (i.e., 19A). The reduction in carriage has been accompanied by a reduction in vaccine-type IPD. Based on surveillance data from the Manhiça demographic surveillance system (DSS), it has been estimated a statistically significant reduction in vaccine-type IPD of 87.7% (95% CI 44.1–97.3). There was also a marginally significant reduction in X-ray-confirmed pneumonia (64.9%, 95% CI -4.4–88.2).
3.2 Impact of PCV on nasopharyngeal carriage in Bangladesh	Manuscript for the impact of PCV on nasopharyngeal carriage was completed in Dec 2016,	Findings from the pneumococcal impact study in Bangladesh also suggest some reductions in both the overall transmission of pneumococci and serotypes included in the vaccine (VT) as measured through population-based nasopharyngeal carriage surveys pre and post vaccine introduction. During the pre-vaccine period (before March 2015), a total of 1901 specimens were collected and processed among different age groups. In the post vaccine period, a total of 2060 specimens were collected.

Study	Status of Activities	Key findings
		• Among 4-11 months age group, pneumococcal colonization decreased from 65% to 61% and VT coverage reduced by 8% (32% to 24%). • Among 12-23 months age, pneumococcal colonization decreased from 63% to 52% and VT coverage reduced by 10% (39% to 29%). • In 24-35 months age group (age group eligible for the vaccine Yr3 of the study), pneumococcal colonization decreased from 52% to 48%, whereas VT coverage remained same (44% and 43%).

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