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GAVI

Baseline Study for pneumococcal vaccine AMC

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EXECUTIVE SUMMARY

One of the strategic objectives of the GAVI Alliance (GAVI) is to accelerate the uptake and use of underused and new vaccines and associated technologies in developing countries. Diseases caused by *Streptococcus pneumoniae* have been identified as a priority area to be targeted by routine immunisation. Each year, invasive pneumococcal disease (IPD) takes the lives of up to one million children under five years of age, making it the leading vaccine-preventable cause of death among young children. The most effective way to prevent these deaths is to ensure access to effective, safe and affordable vaccines.

An innovative new approach to public health funding is the Advance Market Commitment (AMC). An AMC is a way of stimulating and accelerating the development and manufacture of vaccines for developing countries. Through an AMC, donors commit money to guarantee the price of vaccines once they are developed, provided they meet stringent, pre-agreed criteria on effectiveness, cost and availability, and that developing countries demand them. Hence, an AMC provides a pull incentive that rewards developers and suppliers of successful vaccines. By guaranteeing an affordable long-term price, the AMC also supports sustained use of the vaccine.

In 2007 GAVI began working with partners on a pilot AMC to fund the introduction of suitable pneumococcal vaccines in countries eligible for GAVI support. AMC donors have committed $1.5 billion for new expanded-protection pneumococcal conjugate vaccines (PCV).

The goal of this pilot AMC is to introduce an effective and affordable pneumococcal vaccine in developing countries to reduce morbidity and mortality from pneumococcal diseases.

The specific AMC objectives are:
1. To accelerate the development of pneumococcal vaccines
2. To bring forward the availability of effective pneumococcal vaccines
3. To accelerate vaccine uptake
4. To pilot test the effectiveness of the AMC mechanism.

The Swiss Centre for International Health (SCIH) of the Swiss Tropical and Public Health Institute (Swiss TPH) was commissioned by GAVI to conduct a baseline study for the pneumococcal vaccine AMC.

The goal of the AMC baseline study was to establish the environment prior to the AMC with baseline estimates for a selection of indicators related to the objectives of the AMC and to model counterfactual scenarios to ascertain the potential impact of the AMC vis-à-vis traditional financial and procurement strategies.
Key objectives and activities for the baseline study were:

- To define a set of indicators related to vaccine industry and disease burden which accurately capture the environment prior to the AMC.

- To collect baseline data, starting in 2005, from the vaccine industry and from countries where the vaccine would be used, consisting of quantitative and qualitative data on the epidemiology of pneumococcal disease in GAVI-eligible countries and vaccine development and production from 2005 to 2010, by AMC objective. The baseline data establish the environment prior to the AMC and will be used to understand changes in the size and content of the vaccine pipeline, pneumococcal vaccine uptake and coverage, and mortality from pneumococcal disease.
- To define counterfactuals – by developing a model for quantification – that will serve as the benchmark for testing the incrementality of the AMC and the attribution of results to the AMC concept. In particular, to develop two counterfactuals and to conduct quantitative modelling 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.
- To provide additional recommendations for future monitoring and evaluation (M&E). As part of the baseline study a standardised core set of indicators and tools to collect, summarise and analyse data would be developed and made available for future monitoring. This will allow future data collection for comparisons against the baseline during the life of the AMC mechanism.

2005 was agreed on as the baseline reference date as this was the year that the AMC concept was first formulated in the Center for Global Development (CGD) report 'Making Markets for Vaccines' (CGD, 2005) and in a Report by the Italian Ministry of Finance to the G8 countries (Tremonti, 2005). Where this was possible and appropriate we also collected data for 2009/2010 in line with the formal activation of the AMC pilot project and the subsequent provision of the first supply contracts.

Study approach

Our baseline study followed a stepwise approach with a series of incremental elements. First, the AMC objectives were used as the guiding principles and overarching framework, while the AMC Report of the Monitoring and Evaluability Study (GAVI, 2008) acted as the main initial reference document. Second, we used a logical framework-type approach to develop appropriate evaluation questions and indicators to address them. From this, 12 final key indicators were developed within an indicator matrix which summarised the key indicators by AMC objective. Final methodologies for data collection were developed and data collection and analysis were undertaken. Data collection used a variety of methods ranging from literature reviews and interviews to the design and testing of counterfactual models.

Baseline findings: country and industry

The table below summarises the indicators by AMC goal and objectives and the respective baseline findings. It is important to note that for a number of the indicators the current value is zero due to the newness of the AMC mechanism and the lack of availability and uptake of pneumococcal vaccines meeting the AMC Target Product Profile (TPP) in 2005 or in 2009. This situation is expected to change as the AMC pilot progresses.

Table I: Baseline findings country and industry

Indicators	Results
Goal: To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030	
1. Cumulative number of cases of IPD (invasive pneumococcal disease) averted due to TPP vaccines in GAVI-eligible countries	2005 = 0 2009 = 0
2. Cumulative number of future deaths averted due to TPP vaccines in GAVI-eligible countries	2005 = 0 2009 = 0
Objective 1: To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP).	
3. Cumulative number of TPP candidates	2005 = 3 2009 = 5
4. Median time between key milestones in the development of TPP candidates	Insufficient data
5. Cumulative number of AMC eligible TPP vaccines	To September 2010 = 2
Objective 2: To bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price, for a limited quantity of the new vaccines, that represents value for money and incentivises manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand.	
6. Total number of doses of TPP vaccine offered to UNICEF SD per year for GAVI-eligible countries	2005 = 0 2010 = 7.2 million
7. Number of doses of TPP vaccine contracted under AMC by year	2005 = 0 2010 = 7.2 million
Objective 3: To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after AMC finance is used up.	
8. Cumulative number of countries that have applied for GAVI support for PCV	2005 = 0 2009 = 33
9. Cumulative number of GAVI-eligible countries introducing TPP vaccines	2005 = 0 2009 = 0
10. Cumulative number of doses of TPP vaccine shipped to GAVI-eligible countries	2005 = 0 2009 = 0
11. PCV3 coverage in GAVI-eligible countries	2005 = 0 2009 = 0
12. Time to national peak coverage	2005 = 0 2009 = 0

Note: We use ***TPP vaccine*** to denote a pneumococcal conjugate vaccine meeting TPP criteria

Methodology and results: counterfactuals and quantitative model

Two counterfactuals were defined: Counterfactual 1, which we describe as 'early conventional procurement' and Counterfactual 2, which we describe as 'late conventional procurement with earlier country-by-country negotiations'. The main difference between the two counterfactuals is that in Counterfactual 2, it is assumed that the UNICEF procurement arrangement fails to conclude supply agreements successfully and therefore it is not operative for a given period of time. Within this time period, the only form of supply would be through country-by-country negotiations with vaccine producers. The counterfactuals describe a pre-defined sequence of events involving three vaccine producers: two multinational firms and one emerging-market supplier.

The counterfactuals were defined and validated through two interview programmes with experts. From these interview programmes and a review of published and grey literature, we identified two vaccines, *Haemophilus influenzae (*Hib)-containing and rotavirus vaccines, which would provide some relevant historical context and data for the two counterfactuals defined.

We developed an Excel spreadsheet model to estimate empirically the interactions between vaccine supply and demand in our defined counterfactuals and to investigate how market outcomes may change in response to changes in our models' input parameters. The outputs of the models are: quantity of vaccines supplied; discrepancies between demand and supply (which we define as 'supply shortfall'), and health impact measured as cumulative number of deaths and DALYs averted over the models' time horizon. A summary of the key input parameters used in the models for simulating the two counterfactual scenarios is presented in the table below.

Table II

Model parameters (inputs)	Assumptions	Source/References
Counterfactual1		
Firm prices	We adopted the highest weighted average price (WAP) reported by UNICEF ($6.60) for Hib-containing pentavalent vaccines as the price charged within the pre-build-out-period. We chose the highest WAP on grounds that UNICEF does not always have a strong bargaining position to extract 'low' prices in the region of $3.50 per dose from (multinational) vaccine manufacturers. And also, because we believe the Hib-containing pentavalent vaccines are the closest in terms of technical complexity to the PCVs. We assumed that this price is fixed over the models' time horizon (i.e., there is no price competition) to avoid making the model more complex.	Values taken from data collected by the SCIH team.
Costs for new plant	With this variable we followed precisely what was presented in Excel spreadsheet created by the AMC Economic Expert Group (EEG).	Data taken from the EEG model.
Plant capacity	We noted from data on a number of long-term agreements (LTA) that the maximum quantity of doses for the pentavalent vaccines contracted by UNICEF from a given vaccine supplier in any given year was 15 million doses and this was a supply contract with a multinational vaccine manufacturer. The maximum contracted doses from an emerging-market supplier were 3.5 million. We therefore assumed that the existing production plant used during the pre-build-out period by the multinational firms in our models will have a capacity of 15 million doses. We considered that if a multinational vaccine supplier finds it worthwhile to build a new dedicated plant for supply to low-income countries, they will build a higher capacity plant. We assumed conservatively that the new dedicated plants built by the multinational firms will have a capacity of 25 million doses whilst the emerging-market supplier will build a production plant for 15 million doses. These are arbitrarily chosen figures to reflect a higher plant capacity being built.	Data provided by the SCIH team (e-mail correspondence with GAVI/Ann Ottosen, Contracts Manager, Vaccine Centre, UNICEF Supply Division).
Capital cost	We assumed that the upfront capital costs of setting up a new plant for the first multinational firm supplying a 10-valent vaccine will be $110 million whilst that for the second multinational firm supplying a 13-valent vaccine technology will be $150 million. This follows Scherer's (2007) report that upfront vaccine plant investments (covering plant administration, quality control, laboratory operation, health and safety, utilities etc.) is in the range of $100-150 million. This is to some extent consistent with values presented in the EEG model.	Data coming from the Economic Expert Group model and Scherer (2007).
Incremental cost	We assumed that the incremental production costs (i.e. variable costs plus an allocated margin reflecting fixed and quasi-fixed costs) per dose supplied to low-income countries using the existing pre-build-out capacity is $2.83. This price is the end-point of the forecasted decline in the WAP for the pentavalent Hib-containing vaccines, which we consider as reflecting the long-run marginal cost of supply that allows a given vaccine producer to 'break even'. This assumption had to be made to mitigate the difficulty and unwillingness of vaccine suppliers to disclose their production cost schedules.	Data taken from forecasted price trends for the pentavalent vaccines (UNICEF, 2010).

Counterfactual2		
Firm prices	In Counterfactual 2, the UNICEF procurement is assumed not be operative for a given period of time (5 years). During this period, any form of vaccine supply comes from country-by-country negotiations with vaccine producers. Hence, one cannot use UNICEF's WAP as the prevailing market price. We assume that during this period, the first and second multinational firms will charge $10.00 per dose as this represents the average price in the public sectors of middle-income countries. The data come from PneumoADIP/Applied Strategies (2009). After this period, which encompasses the pre-build-out period for the multinational firms, prevailing market price reverts back to $6.60 per dose (as in Counterfactual 1).	Data coming from PneumoADIP/Applied Strategies (2009).
Costs for new plant	The same assumptions as in Counterfactual 1	Data taken from the Economic Expert Group (EEG) model.
Plant capacity	The same assumptions as in Counterfactual 1	Data provided by the SCIH team (e-mail correspondence with GAVI).
Capital cost	The same assumptions as in Counterfactual 1	Data coming from the Economic Expert Group model and Scherer (2007).
Incremental cost	The same assumptions as in Counterfactual 1	Data taken from forecasted price trends for the pentavalent vaccines (UNICEF, 2010).

Base-case analyses of our models for the counterfactuals identified show that differences between supply and demand (i.e., supply shortfall) for the pneumococcal conjugate vaccines are lower in Counterfactual 1 relative to the supply shortfall observed in Counterfactual 2. This is depicted in Figures I and II. below.

Figure I: Demand and supply results for Counterfactual 1

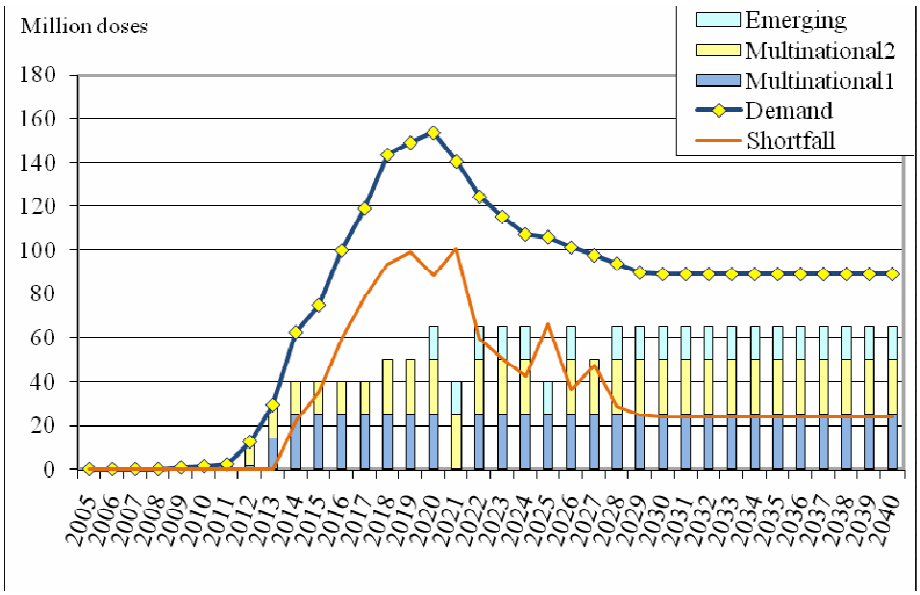
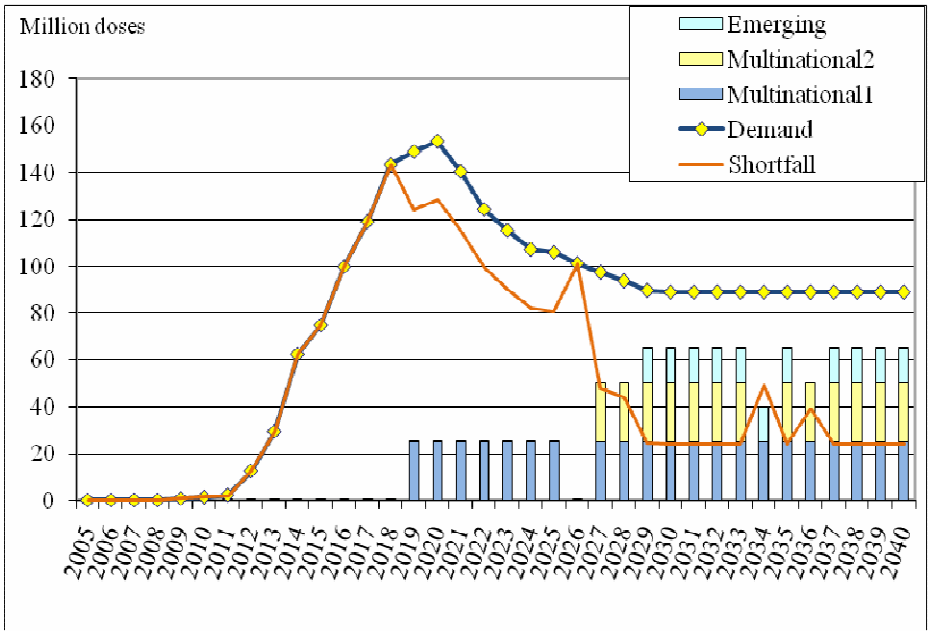


Figure II: Demand and supply results for Counterfactual 2



We conducted a net present value analysis to investigate, given the structure and input values of the models, whether our assumptions about market entry by three vaccine suppliers are reasonable. Table III and Table IV show the results of our analysis, which confirms market entry under the assumptions made and values used in the models, because the overall profit return over the time-horizon considered is positive.

Table III: Net Present Value (NPV) analysis for Counterfactual 1

		Multinational 1	Multinational 2	Emerging
Pre Build-out	**NPV of profits**	33	107	n/a
New Plant	**NPV of operating profits**	266.99	93.64	44.58
	NPV of capital costs	59.45	53.40	31.79
	NPV of profits net of capital costs	**207.53**	**40.23**	**12.80**

Table IV: Net Present Value (NPV) analysis for Counterfactual 2

		Multinational 1	Multinational 2	Emerging
Pre Build-out	**NPV of profits**	0.59	-0.26	n/a
New Plant	**NPV of operating profits**	151	30	13
	NPV of capital costs	35	21	12
	NPV of profits net of capital costs	**115.59**	**9.31**	**0.94**

One cannot, however, rely solely on the results from the base-case analysis conducted, since the counterfactuals described cannot and do not capture all possible sequences of events; for instance changing strategic behaviours of vaccine suppliers from both high-income and low-income countries. We conducted sensitivity analysis to estimate the potential impact on the base-case results of changes in a number of the models' parameters.

Our sensitivity analyses suggest that demand for and supply of beneficial vaccines to low-income countries will be determined by the structure, conduct and performance of the global vaccine market in terms of prevailing prices, actual demand realised (and how that deviates from demand estimates and forecasts), and how vaccine suppliers view the profitability of investing in dedicated production plants for vaccine supply to low-income countries. The latter in turn will determine the number of vaccine suppliers at any point in time and thus the ability to ensure security of supply.

For example, we found that if the prevailing market price per dose of vaccine is $4.20 and even if 100% of forecasted demand is realised, no vaccine producer (given our assumed production cost schedules) will enter the market. On the other hand, if the prevailing market price is $8.00 per dose, even if 50% of forecasted demand is realised, we will have a vaccine market characterised by multiplicity of vaccine suppliers (specifically, in our models we observe market entry by all of the three suppliers considered).

We explored what would be the effects of an external policy intervention designed to accelerate the introduction dates of the pneumococcal conjugate vaccines in GAVI-eligible low-income countries as well as scaling up the quantity of vaccine supply. Figures III and IV below show results of analysis conducted to investigate the effect of an external policy intervention incentivising vaccine suppliers to build production plants of higher capacity much earlier in the time period considered by our counterfactual models. As before, outcomes are always better in Counterfactual 1 relative to Counterfactual 2.

Figure III: Demand and supply in Counterfactual 1 with earlier building of a new dedicated plant (capacity of 40 million doses)

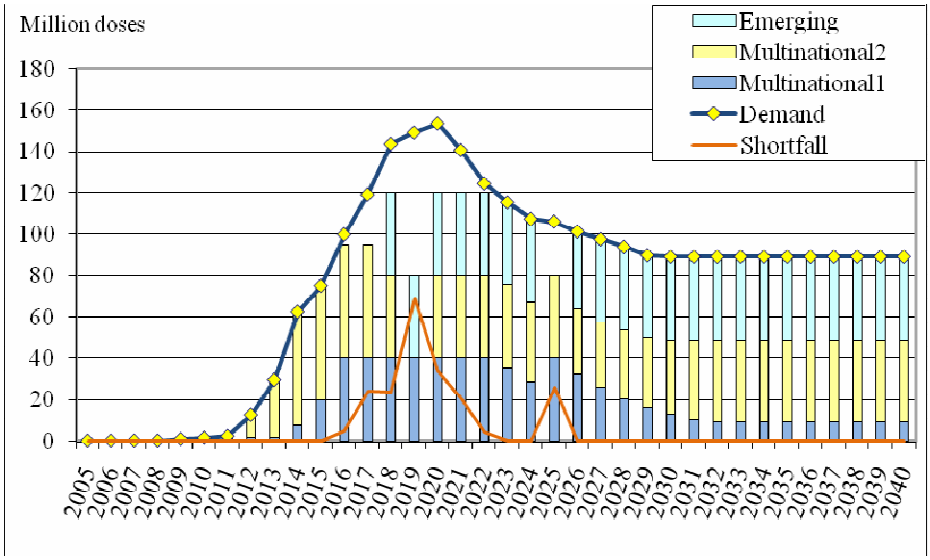
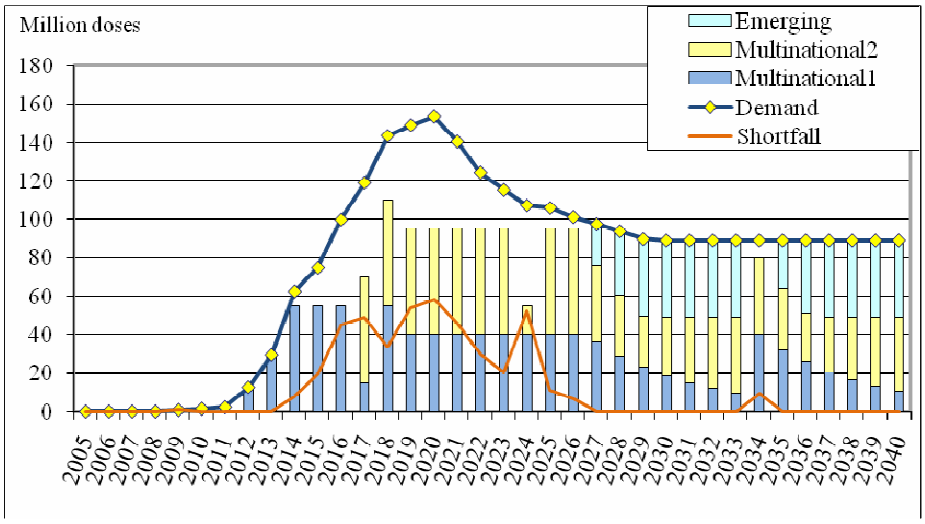


Figure IV: Demand and supply in Counterfactual 2 with earlier building of a new dedicated plant (capacity of 40 million doses)



One interesting result from our analysis is the impact of the accuracy of demand forecasts. Supply shortfall is lower whenever the proportion of forecasted demand realised falls short of 100%. What might appear as inadequate vaccine supply

when supply is compared to forecasted demand may not necessarily be a problem that warrants an external policy intervention to correct the apparent shortfall in vaccine supplies.

The downside of such inaccuracies in forecasted demand is that they constitute a demand risk for vaccine suppliers – in that they are likely to suffer a loss (or are less likely to break-even) if they build production plants of a given capacity on the basis of forecasted demands, but actual demand falls short of these forecasts. This demand risk means market entry by vaccine suppliers may require a higher (risk-adjusted) profit margin to make investments in plant and supply capacity worthwhile.

We want to emphasise that the quantitative estimations conducted are illustrative and the results thereof are subject to the underlying assumptions and the (imputed) data used in developing the counterfactual models. The results (and policy implications) are valid to the extent that the underlying assumptions and data employed, as well as the pre-defined sequence of events depicted in our counterfactuals, reflect the real situation.

Lessons learnt and issues raised

In this report we discuss ways forward for future M&E activities based on our experience with this study, and also highlight issues that arose during baseline data collection. Although this study was designed as a stepwise process, in reality the baseline study became an iterative process with two major points of reorientation. These points of reorientation were the result of recognition of the need to focus more attention on the counterfactual model and recognition of problems encountered during data collection. This process was made possible by close collaboration and exchange within the baseline study team in order to ensure integration of the various components of the study into a comprehensive and consolidated baseline study and body of knowledge.

The key lessons learnt with respect to the datasets of the baseline study relate primarily to the availability and reliability of data. For instance, data collection was hampered by the difficulty of access to and availability of industry data. Future monitoring of the vaccine candidate pipeline would benefit greatly from better access to such data. This would require regular and routine discussions with key pharmaceutical companies and/ or access to industry intelligence databases. Gaining an accurate picture of the whole development pipeline is made especially difficult by the fact that companies can follow different regulatory processes.

One of our aims was to develop baseline methodology to assist future M&E activity. Therefore we have tried to make the methodology as flexible as possible to be able to capture data at the key pipeline milestones. This was done intentionally in order to assist future M&E activity. Furthermore, we had to use a proxy indicator relating to doses supplied to UNICEF Supply Division in order to provide information related to manufacturing capacity. Specific negotiations with companies would be needed to acquire accurate information about the total doses supplied and remove the need for the proxy. For the time being, however, the proxy is sufficient as there is no supply of TPP vaccines to GAVI-eligible countries apart from the UNICEF procurement process. However, if in the future, more

countries start direct procurement of vaccines, this will reduce the validity of the proxy and necessitate the obtaining of specific figures.

Another issue encountered during baseline data collection related to the accuracy of all three components, sensitivity to change (mainly for the country component) and specificity (also for epidemiological data). For instance, global estimates of the burden of pneumococcal disease are of limited value for monitoring the impact of PCV, mainly because they may not be carried out frequently enough, and data generated in global estimates may not be sensitive enough to changes in PCV coverage overall at the beginning of PCV introduction. In addition, the question of defining appropriate indicators related to invasive pneumococcal disease (IPD) should be considered. They have to be specific enough to allow the monitoring of disease related indicators and to permit the attribution of changes in incidence to PCV vaccination status, but they must also be feasible to collect.

Finally, with regard to the counterfactual models, reproducibility and assumptions were and remain important challenges to empirical estimations of outcomes in any model designed to simulate the world without an intervention such as the AMC for the PCVs. The quality and availability of data will determine the relevance of the policy implications that can be drawn from any quantitative modelling work.

In conclusion, this report offers a technical tool for future M&E of the pneumococcal AMC, with defined indicators and a counterfactual model to monitor the impact of the AMC. It also points out lessons learnt which will help in the development of similar methodology for the evaluation of future AMCs.

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Abbreviations

ADIP	Accelerated Development and Introduction Plan
AMC	Advance Market Commitment
AVI	Accelerated Vaccine Introduction
BLA	Biological License Application
CDC	Centre for Disease Control and Prevention
CGD	Centre for Global Development
DALY	Disability-adjusted life years
DTP	*Diphtheria, tetanus, pertussis*
EEG	Economic Expert Group
EMA	European Medicines Agency
EPI	Expanded Program on Immunisation
FDA	Food and Drug Administration
GAVI	The GAVI Alliance (Global Alliance for Vaccines and Immunisation)
GBD	Global Burden of Disease
HIC	High income country
Hib	*Haemophilus influenzae* Type B
IAC	Independent Assessment Committee
ICC	Inter-agency Coordinating Committee
IFF	International Finance Facility
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IND	Investigational new drug
IWG	Implementation Working Group
IP	Intellectual property
IPD	Invasive pneumococcal disease
JRF	Joint Reporting Form
LIC	Low income country
LMIC	Low and middle income countries
M&E	Monitoring and Evaluation
MDG	Millennium Development Goals
MFN	Most Favoured Nation
MFC	Most Favoured Customer
MOH	Ministry of Health
NDA	New Drug Application
NIH	National Institutes of Health
NPV	Net present value
NTHi	non-typable strains of *Haemophilus influenzae*
OECD	Organisation for Economic Cooperation and Development
PAHO	Pan American Health Organisation
PATH	Program for Appropriate Technologies for Health
PCV	Pneumococcal Conjugate Vaccine
PPV	Pneumococcal Polysaccharide Vaccine
PQ	Prequalification
QA	Quality Assurance
RCT	Randomised clinical trials
R&D	Research and Development
RFP	Request For Proposals
SAGE	Strategic Advisory Group of Experts
SCIH	Swiss Centre for International Health
SDF	Strategic Demand Forecast
SEC	Security Exchange Commission
TPP	Target Product Profile
UNICEF	United Nation's Children's Fund (UNICEF SD = Supply Department)
VICP	Vaccine Injury Compensation Program
WAP	Weighted Average Price
WHO	World Health Organisation

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Contributions of SCIH team
Adrian Towse, Ebenezer Tetteh and Martina Garau from OHE Consulting defined the counterfactuals and developed the quantitative models.
Rebecca Hanlin and Dinar Kale from the Open University designed methodology for the industry survey and conducted the data collection and analysis.
Karin Wiedenmayer from SCIH managed the baseline study as team leader and Xavier Bosch from SCIH developed and conducted the country level epidemiological baseline study.

Role of Committee for AMC Baseline Study
The AMC Baseline Committee was set up by the GAVI Secretariat to provide valuable expertise throughout this project.

The role of this group is to advise GAVI in:
- Ensuring that the scope of the AMC baseline study is well defined
- Ensuring that the outcome is of maximum relevance to the AMC stakeholders
- Ensuring that the evaluation is conducted in a thorough and independent manner

The AMC Baseline Study Committee and the GAVI AMC secretariat contributed with reviews and valuable inputs to the definition of the indicators and the indicator matrix for the baseline surveys. The counterfactual definition and modelling work was done by OHE Consulting, independently of GAVI.

Members of the Committee:

Norway: Lene Lothe, Senior Advisor, Department of Global Health and AIDS, Norwegian Agency for Development Cooperation

United Kingdom: Jeff Tudor, Policy Manager Global Funds and Development Finance Institutions Department

GAVI Alliance: Mr Abdallah Bchir, Senior Programme Officer, Evaluation

George Institute: Javier Guzman, Director of Research

PART I – BACKGROUND AND APPROACH

1 Background

1.1 GAVI and pneumococcal vaccines

The mission of the Global Alliance for Vaccines and Immunisation (GAVI) is to save children's lives and protect people's health by increasing access to immunisation in poor countries. This will contribute to the reduction of under-five mortality targeted by the international community in the Millennium Development Goals (MDG) by increasing access to existing and new vaccines. One of the strategic objectives of GAVI (Global Alliance for Vaccines and Immunisation) is to accelerate the uptake and use of underused and new vaccines and associated technologies in developing countries.

Diseases caused by *Streptococcus pneumoniae* have been identified as a priority area for the use of vaccines. The rapid introduction of these vaccines into the developing world could have a profound effect on childhood mortality.

Pneumococcal diseases are a major public health problem all over the world. In 2005, WHO estimated that 1.6 million people (including 0.7 to 1 million children under-five) die each year from pneumococcal disease. Over 90% of these deaths occur in developing countries (WHO, 2007). Serious pneumococcal diseases caused by *Streptococcus pneumoniae* are the leading cause of death in children under five years.

There are 90 distinct pneumococcal serotypes which vary depending on age, time and geographical region. It is estimated that the 13 most common serotypes lead to 70% – 75% of invasive disease in children, globally. For a commentary on the various scientific estimates of the pneumococcal disease burden see Matthew (2009). Vaccination is the most obvious tool to prevent and reduce the burden of pneumococcal disease. Limited access to care and antibiotics in low income countries, and the recent development of widespread microbial resistance to essential antibiotics, underline the urgent need to make efficient pneumococcal vaccines available and to achieve optimal coverage.

2 Rationale for the AMC strategy

The Advance Market Commitment (AMC) is an innovative new approach to public health funding. An AMC is a way of stimulating and accelerating the development and manufacture of vaccines for developing countries.

In the case of vaccines against pneumococcal infections, the vaccines available in 2005, before the AMC was proposed, did not meet developing countries clinical needs and were not affordable for low income countries.

2.1 Vaccine availability pre AMC

The pre-AMC situation was characterised by the following pneumococcal vaccine products.

One vaccine was Pneumorax®, a 23-valent unconjugated polysaccharide pneumococcal vaccine with 90% serotype coverage for use in high-risk adults and older children. Although the underlying mechanism is not fully established, Pneumorax®, and unconjugated polysaccharide vaccines in general, were not effective in younger children under 2 years. However, this flaw may have been corrected by covalent conjugation of the polysaccharide to (bacterial) protein carriers. This is believed to confer immunity that is memorised by the body cells. Conferred immunity is boosted by subsequent vaccine doses and exposure to the disease-causing organisms. By protein conjugation, the efficacy of the vaccine is increased because it offers protection against reinfection and maintains herd immunity externalities (Finn, 2004; WHO, 2007).

Another vaccine, Prevnar®, which became available in the US in 2000, can be used to vaccinate children under 2 years of age. It is a 7-valent pneumococcal conjugate vaccine (PCV), produced and distributed by Wyeth (now Pfizer). It provides immunity against 65-80% of serotypes prevalent in high income countries. However, this coverage varies depending on the geographical area, and is expected to be lower in populations in developing countries (WHO, 2007). Some of characteristics of the 7-valent Prevnar® do not meet developing countries' clinical needs or take into consideration the healthcare infrastructure in these countries. In particular, the current presentation of Prevnar® is in single-dose, pre-filled syringes which need to be stored at 2° – 8° C. These are less convenient than multi-dose vials as it needs more storage space and increased capacity in the cold chain (up to 300%). There are also safety issues and major problems with disposal of non-auto-disabled syringes in developing countries' healthcare settings.

There is also a 9-valent PCV, which was a line extension of Prevnar® to cover two additional serotypes of the pneumococcal microbe. The efficacy of the 9-valent PCV was tested in The Gambia between 2000 and 2002 and in South Africa (WHO, 2007). However, Wyeth (now Pfizer) discontinued development of the 9-valent PCV after the Gambian trials, choosing to pursue a 13-valent version. It seems that the main focus of the clinical trials done for the 9-valent PCV was to confirm vaccine efficacy in children from low-income countries. The 7-valent PCV was tested in children from industrialised countries and it is well known that vaccine immunogenicity and efficacy findings in one patient population cannot be extrapolated to other patient populations whose genetic characteristics are different.

A 10-valent PCV manufactured by GSK was in development in 2008, being investigated for its efficacy against serotypes 1, 5 and 14, which account for between one-third and one-half of invasive pneumococcal disease in children less than 5 years old. The 10-valent PCV seemed to add protection against important serotypes and has a more convenient presentation being supplied in a 2-dose vial. A 13-valent PCV manufactured by Wyeth (now Pfizer) was in Phase I/II trials in 2004. In addition, we also know of around 20 future candidates in the pre-clinical and Phase I stage.

2.2 The economics of vaccines – some literature findings

Economic literature on the vaccine market highlights a number of features and characteristics that distinguish large-molecule vaccines and biopharmaceuticals from small-molecule chemically synthesised pharmaceuticals. In this section, we provide a brief summary of the key characteristics of markets for vaccines drawing mainly on the following literature: Danzon and Pereira (2005); Danzon, Pereira and Tejwani (2005a/b), Pauly (2005), Danzon and Stephenne (2007), Scherer (2007) and Berndt, Denoncourt and Wagner (2009).

Supply Side

On the supply side, the market for vaccines is characterised by a sequence of high fixed costs of investment at the different stages of R&D, production and distribution. The sequence of high fixed cost investments reflects in part the cost of complying with regulatory requirements, which are especially stringent because vaccines – in contrast to chemically-synthesised pharmaceuticals and some biopharmaceuticals (especially therapeutic ones) – are administered (with occasional booster shots) to healthy people, often infants and children. Stringent regulatory requirements mean in some cases that randomised phase III clinical trials of very large sample sizes are needed to establish the safety profile of vaccines; the focus is to identify the incidence of rare side effects.

For 'new' vaccines that combine different vaccines, or are protein conjugates of existing vaccines, regulatory requirements require evidence of non-inferiority in terms of clinical efficacy and safety against existing vaccines rather than against a placebo. This requirement for comparison with existing vaccines further increases the costs of developing vaccines. In general, the sequence of high fixed cost investments means that the timescales for putting in place a vaccine production plant is long (usually 2 to 5 years), and time-lines for expanding production capacity are equally long. This applies especially to technically more complex vaccines.

Given the cost of expanding production capacity and the long timescales involved, the market for vaccines is relatively prone to short-run shortfalls in product supply. One way of correcting this is to build excess surge capacity into vaccine production plants but this option is not without cost. A more reliable option is to have a multiplicity of producers of any given vaccine such that when one producer experiences a capacity shortfall, there is an alternative producer to maintain security of supply. However, the high fixed cost investments involved in vaccine supply work against having such a multiplicity of suppliers.

Economic theory indicates that given high fixed costs investments, vaccine markets will be characterised by a one-, two- or few-supplier equilibrium. Even if market entry is characterised by a multiplicity of vaccine suppliers (as a result of

significant aggregate demand), encouraging aggressive price competition, whilst beneficial to buyers in the short run, will only reinforce a few supplier-equilibrium as suppliers begin to realise that prices close to marginal supply costs do not cover long run fixed cost investments. There is therefore often limited, or in some cases non-existent, price or quantity competition in the same therapeutic class of vaccines. Competition usually evolves in the form of dynamic innovation-based competition that leads to a complete shift of market demand from existing vaccines to therapeutically-superior vaccines.

If clinical uptake and the use of clinically superior vaccines are supported by widespread clinical recommendations and/or mandates from governments and international health organisations such as the World Health Organisation (WHO), the exit of older therapeutically-inferior vaccines is more likely. Indeed, the mere anticipation of dynamic competition from therapeutically superior vaccines can undermine any incentives suppliers of current vaccines have to expand production plant capacity to meet unsatisfied or excess demand. Vaccine production plants tend to be product-specific.

Considering the high fixed cost investment, Ramsey optimal pricing theory suggests that the supply side of the vaccine market will benefit from being able to set prices differentially across high- and low-income consumers, purchasers or countries, if we assume that income is a reasonably good proxy for price demand elasticity. But an even larger benefit will be that global welfare will increase as low-income countries will have more access to vaccines from differentially lower vaccine prices (Danzon and Towse, 2003). However, for global vaccine manufacturers there are difficulties in practicing differential pricing.

One problem of segmenting markets is that lower prices offered to low-income countries can spill over into high- or middle-income countries. These price spillovers do not only constrain the scope for differential pricing; they also impact negatively on the sequencing of market launches leading to delays before products are launched in low price markets.

Empirical work done by Danzon, Wang and Wang (2005) confirms that such price spillovers (through price regulation, price referencing and/or parallel importation) undermines the willingness of producers to supply some country markets. A more recent paper by Danzon and Epstein (2008) found that manufacturers may delay launching a product in low-price markets to avoid undermining higher prices in other countries. Lanjouw (2005) found that price regulation in low-income countries has a negative impact on launch timing of new products; it is less likely that they will become available quickly.

One answer to this problem, which we believe is a less costly way of achieving market segmentation for differential pricing, is to enable it to be possible to have confidential discounts off listed prices for vaccines. Confidential price discounting mitigates both problems of physical arbitrage (parallel importation) and informational arbitrage (through price referencing). However, confidential discount contracts can be undermined by Most Favoured Nation (MFN) or Most Favoured Customer (MFC) regulations and similar requirements for matching prices. For example, offering low prices in a UNICEF procurement process for GAVI-eligible countries could conflict with price agreements with international agents serving

middle and low income countries such as the Pan American Health Organisation (PAHO) where those agreements include MFN clauses.

Demand Side

On the demand side, the market for global vaccines is mainly characterised by public provision, reflecting in part the well known problem of private market failure in the supply of goods that have externalities. Voluntary private demand for vaccines by clinicians and patients is low and is underpinned by consumers being less willing to pay for benefits that accrue to people other than themselves. Clinical prescriptions for vaccines are rare. Depending on the country-specific context, public provision of vaccines may involve government price control and centralised bargaining.

Prior to 1993, in the US the Centre for Disease Control and Prevention (CDC) used a winner-takes-all competitive bidding, that is competitive price bidding for vaccine supply where the supplier offering the lowest price bid is guaranteed all the vaccine demand. It was soon realised that this introduced uncertainty in demand for vaccines, which in turn contributed to the exit of vaccine suppliers and an unwillingness to expand production capacity (Danzon and Pereira, 2005; Danzon, Pereira and Tejwani, 2005a/b). As with the US CDC, UNICEF in the past used to follow such a winner-takes-all approach, but the situation has changed and currently bids are usually shared among more than one manufacturer to reduce the risk of under-supply. In general, for vaccine supply to low-income countries, we identify two types of 'demanders':

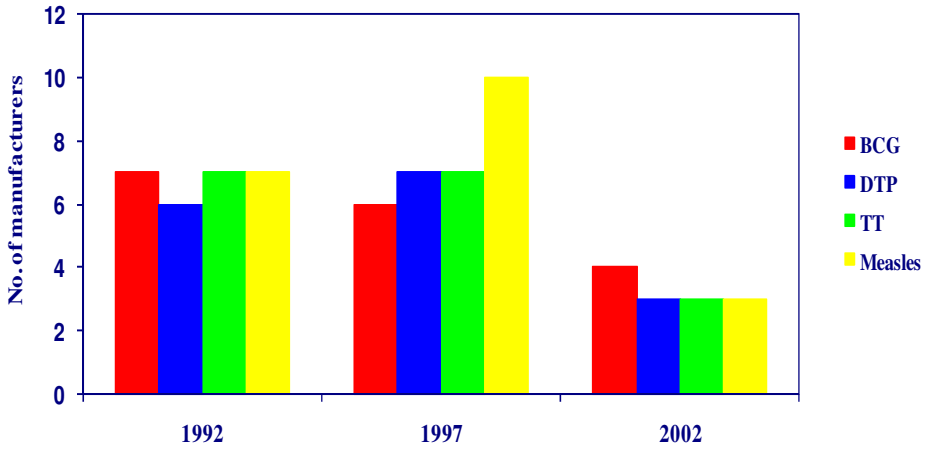
- International organisations, such as UNICEF, WHO and GAVI, which provide clinical recommendations on the most appropriate use of existing products (e.g. WHO position papers), registration/regulatory approval (e.g. WHO vaccine pre-qualifications), financial support and other strategic activities to assist the introduction of old and new vaccines (e.g. UNICEF procurements on behalf of GAVI, and Accelerated Development and Production Plan (ADIP)-type initiatives);
- Recipient countries who are the final decision-makers in terms of: (1) access (as they are responsible for prioritising public health needs and usually have to pay part or all of or the entire purchase price) and (2) distribution of vaccines (as they have to provide the health care infrastructures and human resources to administer the vaccine).

The main purchaser on behalf of low-income countries has been UNICEF which accounts for 40% of the global vaccine market by volume but only 5% by sales value. UNICEF is mostly supplied by vaccine manufacturers from developing and emerging countries (e.g. Brazil, Cuba, India, Indonesia, Korea and Senegal). Products from these suppliers are usually older generation vaccines pre-qualified by the WHO. Where vaccines are supplied by manufacturers in high-income countries these are usually newer vaccines approved by the FDA in the US or the EMA in Europe (Danzon and Stephenne, 2007).

Figure 1 shows that the number of vaccine manufacturers supplying UNICEF has declined since 1992. This in part reflects the few-supplier equilibrium that has been observed to characterise vaccine markets. However, there are other peculiar

features of vaccine supply to low-income countries via (GAVI-funded) UNICEF procurement.

Figure 1: Decline in number of vaccine manufacturers supplying UNICEF[1]



Source: Danzon, Pereira and Tejwani (2005b), Danzon and Stephenne (2007)

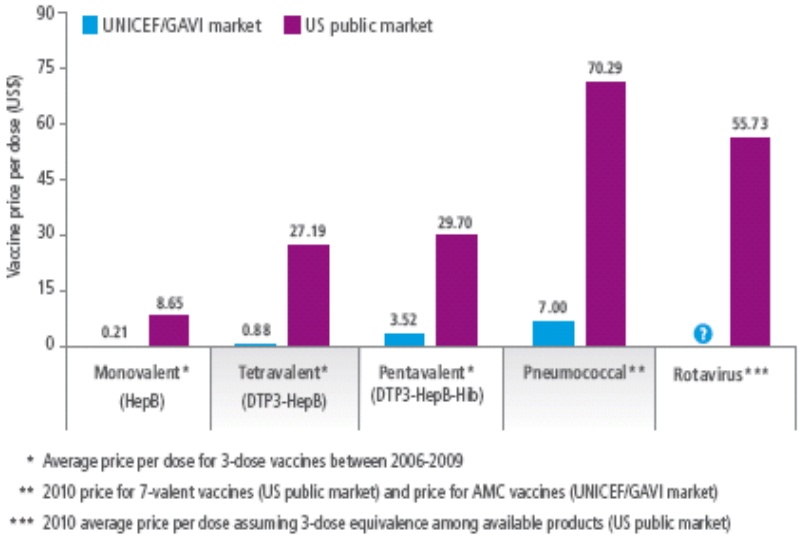
On the basis of literature studies we conclude that the low number of manufacturers may be partly explained by some suppliers' reluctance to respond to UNICEF bids given the risk of negative price spillovers into high- and middle-income countries. Such price spillovers could lead to low prices across all regions of the world which would prevent firms from recovering R&D costs.

If differential pricing was feasible and market segmentation was sustainable, then we would expect to see the same vaccine suppliers that serve high-income countries also serving low-income countries but at lower prices, reflecting the lower national incomes (and hence ability to pay) of developing countries. Also, we would observe newer generation vaccines being supplied to low-income countries at roughly the same time as they are launched in high-income countries assuming there was enough effective economic demand for vaccines at these lower prices in the low-income countries to encourage vaccine suppliers to build the necessary production plants.

Figure 2 below (supplied to us by GAVI) shows the different purchasing prices of vaccines in rich and poor countries. However, what is shown in Figure 2 does not, strictly speaking, represent differential prices for a given vaccine product but different prices for different vaccine products/formulations demanded by different countries. This apparent difference in clinical preferences is shown in Table 1, indicating time lags in the diffusion of new vaccine production technology to low-income countries.

[1] BCG = Bacillus Calmette-Guérin vaccine, which provides immunisation against Tuberculosis (TB); DTPa = diphtheria, tetanus, pertussis, acellular vaccine; DTPw, whole cell DTP vaccine; IPV = inactivated poliomyelitis vaccine; MMR = measles, mumps, rubella three-in-one vaccine; OPV = oral polio vaccine.

Figure 2: Price differences between high and low-income countries



Source: GAVI (2010a)

Table 1: Divergence of products used has emerged between low and high-income countries[1]

	Vaccine products in use					
Primary disease compared to vaccine	**Measles**	**Diphtheria, Tetanus, Pertussis**	**TB**	**Hepatitis B**	***Haemophilus influenzae* type B**	**Polio**
Low-income countries	Mono	Wholecell	BCG	Mono & in combo with DTPw	in combo with DTPw	OPV
Middle-income countries	MMR	wholecell in combo	BCG	in combo with DTPw	in combo with DTPw	OPV
High-income countries	MMR	acellular in combo	none	in combo with DTPa	in combo with DTPa	IPV in combo

Source: Danzon and Stephenne (2007)

In contrast to the situation with pharmaceutical products, there is nothing like a 'generic' vaccine. Because vaccines are derived from living organisms, there is an inherent randomness and heterogeneity in the final products, even when the same active moiety is used in the production process. What may be considered as 'generic' vaccines are best described as 'follow-on' products or 'bio-similars'. We note, however, that the use of different vaccine product types in different countries may reflect differences in clinical preferences, for instance country A may prefer a single vaccine product whilst country B may prefer combination vaccine products.

However, our analysis suggests that because of the smaller economic demand in low-income countries (which is 'inadequate' to cover the sequence of fixed costs investments needed to develop and supply vaccines to them) and the difficulties of practicing differential pricing, the demand by low-income countries is often met with long historical time lags, by (emerging) vaccine suppliers who are different from the original innovators (usually large multinational pharmaceutical and biotechnology firms). This is illustrated by the historical time lags in the case of hepatitis B and Hib vaccines, depicted in Fig. 3 and Fig. 4 below.

Fig. 3: Introduction of hepatitis B vaccines in high- and low-income countries

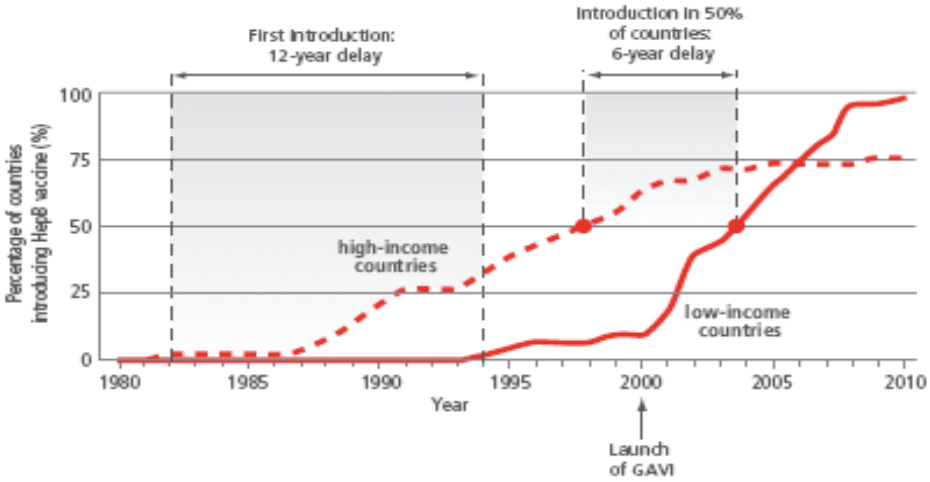
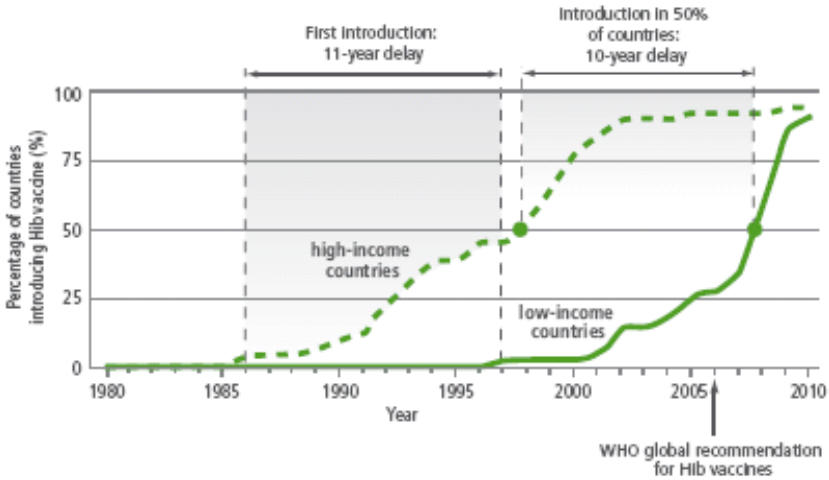


Fig. 4: Introduction of Hib vaccines in high- and low-income countries



Source: GAVI (2010a)

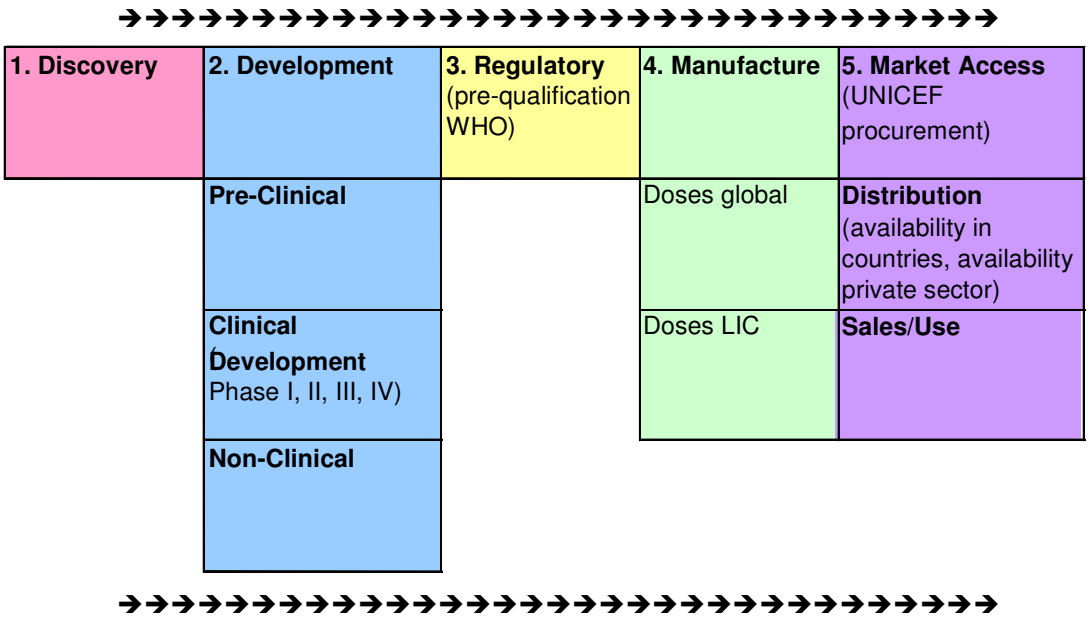
The delay in introduction of vaccines in low-income countries is made up of two parts: the time lag between introduction in high-income countries and in low-income countries, and the time it takes to achieve 'adequate' vaccine coverage (defined as vaccine introduction in 50% of low-income countries). For hepatitis B vaccines, there is a 12-year delay whilst for Hib vaccine the delay is 11 years.

However, the historical time lag between the launching of vaccines in high-income countries and their launching in low-income countries will be drastically reduced if vaccine producers are given the needed economic incentives to supply low-income countries.

2.3 The R&D process

We set out below in Figure 5 a very simplified model of the R&D process for vaccines and drugs. We have broken down the process into the stages that are relevant for considering the impact of different types of incentive. The objective, however, is to keep the model as simple as possible so that the impact of different incentives can be readily understood.

Figure 5: Major stages and sub-components of R&D activity through to patient administration of the vaccine



We have not provided all the details of the development and supply of vaccines, or attempted to capture the iterative processes involved. For example, a company need not go through all of the sequences of actions listed here if it produces different vaccines build on the same R&D platform. Similarly, a company aiming to produce line extensions of existing vaccines leading to a new vaccine that covers additional serotypes of a disease-causing microbe need not go through all the stages highlighted.

We use the term late stage vaccines for vaccines that are beyond Phase II such as pneumococcal and rotavirus vaccines. For these, there may be a need to undertake additional clinical studies and/or build extra production capacity to satisfy the requirements of the populations of low-income countries (in Figure 5 this is part of stage 2 but beyond Phase II and includes stages 3, 4 and 5). On the other hand, typical early stage vaccines, like those for HIV/AIDS[1] and tuberculosis,

represent products that have not completed Phase II and require significant investment to advance early stages of research. (The process starts from stage 1, Figure 5).

The R&D landscape is not static and the sequence of events depicted by Figure 5 is subject to change; for example, there are HIV/AIDS vaccine candidates that have shown promising results in phase III trials conducted in Thailand.

3 The AMC for pneumococcal vaccines

GAVI is stimulating new ways of raising and disbursing money for immunisation to make financing for national programmes more predictable and sustainable. As discussed in Section 1.1, a strategy to increase the availability of an effective and affordable vaccine against pneumococcal disease would be of great benefit for developing countries. An innovative new approach to public health funding is the Advance Market Commitment (AMC). An AMC is a way of stimulating and accelerating the development and manufacture of vaccines for low income countries.

An AMC works by inflating the economic demand presented by low-income countries by guaranteeing prices upfront for a predetermined supply volume. This means that vaccine manufacturers, regardless of whether they are multinational firms or 'domestic' producers from emerging economies, will have an incentive to incur high fixed investment costs to accelerate completion of R&D, to build and/or expand production plants and distribution capacity, specifically to meet demands in low-income countries. Through an AMC, donors commit money to guarantee the price of vaccines once they are developed, provided they meet stringent, pre-agreed criteria for effectiveness, cost and availability, and that developing countries demand them. Hence, an AMC provides a pull incentive that rewards developers of successful vaccines. By guaranteeing an affordable long-term price, the AMC also supports sustained use of the vaccine.

In 2005 a working group of the Center for Global Development (CGD) produced an economic and legal framework for funds to incentivise vaccine development and published the report 'Making Markets for Vaccines: Ideas for Action" (CDG 2005).
Later in 2005, at the G8 Meeting in London, the Italian Minister of Economy and Finance presented a report on AMCs for vaccines (Tremonti 2005).

Under the AMC pilot scheme for pneumococcal vaccines 'The governments of Italy, the United Kingdom, Canada, Russia, and Norway and the Bill & Melinda Gates Foundation committed US$1.5 billion and the GAVI Alliance promised to allocate $1.3 billion through 2015. Implementing countries will provide a small co-payment to contribute towards the cost of the vaccines. The World Bank provides fiduciary support; the World Health Organisation has established the minimum technical criteria for a suitable pneumococcal vaccine and UNICEF will be responsible for vaccine procurement and distribution. Companies that participate in the AMC will make legally binding long term commitments to supply the vaccines at lower and sustainable prices after the donor funds are spent' (GAVI, 2009a).

A more detailed description of the formulation and implementation process for the pneumococcal AMC will be found in GAVI (2010, pp 9-10). As part of AMC project, WHO have developed a product menu that describes the programmatically important characteristics of vaccines if they are to be suitable for use in developing countries. Table 2 below shows a summary of the product requirements that must be met or exceeded if a vaccine is to be eligible for AMC funding.

The goal of this pilot AMC is to introduce an effective and affordable pneumococcal vaccine in developing countries, thus reducing morbidity and mortality from

pneumococcal diseases. GAVI estimates that this AMC could prevent an estimated 7 million childhood deaths by 2030.

The **specific objectives** are:

1. To accelerate the development of pneumococcal vaccines that meet developing country needs (e.g. serotype composition and vaccine presentation) as specified in the Target Product Profile (TPP)
2. To bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing an initial purchase price, for a limited quantity of the 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, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after the AMC finance are used up.
4. To pilot test the effectiveness of the AMC mechanism incentivising the creation of a market for needed vaccines and to learn lessons for possible future AMCs.

Table 2: Summary of target product profile of PCVs

Attribute	Minimum Acceptable Profile
Vaccine serotypes	• Must cover at least 60% of invasive disease isolates in target region • Must include serotypes 1, 5, 14
Target population	Prevent disease among children < 5 years, in particular children < 2 years
Dosage and schedule	Compatible with national infant immunisation programmes. No more than 3 doses in first year of life
Routes of Administration	Intramuscular or subcutaneous
Product presentation	Mono-dose or low multi-dose
Product formulation	Liquid formulation
Storage and cold chain	Stable at 2-8° C with minimum shelf-life of 24 months
Product registration and pre-qualification	WHO pre-qualified

Note: A complete list of product requirements can be found at: http://vaccineamc.org/files/TPP_Master_Table.pdf

Our understanding of the Advance Market Commitment (AMC) concept is that its value, in terms of inflating economic demand presented by low-income countries, applies to both early and late stage vaccines. For early stage vaccines, the AMC commitment will have to be substantially higher than for late stage ones, to cover sunk R&D costs including the costs of failed projects and the opportunity costs of time and invested capital.

In the case of an AMC for a late stage vaccine, the expectations are that by guaranteeing prices upfront for substantial volumes of product, original vaccine innovators (including vaccine producers in emerging markets) will have an incentive to incur high fixed investment costs to accelerate completion of R&D, and to build and/or expand production plants and distribution capacity specifically to meet demands in low-income countries. The AMC established for pneumococcal vaccines is a 'late stage' AMC.

4 Other relevant activities/policies

4.1 WHO recommendation

In 2007, WHO issued a recommendation for the introduction of pneumococcal vaccines into immunisation programs in developing countries, starting with the currently available 7-valent pneumococcal conjugate vaccine (PCV). Countries with more than 50,000 annual deaths among children less than five years of age were recommended to prioritise the introduction of PCV-7 into the national Expanded Program on Immunisation (EPI). WHO also recommended that countries with a high prevalence of HIV, or other conditions which increase the risk of pneumococcal disease, should vaccinate with 7-valent vaccines (WHO, 2007).

4.2 Accelerated Development and Introduction Plans (ADIPs)

PneumoADIP was created in 2003, supported by a five year $30 million grant from the GAVI Alliance (GAVI, 2009a). PneumoADIP aimed to achieve its goals through partnerships with countries, donors, academia, non-government organisations, international organisations such as WHO, and industry. It was organised around three main areas of activity:

- Establishing the value of vaccination by demonstrating the burden of meningitis and pneumonia caused by pneumococcal bacteria and demonstrating the value of prevention through vaccination.
- Communicating effectively to key decision makers knowledge about disease burden and the value of vaccination.
- Delivering the value of the vaccine by assuring that there is a predictable supply of quality vaccine at an affordable price, and an adequate system to deliver it to the children who need it, and the financing to sustain its use (PneumoADIP, 2008).

PneumoADIP activities terminated in December 2008, and since late 2009 programmes supporting the uptake of pneumococcal vaccine have been replaced by the Accelerated Vaccine Introduction initiative (AVI).

4.3 Vaccine donations

Thanks to a GAVI-supported collaboration between developing countries, donor governments and industry, Rwanda became the first GAVI-eligible low-income country to introduce the 7-valent PCV, nine years after its introduction in the US in 2000 and in the European Union in 2001. Wyeth (now Pfizer) provided GAVI with more than 3 million doses to help Rwanda and, subsequently, Gambia (see PneumoALERT, 2009). The company did not respond to an invitation to tender for 7-valent PCV but chose instead to donate vaccines to these two countries.

It is not clear what were the underlying reasons for Wyeth (now Pfizer) not to respond to the invitation to tender for Prevnar®; one reason might be that the company wanted to avoid the risk of price spillovers. Prices offered to UNICEF, if published, might be referenced by other purchasers. Whether published or not they could be referenced via MFN clauses. For example, the Pan American Health

Organisation (PAHO) employs these clauses in its operations. Other reasons may relate to Wyeth's (now Pfizer's) anticipation of dynamic competition from Glaxo Smith Kline (GSK) 's 10-valent PCV as well as the entry of its own 13-valent PCV.

5 Current vaccine situation

Currently there are three main formulations of pneumococcal vaccines on the global market. Besides the 7-valent PCV (Prevnar®), we know a 10-valent PCV, Synflorix®, manufactured by GlaxoSmithKline (GSK) was approved by the EMEA in 2009. It is the first licensed vaccine to include serotypes 1, 5 and 14, which account for between one-third and one-half of invasive pneumococcal disease in children less than 5 years old. Besides offering protection against these important serotypes, Synflorix® has a more convenient presentation, being supplied in a 2-dose vial which makes it more suitable for use in resource-poor settings. A 13-valent PCV (Prevnar® 13) manufactured by Wyeth (now Pfizer) was in phase I/II trials in 2004 and gained regulatory approval in the US in late 2009.

The AMC Secretariat announced the first signature of AMC supply agreements following the first call for AMC supply offers, published by the UNICEF on September 4th 2009. GSK has signed a provisional supply agreement (PSA) with UNICEF for 30 million doses of its 10-valent vaccine annually starting in January 2012 for a period of 10 years. Likewise, Wyeth (now Pfizer) has signed a PSA for 30 million doses annually for its 13-valent vaccine from January 2013 for a period of 10 years.

The supply agreements were provisional to the extent that the vaccines would not be procured until the candidate vaccine was deemed eligible for AMC funding by an AMC Independent Assessment Committee (IAC). However, both PSAs have now become effective as both candidate vaccines have been deemed eligible for AMC funding, Synflorix® on 16 April 2010 and Prevnar® 13 on 23 August 2010.

In addition to the PSAs, GSK and Pfizer have agreed to provide, in total, 7.2 million doses, 24.2 million doses, and 20 million doses for years 2010, 2011 and 2012 as part of an interim 'AMC Capacity Development Period', which is defined as the period during which suppliers develop dedicated manufacturing capacity to serve GAVI-eligible countries (GAVI, 2010c).

6 Conceptual framework of the consultancy

6.1 Mandate

The Swiss Centre for International Health (SCIH) was commissioned by the GAVI Alliance to conduct a baseline study for the pneumococcal vaccine AMC.

The goal of this **AMC baseline study** was to establish the environment prior to the AMC and understand how the environment might evolve without an AMC so as to be able to monitor and evaluate the impact of this intervention. A robust monitoring and evaluation framework is critical and will facilitate estimation of AMC impact and track the value received for public funds invested.

2005, the date when the AMC concept was first formulated in the CGD report (CGD 2005) and the Tremonti report (Tremonti 2005), was set as the starting date and baseline as these events may have had an impact on vaccine industry strategy and investment

The economics of vaccines, the R&D process, the pre-AMC vaccine environment and the role of the AMC, described in more detail in Section 2 above, have been taken into account for the design of the AMC baseline study.

Below, we describe the conceptual framework and the approach chosen to develop and conduct the mandated baseline study.

Deriving from the overall goal and objectives of the AMC (Section 3) and the underlying general pneumococcal disease and AMC environment, the activities of this consultancy comprise three broad components. These are interlinked but each necessitates a specific approach: country level survey, industry level survey and counterfactual modelling.

6.2 Specific objectives of mandate

Objectives and related strategies of the **baseline study** are:

1. To describe activities of the industry in pneumococcal vaccine development, investment and manufacturing since 2005.
   This has been approached by collection of data on pneumococcal vaccine development and manufacturing as well as attitudes regarding the global contextual environment within which the AMC mechanism fits

2. To describe the situation regarding pneumococcal disease in GAVI-eligible countries starting in 2005.
   This has been approached by collecting data on pneumococcal epidemiology, vaccine demand and need, capacity for uptake, and willingness and ability to purchase and subsidise vaccines, as well as perceptions of key stakeholders concerned with pneumococcal vaccination and the AMC model.

3. To estimate what would have happened if no AMC had been implemented, as a control for measuring the incremental impact of the AMC initiative on pneumococcal disease and mortality.
   This has been approached by identifying and modelling two counterfactuals assuming different scenarios of vaccine introduction strategies.

These strategies as formulated in the Terms of Reference (TOR's) of the Request for Proposals (RFP) will provide a base from which effectiveness of the pilot AMC and its achievement of goal and objectives against the baseline situation can be measured in the future.

6.3 Study approach

The study questions of the AMC pilot relate to the intended consequences and chain of events of this new financing and introduction strategy in terms of pneumococcal vaccine development, availability and uptake, focusing on the timing, type, price, and quantity of pneumococcal vaccine introduction in GAVI-eligible countries.
The baseline study provides three outputs:

1. Baseline data: Quantitative and qualitative information on the epidemiological status of pneumococcal disease, and industry activities from 2005 to 2009. The baseline data generated establish the environment prior to the AMC and will be used to understand changes in vaccine market developments and pneumococcal vaccine uptake, coverage and mortality.
2. Model for measuring counterfactuals: Two counterfactuals and quantitative modelling to estimate what would have happened if no AMC had been implemented and to measure the incremental impact of the AMC initiative on the vaccine market and pneumococcal disease and mortality.
3. Methodology for M&E: As part of the baseline study a standardised core set of indicators and tools to collect, summarise and analyse data were established. These are available for future monitoring of this pilot AMC. The establishment of these indicators will allow data collected in the future to be used for comparisons against the baseline as the AMC is implemented.

We based our stepwise approach to the baseline study on the following elements: the AMC objectives as the guiding principles and overarching framework, and a conceptual framework as a systematic representation of the AMC environment. Based on AMC objectives we developed appropriate evaluation questions and indicators through a logframe approach using the AMC M&E Report of the Monitoring and Evaluability Study (GAVI, 2008) as the main reference document.

6.4 Conceptual framework

The AMC is an intervention designed to have a direct effect on:
1. Industry behaviour in the development and manufacturing of pneumococcal conjugate vaccines (PCV),
2. Vaccine uptake and uptake of the vaccine in GAVI-eligible countries.

This will lead to reduced morbidity and mortality from pneumococcal diseases.

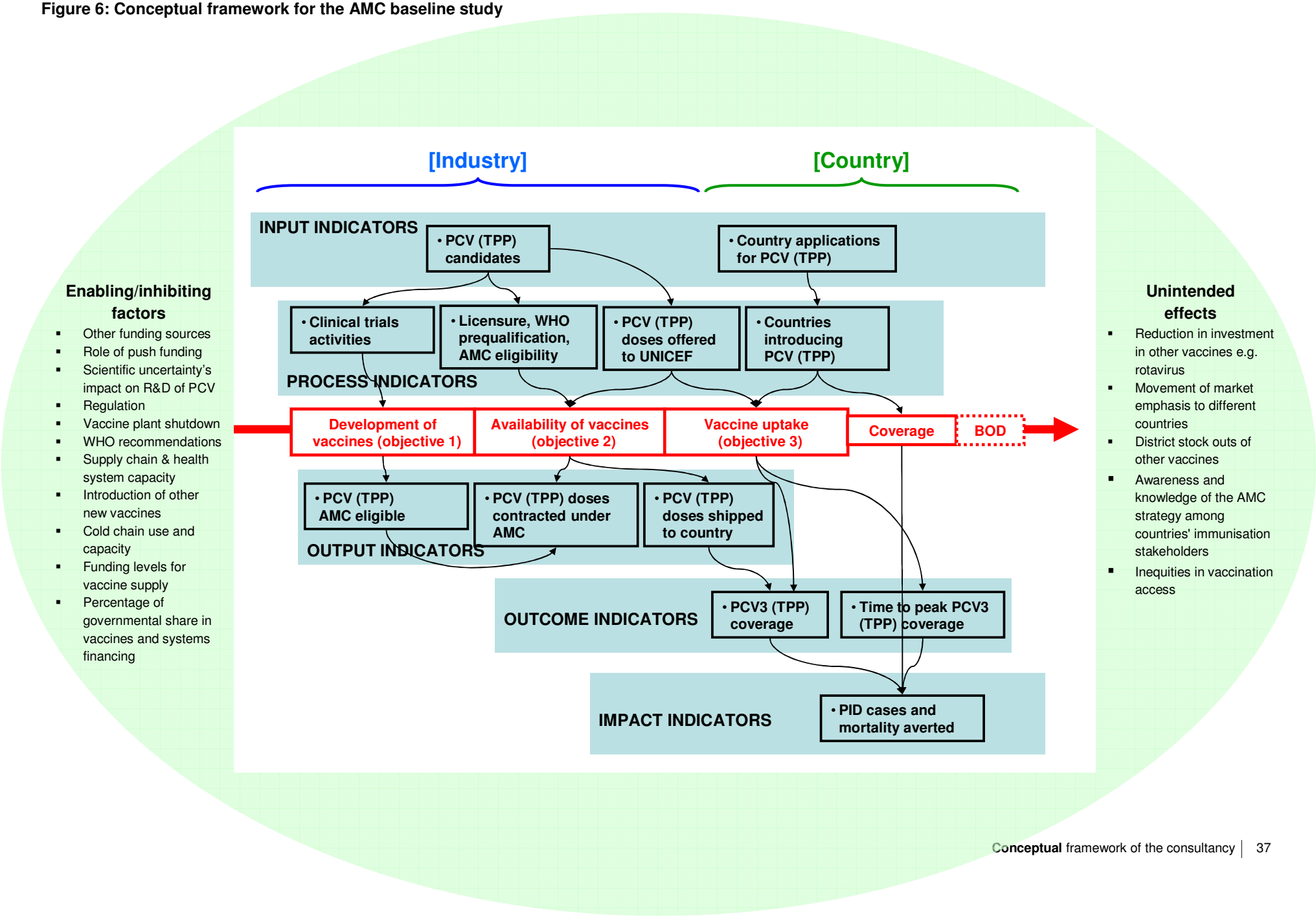
The chain of events and expected success of the pneumococcal AMC begins with binding agreements from donors to make the market for pneumococcal vaccines (as defined in the TPP) more profitable and predictable. This encourages acceleration and expansion of PCV development activities (objective 1), and increased investment in production capacity by vaccine manufacturers (objective 2). The donor commitment is also expected to have an impact on country uptake both through increased/accelerated supply of appropriate vaccines and through increased demand: the AMC increases the certainty of donors' financial support to GAVI for PCV and thus for countries. The AMC establishes a cap on the long term price of the vaccine so that it is affordable for countries over time. This is meant to influence uptake as countries are better able to predict the long term vaccine prices, and make more informed introduction decisions (objective 3). Shipping of doses of TPP compliant PCV, delivery to EPI systems and administration of vaccines to children in GAVI-eligible countries will increase immunisation coverage which, ultimately, will decrease mortality due to pneumococcal diseases.

Acknowledging the variety and complexity of the processes involved from vaccine production up to vaccine administration, this baseline study and further evaluations needed to be structured around a consistent conceptual framework.
In order to provide theoretical support for the study design and clarify the chain of events, we have translated our approach into a simple graphical representation accommodating the baseline study within a common evaluation framework. The systematic organisation of M&E components integrates the elements of the baseline study and depicts the expected sequence of events leading to the expected success of the AMC. The conceptual framework illustrates the logical chain of events and the linkages of AMC objectives, M&E domains and indicators on a timeline.

Figure 6 represents the conceptual framework for the AMC baseline study. This framework:

- illustrates the relationships of the baseline study components and the industry and country level events to be captured by the counterfactual model;
- presupposes that outputs from a given process are the inputs for the next process;
- distinguishes between outputs, outcomes and impact: outputs are understood as the direct results of a given process; i.e. what allows us to establish that a given process has actually taken place; outcomes are the effects of the processes described in relation to the interface between the health system and the ultimate beneficiaries of the intervention; and impact is the final expected effect of the AMC in the health status of the population;
- uses the terms of 'inhibiting" and 'enabling" factors to describe those that- despite being external to the scope of the AMC intervention- may have an adverse or favourable effect in the development of the intervention, respectively.

Figure 6: Conceptual framework for the AMC baseline study



6.5 Contextual factors and effects on AMC

As highlighted within our conceptual framework above, the pneumococcal AMC pilot takes place in an economic, epidemiological and industrial macro-environment that can both enable and inhibit the inputs, processes, outputs, outcomes and impact of the AMC pilot affecting the chain of events of PCV development (objective 1), manufacture and supply (objective 2) and the supply chain and health systems' capacity for uptake (objective 3). There may also be unintended effects. For instance, late pipeline development and early licensing of multinational companies may discourage emerging country manufacturers – sone possible unintended effect of the AMC.

These factors and effects are the key to understanding the wider global context in which PCV development, manufacture, supply and uptake takes place and for the attribution of AMC effects. It will be necessary to routinely collect details on these factors with indicators. These indicators will allow other factors which might arise over the AMC period to be captured.

We have summarised potential contextual factors and effects that may only become visible as the AMC mechanism is being implemented in Table 3.

Some unintended consequences as well as enabling and inhibiting effects of the AMC may become visible only once the AMC has been fully implemented. Therefore Table 3 is an indicative list which should be reviewed and updated regularly in future studies and M&E to take into account other effects which become relevant. However, the counterfactual modelling approach used here has taken into account and reflected on relevant enabling, inhibiting and unintended effects, depending on data availability, in order to generate the most realistic model possible (see Part II Sections 7 and 8).

Table 3: Potential contextual factors and effects on AMC (examples)

AMC objective	Effect: enabling, inhibiting unintended
1) PCV development	Other funding sources Role of push funding Scientific uncertainty's impact on R&D of PCV meeting TPP Reduction in investment by vaccine developers
2) PCV availability	Regulations Movement of market emphasis to different countries Interaction between UNICEF and PAHO Vaccine plant shutdown
3) PCV uptake	Funding levels for vaccine supply to low-income countries Percentage of governmental share in vaccines and vaccination systems financing Introduction of other vaccines which may conflict with introduction of PCV Awareness and knowledge by countries' stakeholders (role of information and evidence gathering) Speed of WHO recommendations being made Supply chain and health system capacity EPI resources and processes: cold chain capacity. Inequities in vaccination access (Districts with DTP3 coverage over 80%) District stock-outs of other vaccines

6.6 Evaluation questions

As part of the process of defining *'what is to be evaluated'* and by reflecting on the AMC goal and objectives, a number of broad key issues were identified, and on the basis of these, evaluation questions were formulated (Table 4). From these evaluation questions we identified and developed indicators that are intended to provide the necessary data for measuring progress and success in terms of outputs, outcome and the epidemiological impact of the AMC strategy over time. In a further step, means of verification of indicators, i.e. their respective methods and sources, are described.

Risks related to this approach are related to the complexity of the evaluation questions such as the accessibility and availability of historical data and perceptions, as well as to the feasibility and cost of data collection.

Table 4: Initial evaluation questions

Goal and objectives	Evaluation questions
Goal: To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030	How has the AMC influenced pneumococcal disease incidence, morbidity and mortality in children under 5?
Objective 1: To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP)	To what extent has the TPP vaccine pipeline been accelerated and expanded and what factors have affected progress?
Objective 2: To bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price, for a limited quantity of the new vaccines, that represents value for money and incentivises manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand**.**	Has the AMC increased TPP vaccine production and manufacturing and what factors have contributed to this? Has the AMC increased the number of doses available at the level of GAVI-eligible countries supplied by manufacturers through GAVI's procurement process?
Objective 3: To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after AMC finance is used up.	What demand is there from GAVI-eligible countries for TPP vaccines? To what extent has this demand been met in terms of: - supply from manufacturers of vaccines - coverage rates?

6.7 Indicator matrix

As described above, we formulated evaluation questions deriving from the AMC goal and objectives. Corresponding indicators were developed that should answer the evaluation questions. The indicator matrix (Table 5) summarises these elements by AMC objective, including detailed indicators, their justification, data requirements, sources and suggested frequency of collection.

Full details of the justification for these indicators, the data collection and analysis process used in the baseline study, including sources, collection frequency and presentation details, are outlined in the methodology section of this report, Part II, Section 9. Baseline figures for these indicators and comments on the findings are described in the corresponding sections of Part III. Lessons learnt and issues raised for future data collection are outlined in Part IV.

SCIH in consultation with GAVI has used the following guiding principles when choosing the most appropriate set of indicators and associated data collection instruments:

- Ensuring that the indicators are linked to the goal and objectives, and that they are able to measure change over the program time period.
- Ensuring that standard indicators are used to the extent possible for replicability and comparability over time or between population groups.
- Considering the feasibility of data collection and analysis.
- Keeping the number of indicators to the minimum needed, with specific reference to the scope of the AMC that requires and will use indicators to make programming and management decisions.

Table 5: Indicator Matrix

Indicators	Justification	Data requirements	Source, Frequency
Goal: To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030			
1. Cumulative number of cases of IPD averted due to TPP vaccines in GAVI-eligible countries	Reducing morbidity and mortality is the overarching goal of the AMC.	Number of IPD cases averted in GAVI-eligible countries due to TPP vaccines by year	WHO Frequency: Annual
2. Cumulative number of future deaths averted due to TPP vaccines in GAVI-eligible countries		Number of future deaths averted in GAVI-eligible countries due to TPP vaccines by year	WHO Frequency: Annual
Objective 1: To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP)			
3. Cumulative number of TPP candidates	Currently there are only a few candidates potentially meeting the TPP. It is theorised that the AMC will encourage an increase in the number of candidates being developed, thus increasing the likelihood that TPP requirements will be met.	Number of TPP candidates - broken down by development milestone with corresponding date - baseline years: 2005 and 2009	Web search including industry databases (baseline used Thomson Pharma and Biopharm Insight) e-mails to companies Frequency: Annual
4. Median time between key milestones in the development of TPP candidates	The AMC is concerned with accelerating the PCV development process. It is believed that the AMC will have an impact on the timeline for one or more phases of the development process.	Median months for the clinical and approval phases based on months between each key milestone. - baseline figures for 2005 and 2009 for each TPP candidate	As above Frequency: During impact evaluation which will be conducted every 4 years
5. Cumulative number of AMC eligible TPP vaccines	This indicator will show how many of the TPP candidates meet the TPP as per IAC evaluation of eligibility.	Number of TPP vaccines with AMC eligibility - broken down by product and date - baseline years: 2005 and 2009	GAVI data Frequency: Annual
Objective 2: To bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price, for a limited quantity of the new vaccines, that represents value for money and incentivises manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand			
6. Total number of doses of TPP vaccine offered to UNICEF SD per year for GAVI-eligible countries	The aim of the AMC is to increase capacity of production to meet GAVI-eligible country demand. The number of offered doses is the best proxy for actual capacity availability. This indicator is needed in addition to doses contracted (see indicator 7 below), since the number of offered doses may exceed contracted supply.	Total number of doses of TPP vaccines offered to UNICEF SD per year (including offered doses for future years) - baseline years: 2005 and 2009 (year of issuance of first call for supply offers)	UNICEF data (via GAVI) Frequency: Annual

Indicators	Justification	Data requirements	Source, Frequency
7. Number of doses of TPP vaccine contracted under AMC by year	The AMC aims to improve availability in terms of increasing production of TPP vaccines for GAVI-eligible countries. It is necessary to measure the number of contracted doses, since the number of doses offered by manufacturers (Indicator 6) may not always be realistic.	Number of doses of TPP vaccines contracted under AMC by year - broken down by company and year - baseline years 2005 and 2010 (year of conclusion of first call for supply offers)	UNICEF data via GAVI Frequency: Annual
Objective 3: To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after the AMC finance are used up			
8. Cumulative number of countries that have applied for GAVI support for PCV	This gives an indication of country interest in introducing PCV. It is theorised that the AMC will lead to accelerated country demand due to the long term commitment to financing pneumococcal vaccine and the certainty on price.	Number of countries submitting applications to GAVI for PCV support. Data on individual countries submission status: needing clarifications, re-submissions and approval. Countries to be counted once only, even if they submit multiple applications. This will also be expressed as a percentage of GAVI-eligible countries.	GAVI Frequency: Annual
9. Cumulative number of GAVI-eligible countries introducing TPP vaccines	Countries plan in advance the introduction of TPP vaccine. This has to be synchronised with the application process (previous indicator) and the actual shipment of vaccine (next indicator).	Year of introduction of TPP vaccines by each GAVI-eligible country.	GAVI Frequency: Annual
10. Cumulative number of doses of TPP vaccine shipped to GAVI-eligible countries	This indicator enables the assessment of the AMC's effect on vaccine supply independent of the capacity of countries to distribute and administer TPP vaccines to the target population.	Amount of TPP vaccines delivered over the year; taking into account delivery schedules.	UNICEF SD Frequency: Annual
11. PCV3 coverage in GAVI-eligible countries	Coverage is the key indicator to determine what proportion of the target population ultimately receives the recommended number of doses of TPP vaccines.	PCV3 coverage estimates by country and year; DTP3 coverage estimates needed for comparison	WHO/UNICEF coverage estimates. Frequency: Annual
12. Time to national peak coverage	Important indicator to assess the extent to which TPP vaccine is scaled up rapidly to reach the target population.	PCV3 and DTP3 coverage estimates by country and year, and number of years taken to match in each country.	WHO/UNICEF coverage estimates. Frequency: Annual

PART II – METHODOLOGY

7 Counterfactuals

In order to estimate the incremental impact of the pilot AMC on the development, manufacturing and uptake of PCVs in low-income (GAVI-eligible) countries, we had to identify two alternative routes of vaccine supply to low-income countries in the absence of an AMC intervention. These will represent two 'counterfactuals' that describe plausible states of the world without an AMC for the pneumococcal vaccines. For clarity's sake, we define below what we mean by the expression 'counterfactuals".

Counterfactuals are used in economic analysis as 'what ifs?' – scenarios that are thought experiments, alternatives to actual history, to assess what would have happened (for example to an economy) if, contrary to fact, some present conditions were changed (McCloskey, 1991; Cameron, 1996). The OECD DAC defines a counterfactual as 'the situation or condition, which hypothetically may prevail for individuals, organisations or groups where there is no development intervention." (OECD, 2002)

In the case of the AMC baseline study, the counterfactuals define hypothetical scenarios which could have taken place had the AMC concept not been introduced in 2005. As stated earlier our reference point is year 2005 as the public announcement of an AMC intervention could have altered the strategic decisions of vaccine suppliers as to their R&D choices as well as investments in vaccine production and distribution capacity.

We want to emphasise that the counterfactuals we aimed to develop are not meant to capture all the nuances of real life; our objective was to provide two counterfactual scenarios that come close to what might have been observed in real life. Our methodology for developing the counterfactuals, in the first instance, relies on the economics literature on the market dealing with vaccines, our understanding of role of a late stage AMC, and our understanding of the pneumococcal vaccine market prior to introduction of the pneumococcal AMC.

7.1 Methodology for defining and validating the counterfactuals

To develop the counterfactual scenarios, we considered the following conditions of the PCV environment (without an AMC intervention):

- On the demand side, which procurement model would be established, which purchase price would prevail, which level of funding from donors would be secured, which vaccine(s) would be included in any procurement request, and which countries would decide to take up the vaccine?

- On the supply side, which multinational companies already in the market with pneumococcal vaccines would expand capacity, which multinational companies would respond to any international procurement invitation, and which company (including emerging suppliers) would enter the market?

We selected two plausible scenarios (in line with the scope of the AMC baseline study) that combine different responses/behaviours of key players from the demand and the supply side. The market conditions deriving from the two counterfactual scenarios can be expected to lead to different levels of uptake (vaccine volume sold), access timelines (when the vaccine would be introduced in poor countries), and of the technical characteristics of one or more PCVs and the timing of their being made available.

Our methodology for developing the counterfactuals entailed four elements (tasks):

1. Developing two plausible counterfactuals, i.e. identifying the most likely scenarios that would occur without an AMC (the no-AMC scenarios), and elaborating a set of assumptions on key conditions of the demand side and on the supply side;
2. Reviewing the appropriateness of the suggested examples of current and historical vaccines (i.e., rotavirus, *Haemophilus influenzae* type b – Hib) that could play a role in representing the counterfactual scenarios;
3. Validating the counterfactual scenarios developed in stage 1;
4. Identifying key indicators of the counterfactual scenarios and identifying relevant data sources to populate them. Quantitative estimation of our counterfactuals could include some real life data and, when this was not available, appropriate assumptions and extrapolations could be used.

To accomplish the first task, we conducted a literature review on the basic concepts of the economics of vaccines, which we presented in Section 2.2, and analysed the pre-AMC situation of the pneumococcal vaccine environment, as outlined in Section 2.1. Below in Section 7.2 we set out our two counterfactual scenarios (early conventional procurement and late conventional procurement with earlier country by country negotiations).

To complete the second task, we noted that two examples of existing vaccines had already been suggested in the AMC Framework report and the SCIH inception report as relevant – the rotavirus and Hib vaccines. The former represents a ‘new’ generation of vaccines which still needs to be introduced and be widely used in developing countries; the latter is a relatively ‘older’ vaccine which can provide some historical data on vaccine uptake in poor countries.

We suggest that data derived from these two examples can indeed be used to inform key input assumptions for quantitative modelling of the counterfactual scenarios. Nevertheless, the two historical examples can only be applied to the counterfactual model with some adjustments to reflect crucial differences between the characteristics of these vaccines and our understanding of the relevant counterfactual. We discuss these questions in more detail below.

Our work on all four tasks included conducting two sets of semi-structured interviews with groups of experts. The first interview programme was to help define the counterfactuals and the second interview programme, with a different group of experts, was to validate the counterfactuals.

7.2 Definition of counterfactuals

Based on the basic concepts of the economics of vaccines, and the pre-AMC situation of the pneumococcal vaccine environment presented and outlined in Section 2, we have developed the following two counterfactual scenarios:

- Counterfactual 1 – Early conventional procurement;
- Counterfactual 2 – Late conventional procurement with earlier country-by-country negotiations.

7.2.1 Counterfactual 1 - Early conventional procurement

Without an AMC, one possible market setting on the demand side could be:

- Funding arrangements: these are established through a conventional procurement model, where UNICEF solicits bids; manufacturers then bid, and UNICEF accepts a bid or bids (trying whenever possible to procure from multiple manufacturers) and issues contracts. GAVI participates in the process through the 'procurement reference groups". Contracts have typically been for three years; these are non-binding indications of intentions to procure.
- Timing: funding arrangements are finalised in the short run, i.e. in the next 2-3 years.
- Total level of funding: donor money raised to fund PCVs is less than that which would be raised with the AMC.
- Local decision makers in GAVI-eligible countries: they endorse the UNICEF agreement and introduce PCVs, subject to funding support from GAVI.

On the supply side, the market could present:

- Number and type of manufacturers entering the low-income country market:
    - One multinational company (GSK) responding to the UNICEF bid and expanding capacity for developing countries.
    - Another multinational company (Wyeth, now Pfizer) needing more support, owing to its limited experience with markets in low-income countries.
    - An Indian manufacturer beginning its R&D programs on a pneumococcal conjugate vaccine (PCV) to pursue the local market.
    - Entry decisions of other emerging manufacturers following standard timelines and procedures: they would watch and monitor the market (number of countries buying PCVs and total demand volumes) and based on that they would make their investment decisions. Upfront funding directly supporting one or more of the emerging manufacturers may

accelerate the process. They are not, however, able to enter the market before 2013-2014[4].

7.2.2 Counterfactual 2 - Late conventional procurement with earlier country-by-country negotiations

The other possible no-AMC scenario could present less favourable assumptions than those made for Counterfactual 1.

On the demand side, we could have:

- The funding arrangements: there is a failure of a centralised and coordinated action to provide funds and to determine the purchasing price in developing countries. This is mainly due to issues concerning difficulties for manufacturers in adopting a differential pricing policy (i.e. selling at different prices in different geographical regions of the world). As in the case of the 7-valent PCV, the manufacturer may prefer to donate vaccine doses to specific countries instead of responding to an invitation to bid due to its agreement with PAHO.
- Timing: the conventional UNICEF procurement system is not successful in the short term as no supplier puts in a bid. Only after prolonged negotiations, is a solution found that allows firms to offer the vaccines to GAVI countries at a lower-than-PAHO price.
- Total level of funding: donor money raised to fund PCVs is less than with the AMC.
- Local decision-makers in GAVI-eligible countries: they prefer to wait and for countries with domestic vaccine production capacity, they may opt to purchase from their own local suppliers.

On the supply side, there could be:

- Number and type of manufacturers entering the low-income country market:
    - Only one multinational company willing to supply GAVI-eligible countries in the short term (most likely GSK).
    - The other multinational company initially targets middle-income countries and private markets in poor countries.
    - Emerging manufacturers' strategic behaviour is not fundamentally different from that outlined in Counterfactual 1, i.e., market penetration following standard timelines[5].

[4] We are aware that market entry decisions by vaccine suppliers from emerging economies may be 'enhanced' by push funding received from (consortia of) private, national and international organizations concerned with global health. Our counterfactuals describe the state of the world *ex post* such push funding (to reduce the overall costs of investments in R&D, production plants and distribution capacity). The important element we aim to capture with our counterfactuals is that of market entry by vaccine producers to supply low-income countries.

[5] We understand that market entry decisions of emerging vaccine producers may not follow standard timelines and expectations. However, our counterfactuals are meant to provide close approximation of plausible alternatives; but not to capture all possible events that could occur.

Based on the key conditions of the vaccine environment outlined above, we have identified the following indicators for the counterfactuals:

a) The overall timescale for access
b) The level of coverage
c) The technical characteristics of the distributed PCVs.

7.2.3 Relevance of historical examples to populate the counterfactuals

The mandate for the AMC Baseline study indicated that rotavirus and Hib vaccines may be the appropriate historical examples to describe the state of the world without the pneumococcal AMC. In order to identify potential examples for the counterfactuals, we first had a look at all vaccines that had been developed over time using year 2005 as the cut-off point to avoid potential confounding that announcement of an AMC intervention may have had on the strategic investment decisions of vaccine suppliers.

The mandate required that historical examples chosen should reflect the following dimensions:

- **Market structure**: evaluation of clinical needs for vaccines (as proxied by disease burden), comparison of vaccine demand in GAVI-eligible countries for the historical examples identified and the constraints of translating clinical need into reasonable (economic) demand.
- **Technological characteristics**: analysis of factors that may influence constraints in vaccine development, manufacturers' production capacity and barriers to market entry etc.
- **Characteristics of vaccine suppliers involved in R&D** (whether these are multinational firms or those from emerging economies)
- **Policy environment**: analysis of main policies adopted to foster the development and uptake of vaccines (specifically constraints on the practice of differential pricing and the implications this has on vaccine supply).

For our purposes, we focussed mainly on 'market structure' and 'technological characteristics'. Figure 7 below shows the list of vaccines we looked at.

Market structure

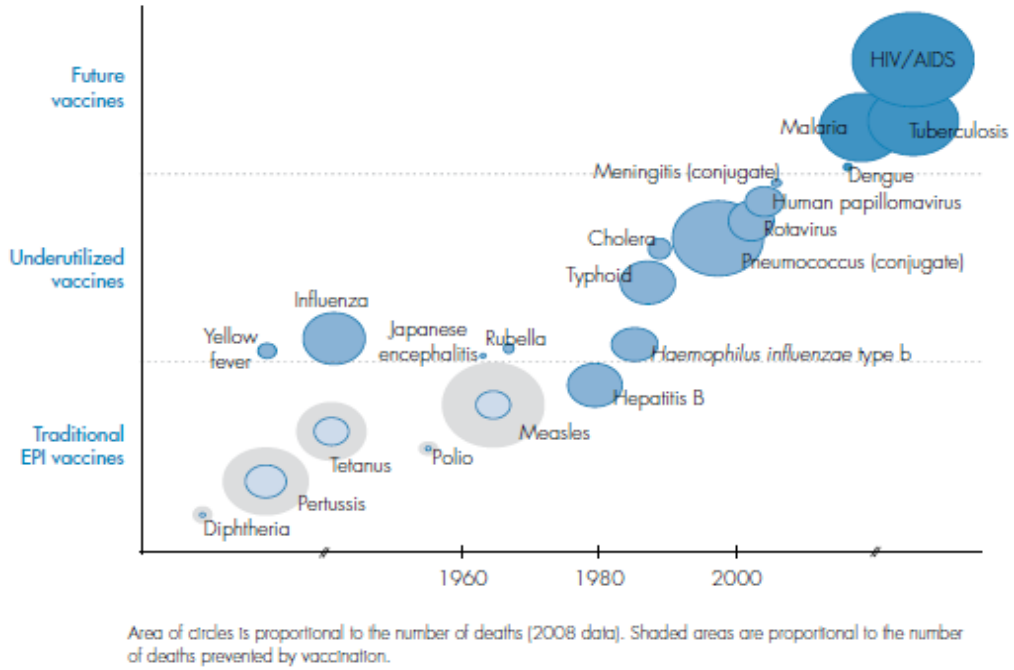
Comparing like with like (on the dimensions specified) and controlling for confounding factors, we determined that the most plausible set of historical examples for the pneumococcal AMC counterfactual would be those in the group of existing under-utilised vaccines in Figure 7. We excluded all traditional EPI vaccines, as well as vaccines that are in the R&D pipeline, because we are trying to understand how the take-up of under-utilised vaccines might be changed under different policy scenarios.

We recommend that analysts using our counterfactuals, through appropriate sensitivity analysis, investigate parameter and structural uncertainty in any models built for estimation.

We therefore narrowed our list of historical examples to vaccines for yellow fever, influenza, Japanese encephalitis, rubella, hepatitis B, Hib, typhoid, cholera, rotavirus, human papillomavirus (HPV) and meningitis.

We first considered all factors that might influence the willingness of vaccine producers to supply to low-income countries using information synthesised in the sections above. We evaluated how the supply- and demand-sides of the vaccine market will interact. Vaccine markets are characterised by one-, two- or few-supplier equilibria reflecting the high fixed cost investments (in R&D, production, regulatory compliance and distribution) needed to bring a vaccine on to the global market. The cost of regulatory compliance will be higher for vaccines that employ new production technologies (for example genetically engineered recombinants, conjugate vaccines and combination products). We anticipate the overall size of fixed cost investments will work against the willingness of vaccine producers to supply such products to low-income countries. This will also affect their willingness to expand production plant capacity.

Figure 7: Vaccine development through time

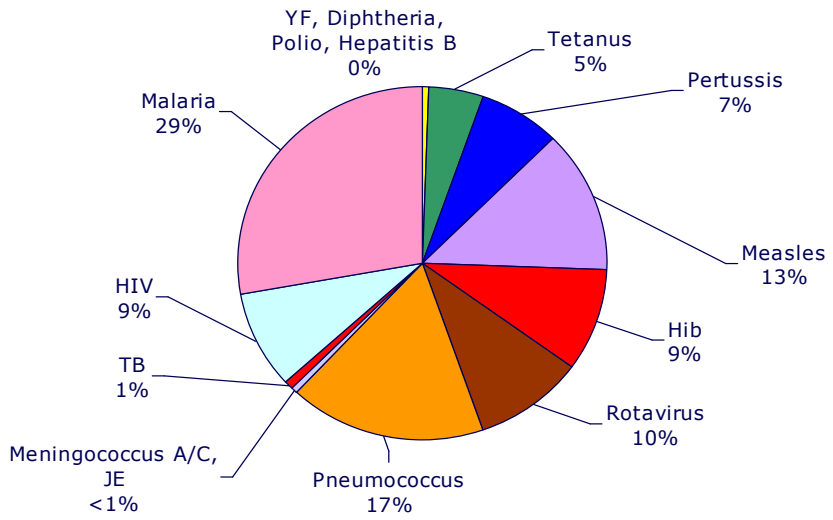


Source: WHO (2010)

Economic demand (which is, strictly speaking, different from clinical need but is necessarily related to it) is needed to incentivise vaccine producers to make the necessary investments. Hence our prior hypothesis is that for diseases where there is appreciable demand for vaccines, suppliers will be more willing to enter into contracts to serve low-income countries. By looking at the disease burden as an indicator of clinical need, and assuming this corresponds to effective economic demand, we conclude from Figure 7 and Figure 8 that the set of examples closest to the pneumococcal disease vaccine are Hib, hepatitis B, rotavirus, HPV and influenza.

The willingness of vaccine suppliers to respond to the size of clinical need will be greater where there are reasonably reliable estimates of the likely size of demand by country and/or region. Reduced uncertainty of demand works well for vaccine suppliers in that they will be in a better position to determine the 'optimal' size of the production plants and the distribution capacity needed to serve low-income countries. It will be necessary to identify and adjust if necessary any estimates taken from other diseases when working on ADIP or ADIP-type arrangements, to increase market awareness and reduce uncertainty around demand estimates.

Figure 8: Causes of under-five mortality in 2002 – an illustration of the clinical need for vaccines[6]



Source: Danzon and Stephenne (2007).

Technological characteristics

We then considered the technological characteristics of the vaccines. On this basis we excluded annual influenza vaccines as relevant comparators as these require seasonal incremental investments in R&D and production capacity to cater for mutating serotypes of the disease-causing virus.

We concentrated on finding historical examples that are similar to pneumococcal vaccines. These are (1) 'polyvalent' vaccines (that is clinical indications cover several serotypes of the same disease-causing microbe or different disease-causing microbes) and (2) they are protein-conjugate polysaccharides. We thus selected vaccines whose production technology would involve a sequence of fixed costs investments similar to that which would be incurred for pneumococcal vaccines.

These criteria reduced our plausible set of potential examples to the polyvalent conjugate Hib-containing vaccines, and meningitis vaccines. There are also

[6] JE = Japanese encephalitis, YF = yellow fever

monovalent presentations of the Hib vaccines, but current clinical preferences indicate that GAVI only offers financing for the polyvalent versions (Hib Initiative, 2009). We considered Hib to be the most appropriate example in this category for the counterfactual. Meningitis vaccines were not further considered, because the disease burden of meningitis is very small compared to that of pneumococcal disease, which is likely to give rise to very different supply responses.

We therefore consider Hib to be attractive as a basis for populating one of the counterfactuals we propose, Counterfactual 2 – Late Conventional Procurement with earlier country by country negotiations, with appropriate adjustments.
However, having only one example is not very helpful in terms of data sets for potential use for quantitative estimation of the incremental impact of the AMC for the pneumococcal vaccines. As a second example, as an alternative to the conjugate meningitis vaccines, we reconsidered the appropriateness of rotavirus vaccine.

A Rotavirus ADIP was set up at the same time as the PneumoADIP. This actually makes rotavirus attractive for populating one of the counterfactuals we propose, Counterfactual 1 – Early Conventional Procurement, with appropriate adjustments.

The work of Rotavirus ADIP was to oversee the conducting of large sample size clinical trials to ascertain the incidence of a severe but rare adverse effect, intussusceptions – by direct funding of late stage R&D costs for two vaccine products, RotaTeq® (Merck) and Rotarix® (GSK). There is no guarantee *ex post* of these R&D investments that vaccine producers will be willing to invest in the needed production plants for supply to low-income countries. To do so close to the launching of the vaccine would require the vaccine production plants to be scaled to optimal sizes for supply to low-income countries during Phase III trials.

We consider rotavirus to be a better counterfactual example than meningitis vaccines because the disease burden is comparable with that of pneumococcal disease and because the work of Rotavirus ADIP will have generated evidence of clinical need and awareness of the disease. Furthermore, we would expect that clinical demand would be appreciable and encourage vaccine suppliers to enter the market. However these suppliers would not necessarily incur the same level of fixed costs investments as they would have done if they had to build protein conjugation lines into their production plants (as in the case of pneumococcal vaccines and of Hib and meningitis vaccines).

In conclusion, we considered that Hib and rotavirus vaccines would be the most appropriate examples to use to populate Counterfactuals 1and 2, although of course they cannot be taken as perfect examples of either. We did, however, retain the conjugate meningitis vaccine as a potential additional candidate for Counterfactual 2 and sought to gather consensus on the appropriateness of this example from the selected experts in the first and second interview programmes.

7.3 Developing the counterfactuals – First interview programme

In order to elicit views on potentially plausible counterfactual scenarios for the vaccine environment with no-AMC and compare key characteristics of PCVs with those of the

two vaccine examples, rotavirus and Hib, suggested for populating the counterfactuals, we conducted a short interview programme involving key experts in the field.

We contacted people drawn from six categories of bodies/organisations (i.e. AMC donor, non-governmental organisation, international organisation, academic, ADIP, others). The complete list of the interviewees is included in the annexes.

Semi-structured interviews were conducted by telephone. An introductory note and a questionnaire were sent in advance to interviewees. The list of questions is available in Annexe 1. The focus of the interviews was on:

- The main factors related to the pneumococcal vaccine environment (both on the demand and the supply side) that should be considered when developing the counterfactuals (i.e. the no-AMC scenarios),
- The main differences that there might be between the PCV environment in the near future with the AMC in place and the counterfactuals scenarios, and
- The vaccine examples (if any) that could be used as the basis for quantitative estimation of the counterfactuals defined.

The main findings of the interview programme are summarised under main themes. We point out areas of agreement and disagreement among the interviewees.

7.3.1 Demand side

Funding arrangement

The most likely no-AMC scenario option for funding arrangements is a conventional procurement system through UNICEF on behalf of GAVI. All interviewees agreed on this. However, it was pointed out that an alternative counterfactual of country-by-country negotiations might become the dominant policy option:

- If the procurement price set by UNICEF is too high. In that case local governments would prefer to negotiate directly with manufacturer/s if they have the necessary infrastructure and procurement capacity;
- If it becomes difficult or not possible for global suppliers to adopt differential pricing across the world's regions. In that case, suppliers prefer to donate products or to negotiate confidential agreements on a country-by-country basis where feasible[7], as that leaves their revenues flows from demand in high- and middle-income countries unaffected.

It is plausible under the no-AMC scenario option that the pot of money available for vaccine funding is likely to be less than in a situation where an AMC is in place. This is mainly due to the success that the pneumococcal AMC has had in attracting a large amount of funding from international donors ($1.5 billion). Whilst some of this funding may have been switched from other areas of health spending support for developing

countries other funding appears to be additional. Furthermore, the AMC was agreed before the financial crisis and this allowed many donors to commit more money than might be possible now.

In an ideal world, funds for supporting vaccines for low-income countries should be related to the health gain delivered relative to cost, which should be similar with or without an AMC intervention, since the costs and resources dedicated to vaccine R&D, production plants and distribution capacity for supply will not necessarily be different. In reality, issues of timing and the choice of funding mechanism used will have an impact on the resources raised.

Impact of PneumoADIP in no-AMC scenarios

The PneumoADIP was an important advocacy initiative created before the launch of the AMC. It significantly improved the perception and awareness of pneumococcal disease and the importance of developing a successful vaccination regime. To the extent that building a robust evidence base on disease burden and clinical needs fosters demand creation by reducing demand uncertainty, the work of an ADIP is complementary to the function of an AMC.

The majority of the experts interviewed believed that the impact of PneumoADIP would not depend on the AMC being in place rather than other policy measures. However, there could be a complementary effect, so that the impact of the PneumoADIP would be less under a no-AMC scenario, and vice versa. In other words, without an AMC, and faced with the prospect of country-by-country negotiation, knowledge of the clinical need might have been of much less value. It could of course be argued that the PneumoADIP will have raised both companies' awareness of countries' needs, and countries' awareness of the potential value of buying the vaccine, making country-by-country negotiations much more likely to lead to quicker uptake. This is something that may need to be tested in a sensitivity analysis.

Countries' demand

It is unclear what the attitude of developing country governments to the availability of a pneumococcal vaccine would be. It is likely to vary. One of the positive aspects of the AMC is that it addresses the problem of the uncertainty of product prices in the long term and that it earmarks donor funds for specific vaccines. Without the AMC, countries may be less willing to include the vaccine in their financial planning and allocate future resources for purchasing a new vaccine.

However, even if the AMC increases confidence about funding security and about there being a fixed, long term price, it will not address the underlying affordability issue. Countries may still not be able to pay for a new PCV after they have graduated from GAVI's support. If this is the case, countries' demand after they graduate from GAVI support may be similar with or without the AMC; one cannot however rule out the possibility that the PCVs may be more 'affordable' in an AMC scenario (with a fixed tail

[7] Of course, if vaccine suppliers are required to reveal transaction prices under MFN clauses, then the use of confidential discount contracts to maintain market segmentation will not be possible.

price) relative to the no-AMC scenario. There are factors that may have an impact, and in certain cases delay access to vaccines in a no-AMC or with AMC scenario. These include:

- Countries' preference for purchasing from their own local suppliers (in essence they may see a trade-off between industrial policy and public health priorities);
- Countries' preferences for, and tendency to request, the most advanced (presumably therapeutically superior) version of a vaccine, and to wait until that is available on the market. Anticipation of dynamic competition within a given class of vaccine products may delay uptake decisions.

Overall access timelines

In terms of any possible delay in uptake in a no-AMC scenario as opposed to an AMC scenario, it was suggested that if we assume that the secured funds are the same, there would be no difference. Whether the same resources were channelled into an AMC, into GAVI central procurement, or made available directly to countries for them to negotiate purchases, would have no impact on uptake. A counterargument to this is that the uptake would be significantly slower under a no-AMC scenario, mainly due to the persistence of uncertainty around the level of the price countries would have to pay in the long term, the supply guaranteed by manufacturers, and the degree and duration of international support. Some interviewees estimated that without the AMC the provision of new PCVs to low income countries could be delayed by up to 10-15 years.

7.3.2 Supply side

Multinational companies

When exploring the supply side, it is important to understand which type of suppliers are most likely to enter developing countries' markets in a no-AMC scenario (multinational companies and/or local suppliers) and when they would be able to meet countries' demand (i.e. their timescale for expanding capacity). The general consensus from the experts interviewed was that the two multinational companies which originally developed PCVs, (Wyeth, now Pfizer, and GSK) invested in R&D in this area prior to the launch of the AMC pilot and therefore it is very likely that both of them would have considered expanding capacity to serve poor countries even without the AMC.

However, some differences in the strategic behaviour of the two multinational companies are possible. As GSK has long experience in the low-income country market, it would definitely make a commitment to building dedicated capacity and attempt to reach an agreement with GAVI for funding. On the other hand, Wyeth (now Pfizer) has limited experience in the field, thus it may take longer and be more resource-intensive to involve the company in the production and distribution process in developing countries, even in the presence of support from GAVI and other initiatives.

It was suggested that without an AMC, and regardless of which multinational companies decided to enter poorer country markets, it is likely that, at an early stage of introduction of the vaccine there would be some shortages (i.e., demand exceeding the supply at the price offered). Historically, multinational companies have not shown an

interest in scaling-up production capacity up to the level needed for global supply (which could be as much as 3-4 times that required to serve richer developed countries). Having alternative sources of vaccine supply (for instance vaccine producers from emerging economies) is therefore an important policy consideration; having a market characterised by a few suppliers is better than a one- or two-supplier equilibrium.

Emerging suppliers

It is known that some local vaccine suppliers from emerging economies had already shown interest in entering the PCV market prior to the AMC launch. However, it is not clear that market entry by such emerging suppliers would be in time for them to benefit (capture premium price revenue flows) from the pneumococcal AMC pilot. Given the variable timeframes in which they would be operating, they might run into problems of not recouping enough revenues to pay for the fixed cost investments incurred – especially if they have to compete on quality and quantity with incumbent multinational companies. If vaccine producers from emerging economies anticipate such problems, their willingness to enter the market for vaccine supply to low-income countries will be dampened.

The general consensus from our interviews was that the impact of the AMC on emerging companies' entry decisions will be neutral (although one respondent thought that the AMC may even discourage investment from such emerging vaccine suppliers because it would enable developed country manufacturers to establish a strong market presence). By 'neutral", we mean that in a no-AMC scenario, the strategic behaviour of emerging-market suppliers would follow standard timelines and processes.

One would expect that local vaccine suppliers making market entry decisions would monitor the market (i.e. seek to understand the overall demand for PCVs distributed by the major multinational companies and hence the residual demand plus AMC funds remaining) and base their investment decisions on the results.

It has been argued that public-private partnerships (with push funding channelled to local vaccine suppliers) may be more effective than an AMC as a way to accelerate vaccine supply to low-income countries from local companies. This is the approach taken by the Pneumococcal Vaccine Project led by PATH, which is already supporting two emerging companies in their R&D activity for PCVs.

Other factors

From a policy perspective, there are other factors that might influence market entry decisions of vaccine suppliers (multinational and emerging producers alike) albeit it is difficult to predict the trends in influence in a no-AMC scenario. These include:

- WHO technical recommendations, which give some general guidelines to countries on what vaccination policies to implement; this is important for demand creation as most countries see that this as a form of insurance protection against the risks of administering vaccine to otherwise healthy people;
- Posted product prices coming out of competitive procurement bids (if we assume that a conventional procurement would take place), the lower the price (and hence

the closer it is to marginal supply costs), the more reluctant vaccine suppliers will be to undertake additional investments;

- The level of GAVI resources committed to pneumococcal vaccines. As pointed out earlier, it is unlikely that conventional routes would lead to a level of funding equal to that mobilised under the AMC (although we acknowledge that in an ideal world, such differences in funding flows need not exist).

7.4 Choice of historical examples

We asked the interviewees whether or not they deemed the rotavirus and Hib to be appropriate examples to populate the counterfactuals scenarios. Their views were as follows.

7.4.1 Rotavirus

The overall opinion on the rotavirus vaccine was that it is a plausible example to use within a counterfactual model framework. The main similarities between pneumococcal and rotavirus diseases are that an ADIP-type initiative was created at the same time to accelerate access to the existing vaccines for both diseases, which are both associated with a large disease burden. However, some key differences between the ADIP initiatives were mentioned:

- The WHO recommendation for the new rotavirus vaccines came after the work of the Rotavirus ADIP, which was focused on the execution of clinical trials to rule out from the new vaccines the rare but sometimes severe adverse event (bowel intussusceptions), linked to the earlier (now withdrawn) RotaShield® vaccine. Clinical trials are underway to establish the efficacy and safety of the new vaccines in the poorest developing countries where child mortality is highest (WHO,UNICEF and World Bank 2009)

There is less awareness among recipient countries of rotavirus as a disease, and less understanding of the benefits potentially offered by the vaccine, than there is with pneumococcal disease. The Rotavirus ADIP was designed to provide funding to develop an additional clinical evidence-base to inform a WHO (global) recommendation. Its work was not specifically for ‘demand creation’, but it could nevertheless be argued that establishing the efficacy and safety of vaccines could foster demand creation indirectly. In contrast, the PneumoADIP invested its resources directly on strategic communication to recipient countries which may have led to a better knowledge and higher level of awareness of the disease. The work of the PneumoADIP was specifically intended to create the evidence for demand creation.

7.4.2 Hib

The overall view on Hib was that it can be used as an example within a counterfactual framework, although it would represent a 'pessimistic' scenario in which global initiatives and other processes did not achieve their goals very successfully. If what happened to Hib were to be repeated with PCVs, it would take a very long time for poor countries to have access to the PCVs.

One difference between Hib and the use of policy interventions for pneumococcal diseases is related to the timing of the policy interventions for Hib, which came much later than those for PCV. In particular:

- Although highly-effective conjugate vaccines against Hib were available from the early 1980's, Hib did not have a well-funded dedicated initiative such as PneumoADIP until year 2005 when the Hib Initiative (a consortium of WHO, John Hopkins Bloomberg School of Public Health, London School of Hygiene and Tropical Medicine, and the US CDC) was put together;
- WHO only made a global recommendation on the use of Hib vaccines after it became clear that by 1997, only 29 countries around the globe were routinely using the highly effective conjugate Hib vaccines;
- Affordable pricing of Hib vaccines only followed after the WHO recommendation and evidence of increasing demand. This in turn encouraged an increase in the number of vaccine suppliers and price competition. This shift away from a one- or two-supplier equilibrium also engineered a move from monovalent conjugated Hib vaccines to 'polyvalent' Hib-containing vaccines (these vaccines are in essence combination products) see WHO, UNICEF and World Bank (2009).

However, introduction of a PCV would be more difficult than introduction of Hib, mainly because pneumococcal disease is extremely complex. There are 90 distinct pneumococcal serotypes which vary depending on age, time and geographical region.

The main advantage from using Hib as an example is that it will help us to understand how the supply side of the PCV market could evolve. In the case of Hib, the market, in terms of supply of pentavalent Hib-containing vaccines was originally characterised by sole-supplier equilibrium. There are currently four vaccine suppliers of pentavalent Hib-containing vaccines; two of which are based in India (Panacea Biotect and Shantha Biotechnics). The market for pentavalent Hib-containing vaccines is now characterised by substantial competition on product prices.

7.4.3 Meningitis

It was suggested the Meningitis Vaccine Project (MVP) is a good example of a mechanism alternative to the AMC to foster development and distribution of affordable vaccines (PATH is collaborating with an Indian company to develop a new version of the vaccine which can be used in Africa). However, the meningitis vaccine is not easily applicable as an example for PCV.

One reason is that the distribution of the disease burden of meningitis is very different. Its prevalence is much lower than that of pneumococcal disease, and it is concentrated in some African regions. Relative to other diseases, meningitis has a lower priority, and there is less information available on the morbidity and mortality associated with it. This, together with the low income per capita in countries where it is present, means that – other things being equal – the effective demand which could incentivise vaccine supply to low-income countries will be much lower than that for PCVs.

We suspect this is the impetus behind the involvement of MVP in developing meningitis A conjugate vaccine for use in mass vaccination campaigns in Africa.

Other reasons why meningitis vaccines may be different in economic terms from the PCVs are that:

- The meningitis vaccine has been available for decades, and the only issue that had to be addressed was affordability in African countries.
- The meningitis vaccine is less complex, therefore much less investment is required than for PCV to support local suppliers. However, since the existing meningitis vaccines available are un-conjugated polysaccharides that are less effective in children (especially those in low-income countries where serotype A is the predominant cause of the disease) the current move is to encourage vaccine suppliers to produce conjugate versions of the meningitis vaccines (targeted at serotype A) for supply especially to African countries.

To sum up; the main reason why meningitis may not be appropriate as a historical example is the fact that it has a much smaller burden of disease. Much more effort will be needed to accelerate introduction of new conjugate meningitis vaccines (suited to the epidemiology of low-income countries) into low-income countries than with PCVs.

7.5 Implications for quantitative modelling (estimation)

In this concluding section, we aim to highlight key issues from the first and second interview programmes that should be considered in any quantitative estimation of the counterfactuals. (A summary of the second interview programme on validating the counterfactuals defined will be found in Annexe 1.) There are three related issues:

- to be clear about the 'output" measures by which the AMC will be compared with the counterfactuals to assess the performance of the AMC
- to understand adjustments that will need to be made to any use of data from the Hib and rotavirus examples;
- to separate the impact of the AMC from other policy measures that will have an impact (positive or negative) on the outputs of the AMC.

On the basis of the analysis to date, special attention should be given to the following:

- The role of vaccine suppliers from emerging economies and the factors that determine their market entry decisions. These emerging-market companies are far more likely to play a role now than in any historical case studies;
- The role of push funding (and in general public-private partnerships) that are designed to reduce the entry barriers – particularly for these emerging vaccine suppliers;
- Interaction between PAHO and GAVI/UNICEF; this in general requires considerations of the scope for segmenting markets in ways that favour differential or tiered pricing. This will impact on assumptions made in the counterfactuals as well as on willingness to supply under the AMC;

- Funding levels for vaccine supply to low-income countries with and without AMC intervention;
- The role of information and evidence gathering in shaping the clinical preferences and willingness of developing countries to procure and use vaccines;
- The speed with which WHO provides recommendations on the use of any specific vaccines.

In all cases we recommend that analysts relying on our counterfactuals carry out sensitivity analysis to evaluate alternative scenarios and issues we have presented in the sections above. Structural and parameter uncertainty should be evaluated to assess the impact of model outputs.

It is evident that our 'high level' counterfactuals cannot describe all the possible complexities of the pneumococcal vaccine market, since the counterfactuals described cannot capture all possible sequence of events (including changing strategic behaviours of vaccine suppliers from both high-income and low-income countries). Therefore any quantitative modelling exercise based on our defined counterfactuals will need to consider a variety of possibilities and use sensitivity analysis to estimate the potential impact on the counterfactuals.

A number of clarifications need to be made and other issues considered in using our counterfactuals. For example, one such issue is market entry by vaccine manufacturers based in developing countries (and whether they have the technical capacity to produce what are considered to be complex vaccines) as well as the strategic behaviour of the original innovators of the pneumococcal vaccines. Another issue that needs to be considered is the role that information and evidence gathering play in shaping the clinical preferences of developing countries. Also important is the speed with which WHO provides recommendations on the use of specific vaccines. These are but a subset of the issues highlighted.

In sum, we are confident that in general the two counterfactuals defined in this report provide a reasonable and plausible indication of what the policy environment and market evolution for pneumococcal conjugate vaccines could be without an AMC intervention. We also highlight the potential for two vaccines (Hib and rotavirus) to provide some relevant context and data for the two counterfactuals.

Nevertheless, counterfactuals of course do not depict all possible sequences of events that might have occurred. Any quantitative modelling exercise based on them must make appropriate assumptions and test for the sensitivity of alternative possible events as raised by the experts who validated the counterfactuals.

8 Quantitative modelling of counterfactuals

The methodological approach for quantitative modelling of the counterfactuals will follow directly the stated goal and objectives of the pneumococcal pilot AMC. However, for this estimation exercise, we will focus on the following objectives of AMC intervention, which are:

- Bringing forward the availability of effective pneumococcal vaccines – through scaling up production capacity, and
- Accelerating vaccine uptake – through predictable vaccine pricing for countries and manufacturers.

In what follows, we describe the analytical framework used; previous modelling work done that is of relevance to our work and specifics of our models for evaluating the counterfactuals. We also describe the type of sensitivity analysis that we will consider in testing the robustness and validity of our model results.

8.1 Analytical framework

8.1.1 A supply-demand perspective

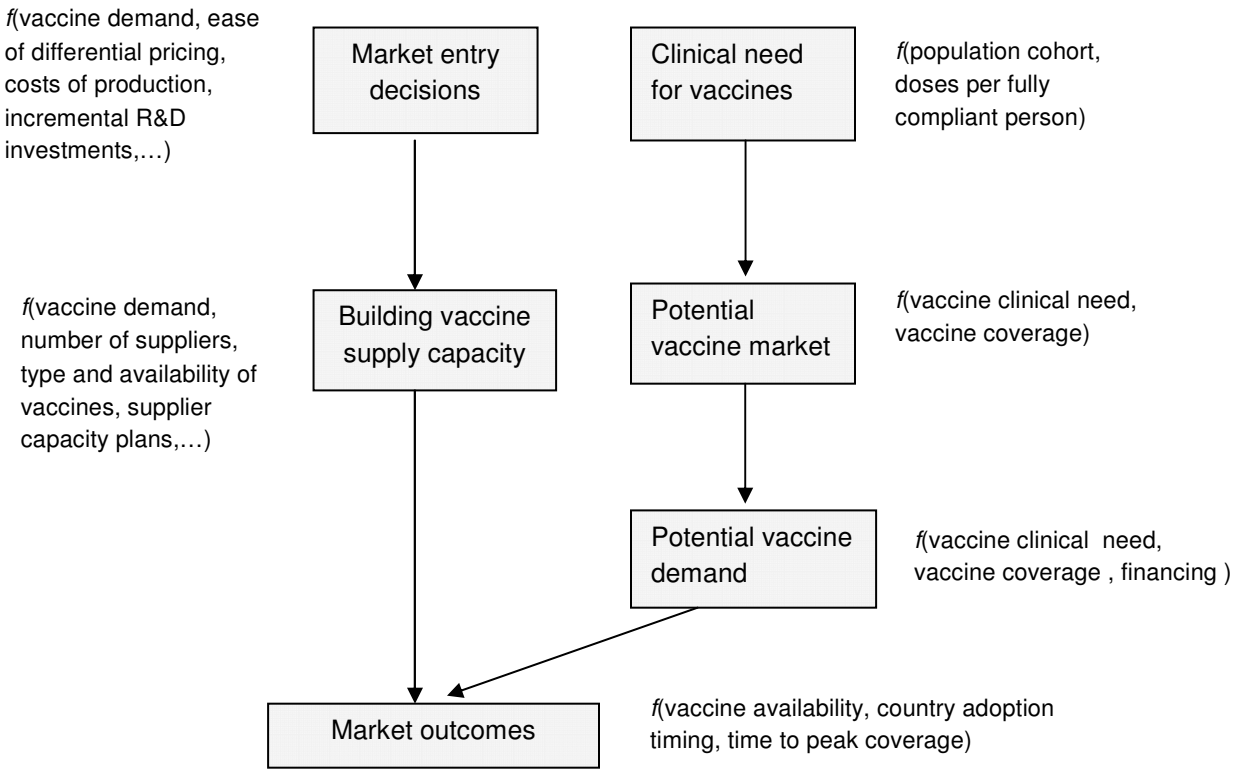
In both counterfactual scenarios defined, we hypothesise that market outcome(s) follow from interaction between 'demand-side' and 'supply-side' factors (or variables). This simple supply-demand framework highlights one important message: aggregate demand for pneumococcal vaccines (this refers to 'economic demand' and not just clinical need) determines, in part or wholly, the willingness of vaccine suppliers to devote resources towards the sequence of fixed cost investments required to supply vaccines to low-income countries, and hence their market entry decisions. In this quantitative exercise, we follow this supply-demand framework and develop a model (specifically an Excel spreadsheet) that portrays the possible market outcomes from interactions between various 'supply' and 'demand' variables.

We assign to the model a time horizon (depending also on data availability) that is long enough to simulate the sequence of events described in the two counterfactuals. To be precise, our model runs from year 2005 to year 2040. This we believe is a flexible, reasonable timeframe that is long enough to accommodate the historical lag (generally thought to be 10 to 15 years) between the launch of a new vaccine in high-income countries and its adoption in low-income countries. The model is designed to tell us not just how 'supply' of pneumococcal vaccines in our counterfactual worlds will match 'demand' (taken as a proxy of economic demand and not just clinical need) but also how quickly 'supply' will (rise to) match demand.

Figure 9 below provides a graphical illustration of the 'supply-demand' framework used for the models. The primary advantage of this simplified framework is that it provides a way to analyse what will happen without a pneumococcal AMC for individualistic country-specific arrangements as well as for the aggregate demand arrangements

employed by UNICEF. With this supply-demand framework, we can model the potential demand for vaccines and cumulative vaccine supply (by multinational and emerging-market producers) over our stipulated time horizon to estimate the state of the world without AMC intervention for the pneumococcal vaccines.

Figure 9: Supply-demand framework for counterfactuals modelling



In all cases, our focus is on an *aggregate market* of GAVI-eligible low-income countries. Because of the sequence of fixed costs investments incurred, rarely will a rational vaccine supplier build production plants just to meet demand in a single GAVI-eligible country. (There are substantial economies-of-scale to be taken advantage of.) So for instance, whenever we refer to 'time to market entry', we mean time to entry of vaccine manufacturers, supplying suitable vaccines to a selective group of GAVI-eligible low-income countries (at affordable prices).

It is important to clarify that within the supply-demand perspective taken, we do not attempt to quantify how the research and development of vaccines (meeting developing country needs) may be in a world without AMC intervention. There are two primary reasons for this. First is the difficulty of modelling R&D outcomes (specifically the discovery and development of vaccines with the desired TPP) in the presence or absence of an AMC intervention: merging such a model with our supply-demand framework will add significant layers of complexity. Secondly, the counterfactuals we defined implicitly assume that the desired vaccine products have already been developed and what is needed is scaling up production capacity to make vaccines

immediately available and accelerate vaccine uptake to provide the maximum possible health benefits – given constraints imposed by healthcare system infrastructure. In other words, the costs of pre-clinical research, product development, clinical testing and regulatory approval are sunk and are largely bygones that should not greatly affect investment decisions for large-scale production and supply to developing countries.

8.2 Previous modelling work of relevance

As good standard practice, it is useful to look at previous work done, the methodological approaches taken (the rationale behind the approaches) and whether this is of relevance to the current work being undertaken. Given the supply-demand perspective taken, we set out to identify existing work that followed in some ways what we envisaged to do. From literature searches and materials obtained from GAVI and SCIH, we initially identified the following work as being of most value to our counterfactual modelling:

- AMC-FIRM model developed by Applied Strategies Consulting (a life-sciences strategy consulting firm)
- The Excel spreadsheet developed by the Economic Expert Group(EEG) for the AMC Implementation Working Group (IWG), and
- The PneumoADIP interactive pneumococcal vaccination policy model.

Our first thoughts were to use the PneumoADIP's interactive vaccination policy model to generate demand estimates (as inputs) for our model. Since then, alternative sources of demand estimates have been brought to our attention, specifically current 'best' demand forecasts generated by the Accelerated Vaccine Introduction (AVI) initiative and previous demand forecasts generated by PneumoADIP with the help of Applied Strategies. We assessed the AMC-FIRM and EEG model to identify if either model was appropriate for developing the counterfactuals. We noted that the AMC-FIRM was primarily developed to estimate the potential size of commitment required, and was used to support the decision to approve an AMC size of $1.5 billion in the expectation of getting more than two vaccine suppliers.

The EEG model, on the other hand, was developed to inform an understanding of the detailed impact of AMC structure on entry of vaccine suppliers and their production plans given the size of the AMC[8], with a focus on likely market outcomes under a broad range of possible AMC terms and conditions – under the assumption that vaccine suppliers will base decisions about timing and participation in the AMC on a standard profit-maximisation objective. From a detailed scrutiny of the EEG model, we concluded that it was the most relevant and could be adapted for modelling the counterfactuals as it was designed to assess how market outcomes will change under different 'supply' and 'demand' scenarios.

[8] Specifically, the modelling was to 'shed light on likely industry behaviour in the face of different AMC structures, assuming that firms would act to maximize profit and would make decisions about the timing and type of AMC participation based on that objective including tail price and building of capacity'. (Expert Group Report to the IWG)

We provide below descriptions of the models or empirical work(s) that we have deemed to be most relevant and appropriate for developing models for our defined counterfactuals. We will rely on this previous work to inform the structure of our model.

8.2.1 Expert Economic Group model

The EEG model was built to assess the impact of different variables (what is referred to as 'program rules') on vaccine producers, public health, donors, and GAVI and participating countries. The EEG, and the IWG, used this spreadsheet model in three ways:

- To evaluate 'what would happen if'?' vaccine producers committed to a certain volume of supply (say 100 million doses per year), under different assumptions: how much money would the firm make, how many DALYs would be gained, and how much will it cost the donors and GAVI?
- To ask 'how much would vaccine producers want to supply?' under different assumptions and program rules. This involves a net present value (NPV) calculations as well as a 'grid search': what happens with 10, 25, 50, 75 and 100 million dose supply commitment? Which one generates the highest NPV for vaccine producers?
- To introduce some uncertainty, where the probability that a firm enters decreases with reductions in the tail price. Here the model weighs a trade-off between (i) low tail-price achieving higher net DALYs gained, and (ii) low tail-price achieving fewer net DALYs if vaccine producers do not participate.

The EEG model was designed around the following sequence of events: a producer with a particular (specific) vaccine technology that meets the TPP profile for pneumococcal vaccines – this could either be GSK's 10- or Wyeth's (now Pfizer's) 13-valent PCV – enters into a commitment to supply *X* doses for each year for *Y* number of years. The vaccine producer incurs a sequence of fixed costs investments (include capital/start-up costs, costs of regulatory compliance and annual fixed costs of production) as well as variable costs per dose produced. In return, the vaccine producer earns a portion of the $1.5 billion AMC fund.

The EEG spreadsheet was designed to handle three separate vaccine producers: 'Global-1' with a 10-valent technology, 'Global-2' with a 13-valent technology, and an 'Emerging-market supplier' with a 10-valent technology (presumably a 10-valent technology will be less costly to produce compared to the 13-valent vaccine technology). For Global-1 and Global-2, there is a pre-build-out period representing the time before the new plant comes on stream. In this period the producers could use existing vaccine product plant/capacity that it has although this is presumably scaled to meet demand in high-income countries only.

The EEG model has an indicator variable (Yes or No) for whether the two multinational firms use this existing production capacity during the pre-build-out period to supply low-income countries. There is also an indicator variable (Yes or No) for whether any of the vaccine producers experiences unplanned plant shutdowns. For the three

vaccine producers considered, it is assumed that plant shutdown occurs once, 8 years after a new production plant is built and this shutdown lasts for only one year.

It is assumed that it will take the vaccine producer 5 years to build a new production plant (dedicated to supplying GAVI-eligible low-income countries). Hence with a 10 year supply commitment, the AMC period expires in year 2023 if the first vaccine producer begins to sell at the beginning of year 2014. For the purpose of having a finite time horizon for the NPV calculations, it is assumed that the vaccine producer earns the full tail-price per dose supplied ($3.50) after the AMC period expires and sells at that tail-price till year 2030. The spreadsheet model incorporates a sensitivity parameter that determines how much of the PneumoADIP demand forecast is actually realised.

So in addition to the base case (of 100% demand realisation), three scenarios are explored: 75% demand realisation, 50% and 25%. There is also a sensitivity parameter which deals with what happens when demand from India is removed or added to the PneumoADIP forecast as well as a 'demand elasticity' variable that was intended to capture the percentage change in demand associated with a $0.20 increase in price above a tail price of $1.40 (at which 100% of demand is realised). This price-demand-elasticity parameter was disabled in the EEG spreadsheet sent to us albeit it is stated that it can be reactivated. Data on demand forecast used in the EEG model were taken from PneumoADIP v2.0 *Strategic Demand Forecast* (SDF) for pneumococcal vaccines in GAVI-eligible countries. Further details of the EEG model will be found in GAVI (2008a/b).

8.2.2 AVI demand forecast for pneumococcal vaccines

The AVI initiative which took over the work of the PneumoADIP has carried out a number of demand forecast exercises, which are a continuation of the work previously carried out by PneumoADIP. The AVI demand forecasts reflects an update on the previous PneumoADIP SDF v1.0 and v2.0 demand forecasts and were generated by the same group of analysts who work on PneumoADIP forecasts. There are two published sets of demand forecasts from AVI: AVI SDF v0.0 and v0.1; currently unpublished on-going work includes AVI SDF v.1.0 and v1.1. There are also some previous, unpublished demand estimates dating back to year 2005.

The difference between the AVI and PneumoADIP demand forecasts is in their objectives. The PneumoADIP forecasts were intended for 'policy development' (i.e., in determining the specifics of the pilot pneumococcal AMC) whilst the AVI demand forecasts are geared towards 'implementation'. Although the underlying methodology and assumptions are broadly similar, the AVI's demand estimates include additional 'influencing' variables.

There are four main methodological differences between AVI's and PneumoADIP's forecasts which stem from inclusion of the following 'influencing variables':

- Incorporation of some assumed amount of vaccine wastage

- Incorporation of a required level of vaccine buffer stocks (a tendency towards stockpiling to avoid significant disruptions in vaccine supply)
- Different definitions of the 'target population cohort'
- Varying vaccine introduction rates in GAVI-eligible countries

Under the AVI's approach, the target population cohort was estimated by making assumptions about birth rates, infant mortality rate and population growth dynamics over time. The latter was derived using UN population dataset with three scenarios of population growth: what is called 'low' variant, 'medium' variant and 'high' variant. The PneumoADIP estimates, on the other hand, are based primarily on surviving infants and not just annual birth cohorts. Included in the AVI estimation exercise was estimates of vaccine target coverage rate (based on rates observed for DTP3) and vaccine uptake rates (based on what was observed for monovalent HepB vaccines and pentavalent vaccines [Hib+HepB+DTP3]).

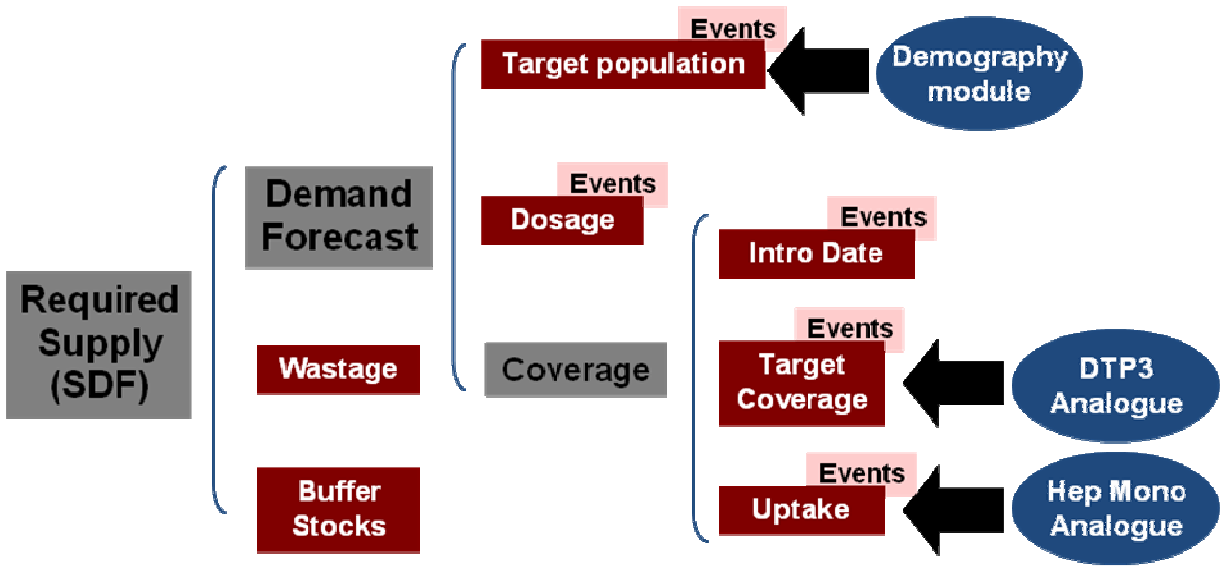
In the previous PneumoADIP forecast, an alternative approach was taken by differentiating countries into 'early', 'middle' and 'late' adopters. Countries were described as 'early adopters' (i.e., those who adopt within the first 5 years of vaccine availability); 'middle adopters' (i.e., those countries within the first 10 years of vaccine availability); and 'late adopters' (i.e., those countries who adopt 10 years or more after vaccine availability) (PneumoADIP/Applied Strategies, 2009). This approach taken by PneumoADIP was rejected by the AVI.

AVI's estimation exercise included a parameter labelled 'vaccine introduction rates' that captures time lags between when low-income countries file/submit an application to GAVI or express an intention to apply, to when the GAVI Board offers its approval for funding the purchase of vaccines. This parameter also captures success rates of applications made by countries to GAVI.

Using the variables listed above, a demand forecast is generated which is then adjusted according to assumptions about vaccine wastage and buffer stocks needed to maintain 'security of supply'. The link between these variables is shown in Figure 10 below.

The AVI demand forecasts represent not just 'demand' (i.e., economic demand derived from clinical need) but REQUIRED SUPPLY (i.e., economic demand adjusted for wastage and stockpiling). The PneumoADIP estimates, on the other hand, reflect actual doses required to vaccinate children (i.e. economic demand). It is important to note that the AVI demand forecasts covers all GAVI-eligible countries (i.e., it includes PAHO countries who are GAVI-eligible). For further details see Malvolti (2009).

Figure 10: Key parameters of AVI's SDF v0.1



The main problem with relying on AVI's demand forecasts in our counterfactual modelling is the number of potential confounding factors at work. Demand estimates that vaccine suppliers will consider in their market entry decisions will be substantially different from the AVI's demand forecasts given that in at least one of our counterfactuals there will be little or no public health priority given to pneumococcal vaccines; and policy advocacy at the country-level and awareness of the disease burden are likely to be lower in low-income countries.

Figure 11 below, for example, shows how the work of AVI and the awareness generated by advocacy for the pilot AMC has 'inflated' uptake rates of pneumococcal vaccines relative to the pentavalent vaccines (Hib+HepB+DTP3) – this is based on AVI's SDF v0.1. Another plausible reason for the 'wedge' between coverage uptake for pneumococcal vaccines and the pentavalent vaccines, in Figure 11, is the expectation that $1.5 billion AMC will be available for (co-)financing vaccine purchase. This 'AMC effect' is probably of greater magnitude since on-going advocacy work is conducted (to varying degrees) for almost all vaccines purchased by GAVI via UNICEF

However, if one considers the AVI demand estimates (see Figure 12 below) as the closest, best-available approximation to the 'true' demand (i.e., economic demand adjusted for wastage and stockpiling), then using the AVI demand forecasts gives us an upper bound of 'demand' in our counterfactuals. In this case, one could use sensitivity analysis to ascertain the outcome of using values for demand forecasts below the current 'best' available estimate (which we consider as the 'true demand'). This approach would be similar to that taken by the EEG model where alternative scenarios corresponding to 100%, 75%, 50% and 25% realisation of the demand forecasted was evaluated.

Figure 11: AVI efforts accelerate uptake of pneumococcal vaccines

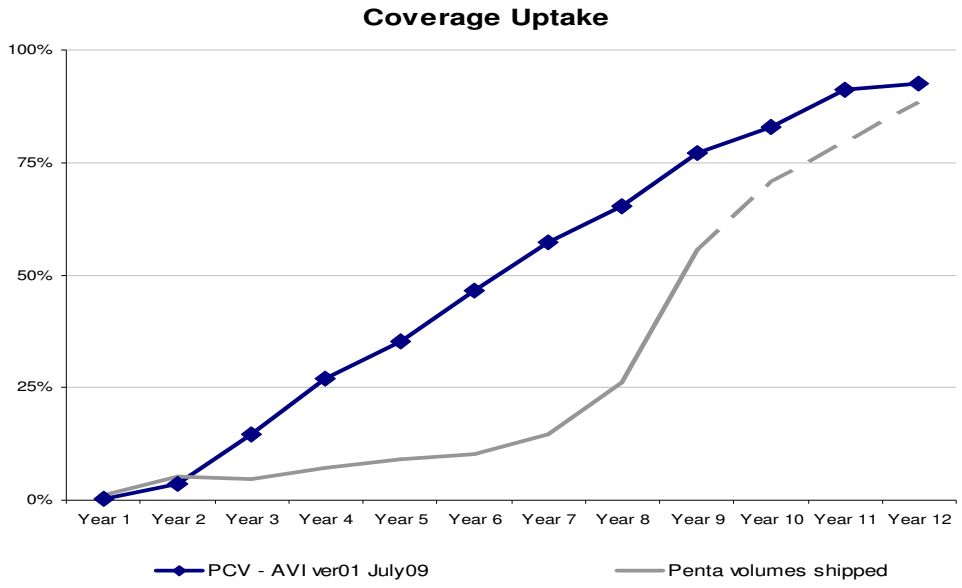
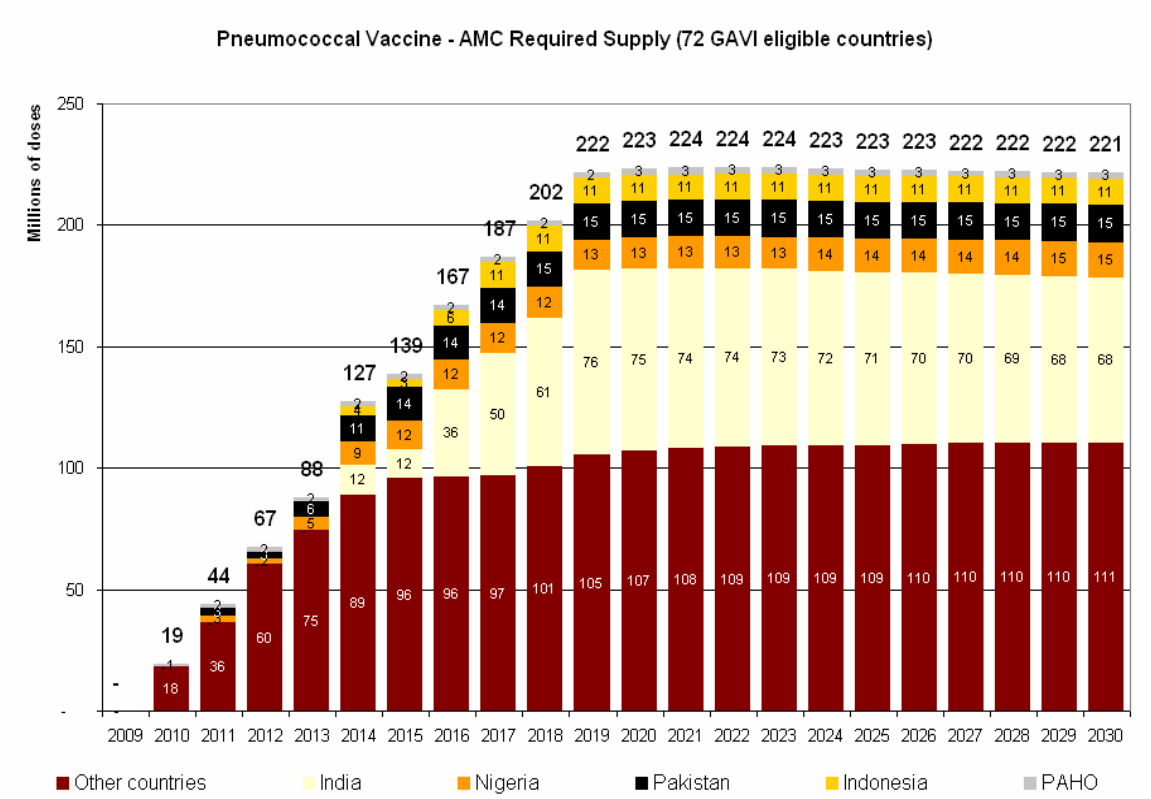


Figure 12: Current published 'best' estimates of Pneumo demand (showing demand from 'large' countries and GAVI-eligible PAHO countries)



An alternative approach is to try replicating what AVI has done but sifting out the combined effects on demand by various confounding factors. This raises the question of how do we disentangle/ 'sterilise' the influences of these factors from AVI demand forecasts. Indeed, recognition of the various confounding factors at work is the impetus behind 'newer' unpublished versions of AVI's demand forecasts v1.0 and v1.1, which attempt to control for bureaucratic delays introduced by GAVI-Board's decisions (and the effect this has on countries' vaccine introduction rates) as well as other 'unspecified' micro-demand variables.

8.2.3 History of PneumoADIP demand forecast

Prior to its closure and the establishment of AVI, the PneumoADIP (with support from Applied Strategies Consulting) carried out a number of demand forecasts for the polyvalent, conjugated pneumococcal vaccines. From our literature searches and requests OHE made with the assistance of GAVI to former staff of PneumoADIP, we noted three versions of demand forecasts: PneumoADIP v1.0, v2.0 and v3.0. The differences between demand forecasts (shown in Figure 13 and taken from the Excel spreadsheet sent to OHE by Lois Privor-Dumm [of the John Hopkins Bloomberg School of Public Health]) arise mainly from 'minor' differences in the underlying methodological approach and assumptions – that reflect continued efforts to refine the forecasts based on evolving events and an updated 'richer' pool of information.

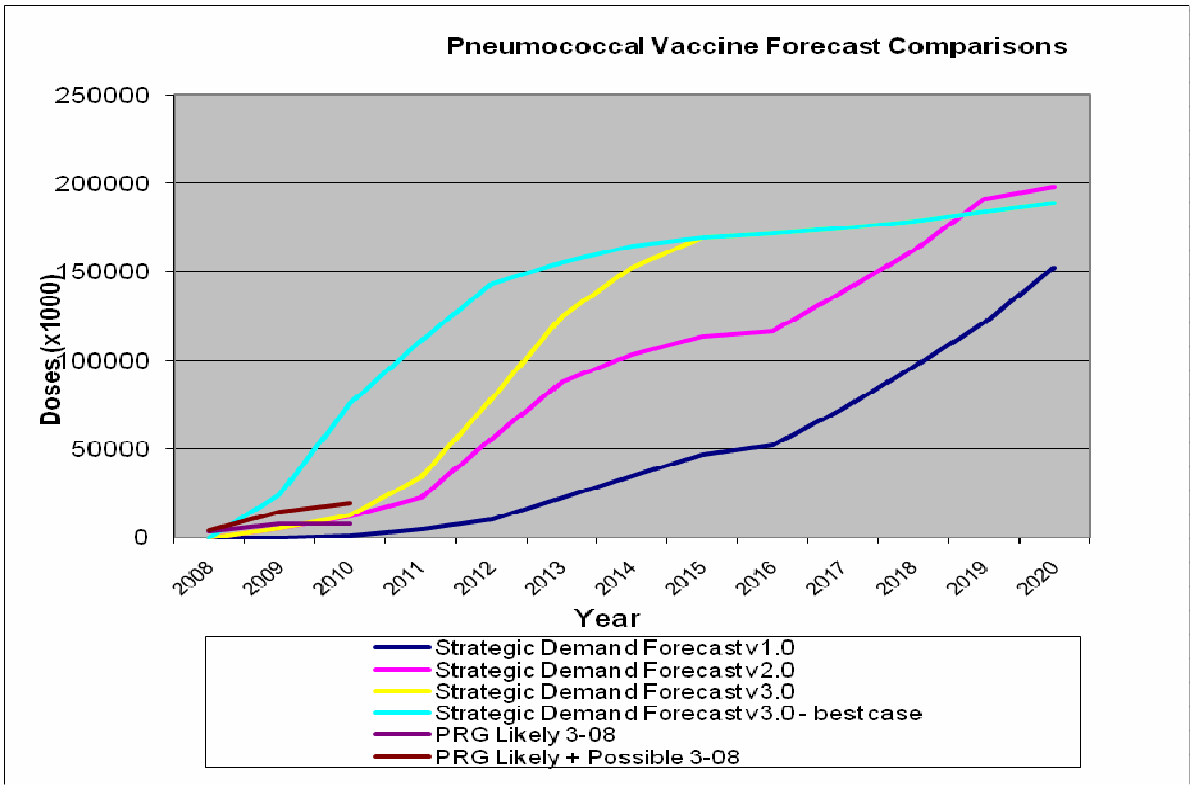
Events motivating the various demand forecasts include:

- Accelerated country adoption and increased vaccine interest expected due to: increased understanding of disease burden, timing of WHO/SAGE recommendation for pneumococcal vaccine use, introduction of the pneumococcal vaccine pilot AMC, and GAVI financing policy
- Updated underlying population and vaccine coverage rate forecasts.

PneumoADIP v1.0, for instance, assumed that the 7-valent PCV will not be introduced in GAVI-eligible countries and therefore countries were not expected to adopt until year 2010. The v2.0 forecasts, however, did assume availability of the 7-valent PCV but that vaccination did not start until year 2008. This, it is stated, had little impact on the overall accuracy of the demand forecasts. All PneumoADIP demand forecasts, nevertheless, take into account the expected introduction of 10- and 13-valent PCVs. See PneumoADIP/Applied Strategies (2009) for further details.

It seems the most important variable driving the differences between the PneumoADIP demand forecasts is the assumed rate of introduction of the PCVs in GAVI-eligible countries. Forecasts of these rates of country adoption are greatly influenced by education and demand creation efforts (by international organisations such as WHO, PAHO and UNICEF) as well as availability of financing for vaccine suppliers and the input of country-specific decision-makers. This provides further justification for our approach of adapting AVI demand estimates to our Counterfactuals by altering countries' vaccine introduction dates.

Figure 13: Demand forecasts by PneumoADIP[9]



8.3 Our models in detail

8.3.1 Counterfactual 1

The model developed for estimation of Counterfactual 1 is similar in structure and assumptions to the EEG model. We chose a time horizon from year 2005 to year 2040 as we believe this provides an ample length of time within which all the events characterised in the counterfactual defined will be expected to happen.

On the supply-side, we assume market entry by three vaccine suppliers: (1) 'multinational-1' with a 10-valent vaccine (2) 'multinational-2' with a 13-valent vaccine technology and (3) 'emerging-market supplier' with a 10-valent technology. The 10-valent technology supplied by the emerging-market supplier need not be a 'biosimilar' to the 10-valent technology supplied by multinational-1. It could be a 10-valent vaccine

[9] 'PRG Likely 3-08' and 'PRG Likely + possible 3-08' refer to alternative demand forecasts for the PCVs generated by the GAVI procurement reference group (PRG) over the time periods indicated in figure 13. Correspondence with Ann Ottosen (Contracts Manager, Vaccine Centre, UNICEF Supply Division) indicates that these demand estimates were generated in spring 2008. Members of the PRG at that time were: Deborah Atherly (PATH), Jan Grevendonk (GAVI), Rehan Hafiz (Pakistan), Gargee Gosh (BMGF), Susan McKinney (USAID), Angeline Nanni (PneumoADIP), Sarah Schmitt (WHO), Patrick Zuber (WHO). Andrew Jones (GAVI) acted as coordinator with inputs from staff of UNICEF Supply Division.

covering a different set of pneumococcal serotypes although the number of serotypes covered is the same. Note that this product differentiation may be an attempt to produce a vaccine that is more specific to the epidemiological profile of the targeted populations (in different geographical regions) or as part of long-term production plans made in expectation of 'serotype replacement'[10].

In our model, as in the EEG model, there is a pre-build-out period where vaccine suppliers (specifically multinational-1 and multinational-2) could satisfy some of the demand expressed by low-income countries with existing production plants. There is no pre-build out period for the emerging-market supplier. Time sequence of market entry decisions of the three vaccine producers described in Counterfactual 1 is as follows.

At the beginning of year 2005, we assume multinational-1 has an existing production plant for the supply of its 10-valent health technology and a ten-year lag before it builds a new dedicated production plant. In other words, supply from the new plant starts in year 2014. (The choice of 2005 as the start date reflects in part point of reference for this study.) Note that the ten year lag time includes the 5 years it takes to set up a dedicated new vaccine production plant. The length of the pre-build-out period is thus 10 years and intended to reflect the observed delays in introduction of vaccines in low-income countries. We considered that, given that the existing supply by multinational-1 signals a reasonably well-functioning market, we could restrict the pre-build-out period for multinational-2 to 7 years. This period includes the 5 years it takes to build a new production plant and our assumption that multinational-2 starts supplying its 13-valent technology with its existing production plant in 2012 (two years before multinational-1 starts supplying with its dedicated new plant). We assumed that new dedicated plant for multinational-2 starts operating in 2018 and two years later, in year 2020, the emerging-market supplier enters the market[11].

It is important to clarify that the manner in which we implemented this historical time lag in the Excel spread-sheets captures more of the delay in reaching 'adequate' vaccine coverage once the vaccines have been introduced in low-income countries; rather than the time lag between vaccine introduction in high-income countries and date of first introduction in low-income countries (see Figure 3 and Figure 4). This is because Counterfactual 1 and Counterfactual 2 describe a sequence of events that implicitly assume some existing albeit 'inadequate' supply of vaccines to low-income countries.

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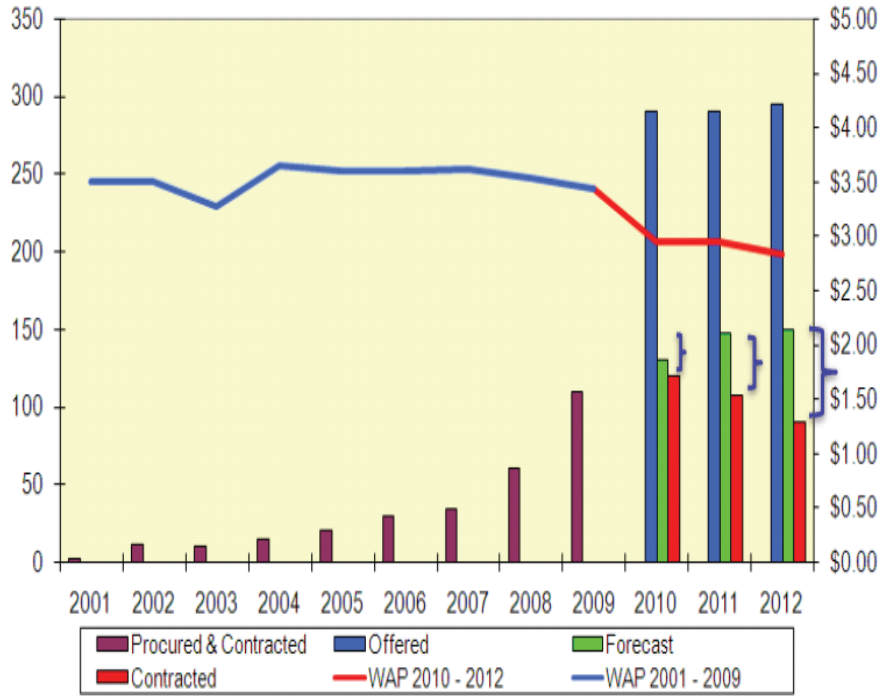
[10] Serotype replacement refers to the observation that a specific vaccine technology by providing immunological protection against certain serotypes of the disease-causing microbe may leave open an 'ecologic niche' that will be occupied by serotypes not included in that vaccine. See Lipsitch (1999).

[11] It is important to note that our choice of the time sequence of market entry decisions is hypothetical; reflecting the lack of and/or difficulty of gathering data/information on market entry decisions of real-life vaccine producers. The model structure, however, offers the flexibility for any analysts to use alternative event dates that are informed by more appropriate data.

Within the pre-build-up period, multinational-1 and multinational-2 will supply vaccines produced from existing production plants at the same prices as are charged for vaccines produced with new production plant capacity. That is to say the price bargaining position of UNICEF does not change, regardless of whether the vaccines are produced using existing production plants or with new ones. Given that the pentavalent Hib-containing vaccines are closest in terms of complexity to the pneumococcal vaccines (i.e., they are polyvalent protein-conjugated vaccines), we adopted the highest weighted average price (WAP) reported by UNICEF ($6.60) for the Hib-containing pentavalent vaccines as the price charged within the pre-build-out period. We chose the highest WAP given arguments that UNICEF does not always have a strong bargaining position to extract 'low' prices in the region of $3.50 per dose from multinational vaccine manufacturers.

Considering the difficulty in getting data on vaccine supply costs, we make an assumption that the incremental production costs (i.e., variable costs plus an allocated margin reflecting fixed and quasi-fixed costs) *per dose* supplied to low-income countries using the existing pre-build-out capacity will be $2.83. This price is the end-point of the forecasted decline in the WAP for the pentavalent Hib-containing vaccines, which we consider as reflecting the long-run marginal cost of supply that allows a given vaccine producer to 'break even'. This is shown in Figure 14 below. We are therefore assuming that vaccine production costs for the pneumococcal vaccines will be similar to that of the Hib-containing pentavalent vaccines.

Figure 14: Weighted average prices for pentavalent Hib-containing vaccines



Source: UNICEF (2010)

In the EEG model, an assumption was made that there is a real (i.e., inflation-adjusted) annual cost growth of 1.5%. We follow this assumption given the likely scenario that the real cost of materials and inputs for setting up vaccine production plants and producing vaccines could increase over time. In our Excel spreadsheet, as in the EEG model, there is an inflation indexing parameter that could be set to values greater than zero to derive a nominal annual cost growth rate.

Since existing production plants are sized only to meet demand in high-income countries, we assume by the end of the pre-build-out period, multinational-1 and multinational-2 would have built new production plants dedicated to meet aggregated demand from GAVI-eligible countries. When this new production plants starts operating, all vaccine suppliers will supply via UNICEF at the 'best price' that the GAVI Board is willing to approve or accept. This 'price' will be the same as that charged during the pre-build period as long as purchasing transactions go through UNICEF. For each of the suppliers in our counterfactual model (i.e., multinational-1, multinational-2 and emerging-market supplier), we assume they will build production plants of a given maximum capacity.

We follow the assumption made in the EEG model that it takes 5 years for the new production plant to be built and once that plant is built, it will shut down once after 8 years of operation. This shutdown period lasts for one year as efforts are made to bring the production plant back online. We consider this a reasonable assumption to make given, for example, problems of bacterial or viral cross-contamination in the vaccine production process that might require shutting the plant down for 'cleaning'. (This may create supply failures or shortages if the market is not characterised by multiplicity of vaccines producers to ensure 'security of supply'.) We believe a 'stable' production process is an unrealistic assumption to make although not impossible.

Within the counterfactual world described, we implicitly assumed that market entry by each of vaccine suppliers (multinational-1, multinational-2 and the emerging-market producer) is guaranteed albeit after a certain lag in time. Theory will suggest that market entry decisions by vaccine suppliers will be determined by correct or incorrect estimates of the (risk-adjusted) NPV of that decision, which should be positive and greater than zero. That is to say the probability that a vaccine supplier will enter the aggregate market of GAVI-eligible countries will be positively related to the estimated NPV. To validate the assumptions made about market entry decisions of our selected vaccine suppliers, we can carry out net present value (NPV) calculations to ascertain whether our assumed market entry will represent a prudent use of investment capital and (internally-generated) income under the other assumptions made in the model.

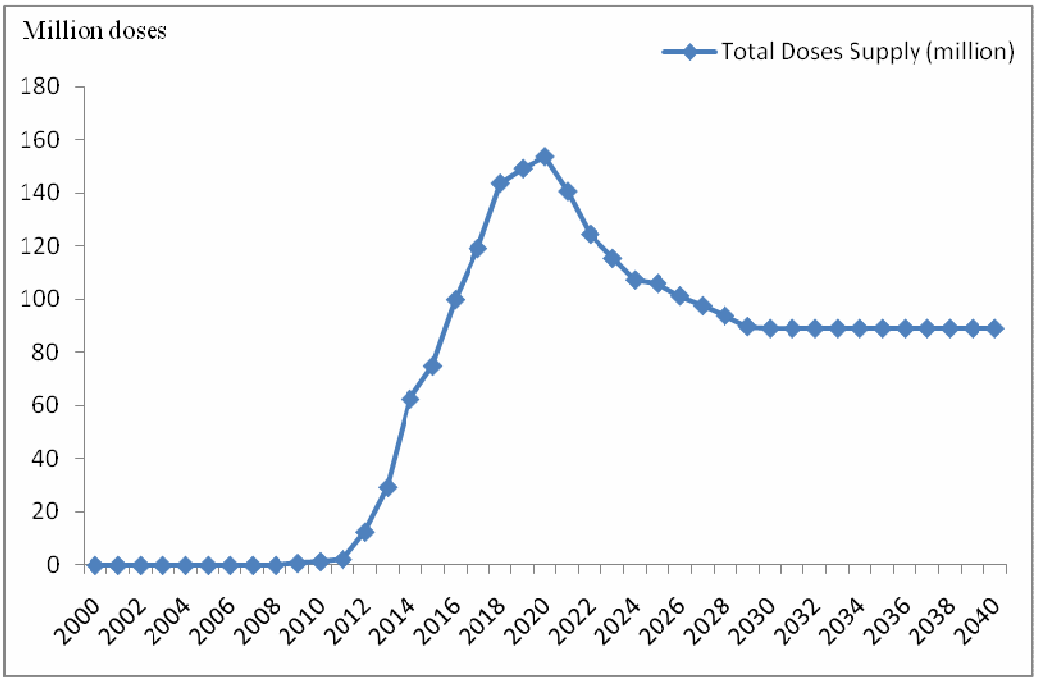
One advantage of these NPV calculations is it allows one to identify which variables will be important in determining the willingness of vaccine producers to incur the needed sequence of fixed costs investments for supply. We therefore carried out NPV calculations with respect to the pre-build-out period and the time period within which a new production plant dedicated solely to supply for low-income countries is in operation. These NPV calculations were calculated over the model's time horizon under the assumption that cost of capital (which we will use as the 'firm discount rate') is 11%. In the EEG model, the firm discount rate is set at 10 %. We employ a cost of

capital of 11% since this is the real cost-of-capital used by DiMasi, Hansen & Grabowski (2003) to estimate the 'price of innovation'.

Finally, we assume there will be no intellectual property (IP) problems for emerging suppliers aiming to develop 'biosimilar' versions of the PCVs. Since these IP issues will apply equally in worlds with or without an AMC intervention for pneumococcal vaccines, the effects should invariably be the same. Further, since emerging suppliers will still have to incur roughly the same sequence of fixed costs investments (clinical trials etc), IP issues may be less relevant in the area of vaccines relative to small-molecule chemically-synthesised pharmaceuticals.

On the demand-side, we made use of demand forecasts generated by AVI that have been tailored to a counterfactual environment without an AMC intervention for the pneumococcal vaccines. Figure 15 is a graphical illustration of AVI's estimates of possible demand for our counterfactuals generated using the same methodological approach presented in Figure 12. That is to say the forecasted counterfactual demand has been adjusted for vaccine wastage and stockpiling. (The data set and the underlying assumptions will be found in the Excel sheets accompanying this report.)

Figure 15: Forecasted demand for the PCVs in the world without AMC intervention



The shape of the forecasted counterfactual demand curve is in part determined by demand from India (whose GAVI eligibility runs from year 2014 to 2018) and the fact that other countries lose their GAVI-eligibility status over time. Note that in discussions we held with AVI, it was agreed than the 'AMC effect'(via influencing vaccine introduction dates) will be the main confounding variable in generating demand estimates that are more appropriate for the world without an AMC for the

pneumococcal vaccines. This 'AMC effect' was controlled for by using vaccine introduction dates recorded for rotavirus vaccines. Demand data used in our model are thus generated by AVI using vaccine introduction dates observed for rotavirus vaccines.

Finally, we considered that differences in ability-to-pay (i.e., 'affordability' of vaccines) may have an impact on demand forecasts given prices that will prevail in the counterfactual may be different in the presence of an AMC. One approach was to rely on the Fiscal Space Analysis work conducted by GAVI staff, which looks at the ability of governments to make budgetary resources available for desired purposes (in this case vaccine purchase) without sacrificing financial sustainability. However, difficulties in defining 'affordability' and clearly specifying some methodology for linking ability-to-pay with the AVI demand data meant we could not consider this approach any further.

8.3.2 Counterfactual 2

On the supply-side, we make similar assumptions for Counterfactual 2 as we have done for Counterfactual 1, in relation to the number of vaccine suppliers, timing of vaccine production plant shutdowns, how long it takes to build new dedicated plants and the type of vaccine technology each supplier brings to the market. In Counterfactual 2, however, the main difference is that the UNICEF procurement arrangement fails for a given period of time, and within this period the only existing transactions for securing supply to the PCVs are via country-specific procurement arrangements. This obviously requires that low-income GAVI-eligible countries have the necessary procurement capacity and the needed financial resources.

What we envisage here, given that the conventional UNICEF procurement system is not successful or operative in the short term, is that there will be longer time periods before vaccine producers (notably multinational-1 and multinational-2) decide to build new production plants for supply to low-income countries. In this case, the only supply channel to low-income countries will be from existing production plants, i.e., Counterfactual 2 will be characterised by a pre-build-out period with prices of vaccine sold at levels higher than what would have been paid via the UNICEF procurement arrangement, if it was operative. In effect, Counterfactual 2 will be characterised by a longer pre-build-out period within which any demand expressed by low-income countries (individually) is met by multinational-1 and multinational-2.

We assume that the market environment in Counterfactual 2 does not support differential pricing (for the same vaccine product not a 'biosimilar') to any appreciable extent. There is, however, some degree of differential pricing for a variety of reasons such as altruism, salvaging bad publicity or simply because low-income GAVI-eligible countries cannot afford the prices that are charged to citizens of high-income countries. Table 6: shows the possible range of vaccine prices. For our purposes we chose $10.00 per dose as this represents the average price in public sectors of middle-income countries.

We assume that entry from emerging-market suppliers will only happen when this prolonged pre-build-out period for multinational-1 and multinational-2 is over. This

ensures that entry of the emerging-market supplier coincides with when the UNICEF procurement arrangement starts functioning as expected. As brought to our attention by the experts consulted during validation of our counterfactuals (see Section 7), the case of Wyeth (now Pfizer) failing to respond to UNICEF's bid for Prevnar® was a one-off event. What appears to have happened was that UNICEF proposed a one-year bid for small quantities (which is unusual as the norm is supply for large quantities over three year periods).

Table 6: Possible vaccine prices in public sectors of GAVI-eligible countries

Public Vaccine Market	Low-income countries	Middle-income countries	High-income countries	Total
Potential Public Vaccine Market (M doses)	160	92	4	257
Estimated Public Vaccine Price ($/dose)	$5.00	$10.00	$50.00	-
Potential Public Vaccine Market ($M)	$802	$918	$215	$1,936

Source: PneumoADIP/Applied Strategies (2009).

We speculate that the decision to offer a one-year bid for small quantities was made in anticipation of availability of 10- and 13-valent PCVs: the 7-valent Prevnar® was soon to going to be obsolete. For this reason, we restrict the period within which there is breakdown in procurement negotiations between multinational vaccine suppliers and UNICEF to a maximum of 5 years after which business with UNICEF resumes as normal. This is arbitrarily chosen figure reflects that in fact breakdown in the UNICEF procurement arrangement will not be a lasting problem. We therefore subject this time period to a sensitivity analysis. (Note that this 5 year period, or whatever N number of years one assumes, prolongs the pre-build-out period by the figure chosen.)

The time sequence of events modelled in the base case for Counterfactual 2 is as follows. Given the 5 year period in which UNICEF's procurement is not operative, the pre-build period for multinational-1 starts in 2010. This is followed (as in Counterfactual 1) by a historical lag of 10 years, which includes the 5 years it takes to set up a new production plant. Multinational-1 therefore starts to supply its 10-valent technology with the new dedicated plant in 2019. As before, the pre-build out period for multinational-2 starts two years prior to when multinational-1 starts supplying with its new dedicated production plant. The pre-build out period for multinational-2 is equally extended by a 5 year period within which it fails to finalise a supply agreement with UNICEF's vaccine procurement division. Our input into the model was that the pre-build-out period for multinational-2 will run from year 2017 to year 2027 (this includes the 5 years it takes to build a new production plant). Two years later, the emerging-market supplier enters the market in year 2029.

Again, we want to emphasise that our choice of the time sequence of market entry decisions is hypothetical; reflecting the lack of and/or difficulty of gathering data/information on market entry decisions of real-life vaccine producers. The model structure, however, offers the flexibility for any analysts to use alternative event dates that are informed by more appropriate data.

As with Counterfactual 1, we performed NPV calculations (subject to the various assumptions made under Counterfactual 2) to ascertain whether our assumptions about timing of market entry hold.

On the demand-side (for Counterfactual 2), we employed the same demand estimates generated by AVI, shown in Figure 15, with a number of caveats. Given an initial period of individualistic country-specific purchasing with vaccine prices charged above what UNICEF usually negotiates with suppliers, we assume in Counterfactual 2 that aggregate demand from GAVI-eligible countries will show a constant elasticity in response to prices charged above $10.00 per dose such that at high price levels demand may fall to zero. The problem with this is defining the form of the demand function for the aggregate market of GAVI-eligible countries over the period within which UNICEF's vaccine procurement is not operative.

To solve this, we borrow Scherer's (2007) analysis of influenza vaccine shortages in the US. Scherer assumes a demand function with a constant elasticity of –0.85 up to a price of $50.00 per dose, above which a linear demand function is assumed such that influenza vaccine demand approaches zero at higher prices. Scherer's (2007) demand function is expressed as: $Q = 350.P^{-0.85}$. This follows the standard expression of a demand curve with constant price elasticity. (Note that the constant term of 350 was chosen to give a market of reasonable size [personal communication with Professor Scherer].)

The next question is whether a price-demand-elasticity of -0.85 is an appropriate characterisation of demands expressed by low-income GAVI-eligible countries. Recent empirical meta-regression work (albeit from datasets in high-income countries) suggests that the price elasticity of demand for medicines/pharmaceuticals is significant different from zero with a mean around -0.209 (Germmill, Costa-Font & McGuire, 2007). Given the rather widespread health insurance protection that citizens of high-income countries have, we consider that price inelasticity of low-income country demands will be higher than -0.209.

We considered Scherer's (2007) demand function appropriate for describing how aggregate demand in GAVI-eligible countries will respond to higher than UNICEF-negotiated prices in Counterfactual 2. However, from correspondence with Professor Scherer, it became apparent that his demand function was based on an assumption that vaccine demand will be relatively price inelastic up to a very high price – an assumption which in the context of low-income countries may be true if there is widespread health insurance protection and/or vaccinations are covered by non-governmental organisations (NGOs). If such an NGO had a fixed budget, the price elasticity will be very near unity.

Given the assumption that in Counterfactual 2, low-income countries are involved in country-by-country negotiations with no external financial support for vaccine purchase, we considered that price demand elasticity will be greater than unity. From existing literature, we noted that estimates of price elasticity of demand for healthcare of –3.6 and –1.7 for infants and children respectively, were reported by Sauerborn, Nougtara & Latimer (1994). Also, Sahn, Younger & Genicot (2003) report price demand elasticity, for healthcare services delivered in hospital settings, in the region of -3.50. Taking into consideration the issues above, we assumed a constant demand function of -3.50. So although we maintain AVI's demand estimates for our defined counterfactuals, actual demand expressed over the pre-build-out period is determined by the expression: $Q = 350.P^{-3.50}$.

8.3.3 Model Parameters

In this section, we set out to describe the input and output variables of our model and how they were selected. In selecting appropriate model inputs and outputs (considering also the model structure adopted) we looked at a number of draft versions of the final indicator matrix presented in Section 6.7 and developed for this AMC Baseline Study. These matrices grouped indicators selected to evaluate the impact of the pneumococcal AMC in view of its goal of reducing morbidity and mortality from pneumococcal disease and its three main objectives.

Note, however, that the final set of parameters considered in the actual model was determined in part by data availability (specifically results of the data collection exercise carried out by other members of the SCIH team) and the feasibility of modelling a particular issue and its relevance to the model outputs. Note also that our model inputs and outputs may not share the precise meanings and definition as variables listed in the final indicator matrix. This is partly because the model structure, inputs and outputs were developed prior to final approval of the indicator matrix.

Our selected model inputs and outputs are nevertheless consistent with what is described in the indicator matrix. Data on the model inputs will be found in the Excel spreadsheets accompanying this report.

Model outputs

We focus our attention on the following model outputs (reflecting market outcomes we expect from interactions between 'supply' and 'demand' variables):

- **Quantity of vaccine supplied** to low-income countries (over different time periods). For Counterfactual 1, this corresponds to total number of doses supplied via the UNICEF procurement arrangement. For Counterfactual 2, this refers to total number of doses supplied through country-specific procurement arrangements (when UNICEF procurement is not operational) and total number of doses when the UNICEF procurement arrangement starts working
- **Discrepancies between vaccine demand and supply (supply shortfall)**. This captures any differences between expected demand forecasts and doses of PCVs

procured at country-level (relevant for Counterfactual 2) or doses procured in aggregate via the UNICEF procurement arrangement

- **Cumulative number of DALYs or deaths averted**. These measures were selected to provide an indication of the potential health impacts and estimated by combining the number of doses supplied with inferred estimates of the number of DALYs or deaths that can be averted (per PCV dose supplied).

We considered cumulative number of DALYs or deaths averted per PCV dose supplied rather than per dose of PCV offered because it is the number of doses supplied that (subject of course to constraints imposed by health system infrastructure) will be administered to the targeted infant populations. Doses 'offered' or contracted may not necessarily be the doses supplied. In both cases of estimating cumulative number of DALYs or deaths averted per PCV dose supplied, we made adjustments to reflect the fact that the number of vaccine doses supplied is not necessarily the number of vaccine doses administered/injected. To the best of our knowledge, methodology for incorporating an injection adjustment factor in such supply calculations is still under development by WHO; hence, for our purposes we assumed an adjustment factor reflecting 10% 'wastage' of vaccines.

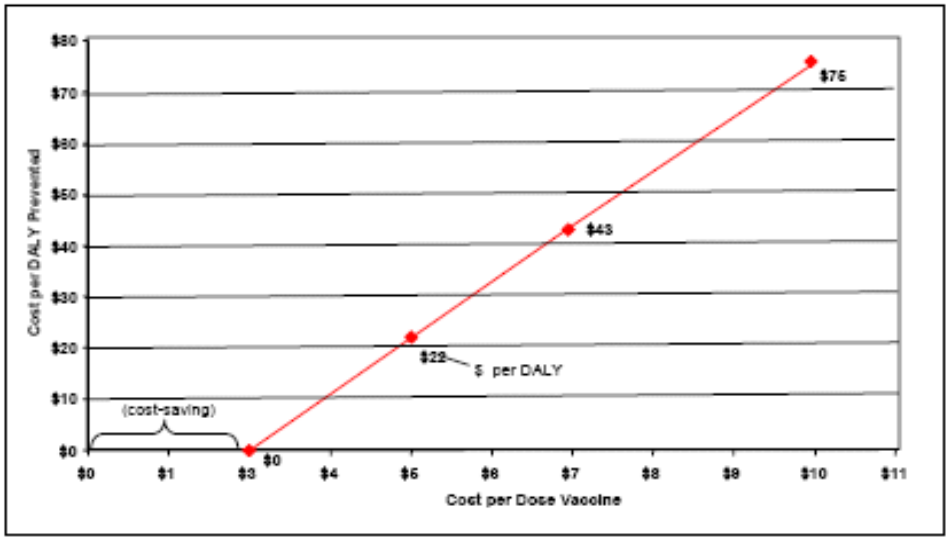
In our approach to estimating the number of DALYs averted per dose, we relied on clinical and economic evidence generated for the 7-valent PCV. In other words, we assuming the vaccine technologies considered in our model will be, at least, as 'good' as the 7-valent PCV. However, in our searches we came across literature that provides estimates of cost-effectiveness of the 7-valent PCV (commonly quoted as $22 per DALY averted) but we could not find appropriate data on the cases averted per dose or DALYs averted per dose. It was possible, however, to estimate the number of DALYs averted per dose indirectly, from the results of the sensitivity analysis presented below. From Figure 16 below, we estimated that the (minimum) DALYs averted per dose of PCV supplied (in our model) will be 0.23 (5/22)[12]. Multiplying that by the cumulative number of doses supplied in our models for Counterfactual 1 and Counterfactual 2 gives us the cumulative number of DALYs averted.

In our approach to estimating the number of deaths averted per dose, we made use of data from the Gambian clinical trial on the 9-valent PCV, by assuming that 7.4 deaths will be averted per 1000 children fully vaccinated. That is to say, for every 3000 vaccine doses administered (roughly 3333 [= 1.1111 X 3000] doses supplied), 7.4 deaths will be averted. Note that this indirect estimate does not consider herd immunity effects and the approach taken is consistent with previous work done by GAVI that suggests that 7 million deaths could be averted by year 2030 through pneumococcal vaccinations. We note that WHO is developing a model to provide 'better' estimates of

[12] The obvious problem with this indirect estimation is that it assumes linearity in clinical effectiveness and cost-effectiveness (CE) with respect to price or doses of PCV supplied. It is easy to see this: at $7 per dose, CE estimate is $43 per DALY averted; which gives DALYs averted per dose as 0.16. At $10 per dose, CE estimate is $75 per DALY averted; which gives DALY averted per dose as approximately 0.15. Given the paucity of data, we adopt the primary indirect estimate.

deaths averted through PCV vaccination: once that model is available, the work presented can easily be upgraded.

Figure 16: Cost-effectiveness estimates of 7-valent PCV according to price per dose of vaccine



Source: GAVI (2006).

Input variables

Data on input variables will, by and large, be taken from the historical data collected on rotavirus and Hib vaccines, which we identified as the 'best', though not perfect, counterfactual examples for the pneumococcal vaccines. Below is a list of the model input variables.

- **Total number of vaccine manufacturers**[13]. This input variable will be disaggregated according to number of multinational vaccine manufacturers and number of emerging-market vaccine suppliers. Its main purpose is to validate the assumptions about market entry
- **Time to market entry of at least one vaccine supplier**. There are two dimensions to this variable: time to market entry of multinational and of emerging-market vaccine manufacturers
- **Number of doses contracted to be supplied**. This variable is meant to capture the possibility that the quantity of vaccine doses supplied will not necessarily be the maximum production capacity of vaccine producers

[13] This is a particularly important indicator as the greater the number of vaccine suppliers the greater the likelihood of ensuring 'adequate' vaccine supply to match forecasted demand and 'security of supply', i.e., hedging against supply interruptions from unplanned vaccine plant shutdowns.

- **Vaccine supply costs**. This input variable will be disaggregated into fixed capital costs (for investment sunk in building vaccine production plants), semi-variable (quasi-fixed) costs of production and variable costs, where data availability allows
- **Number of incidents of unplanned vaccine plant shutdowns** (due to contamination, for example).
- **Vaccine price**
- **Demand forecasts** (in a world without AMC intervention).

Our initial preference was to have, in addition to data on the variables above, data on vaccine production capacity. However, given the difficulty of gathering data on vaccine production capacity, we opted to use the number of contracted doses to be supplied as a proxy of the 'effective' vaccine production capacity available.

From the data collected and sent to us, we focused our attention mostly on the pentavalent Hib-containing vaccines as these, we believe, are the closest to the PCVs in terms of complexity (i.e., they are protein-conjugated polyvalent vaccines.) We noted from data on a number of long-term agreements (LTA) that the maximum quantity of doses for the (pentavalent vaccines) contracted by UNICEF (with different vaccine suppliers in a given year) was 15 million doses and this was a supply contract with a multinational vaccine manufacturer. We therefore assumed that the existing production plant used by multinational-1 and multinational-2 in the pre-build-out period will have a capacity of 15 million doses. (Note that the LTAs we considered were valid over different years.)

We considered that a multinational vaccine supplier who finds it worthwhile to build a new dedicated plant for supply to low-income countries will build a higher capacity plant. We therefore assumed conservatively that the new dedicated plants built by multinational-1 and multinational-2 will have a capacity of 25 million doses (this is less than what is assumed in the EEG model). From our data set, the maximum contracted number of doses for the pentavalent vaccines from an emerging-market supplier was 3.5 million doses. We therefore assumed that the emerging-market supplier in our model will only attempt to match the existing production capacity of the incumbent multinational producers, i.e., it will build a plant with a capacity of 15 million doses.

We also hoped to have data on vaccine supply costs but again difficulties in gathering such data meant we had to rely on existing figures given the EEG model. We assumed that upfront costs for multinational-1 will be $110 million but given that multinational-2 is only supplying a 13-valent technology (compared to 10-valent technology by multinational-1); its upfront costs will amount to $150 million. This follows Scherer's (2007) report that upfront vaccine plant investments (covering plant administration, quality control, laboratory operation, health and safety, utilities etc.) is in the range of $100-150 million. Another set of data that was difficult to come by was the number of incidents of unplanned vaccine plant shutdowns. We had hoped to collect some evidence to support the assumption made in the EEG model but, given the lack of such data, we simply maintained the assumption made in the EEG model.

8.3.4 Relationship between input variables and model outputs

Broadly speaking, the relationship between our input variables and model outputs follows what is depicted in Figure 9 as our model aims to capture the interaction between 'supply' and 'demand' variables that will determine outcomes in the market for pneumococcal vaccine supply to low-income countries. The precise formulae linking the input and output variables of the models will be found in the cells of the Excel spreadsheets accompanying this report. However, to make these spreadsheets 'user-friendly' we have produced a formula sheet (see Annexe 2) that shows the mathematical relationships between the model inputs, and between the model inputs and outputs.

8.3.5 Sensitivity analysis

Quantitative estimation of the AMC counterfactuals is fraught with complexity and various confounding factors. It is important to attempt to control for at least some of these confounding factors including those that might enable or inhibit the working of an AMC intervention for the pneumococcal vaccines. We list below what we believe are the most relevant confounding factors:

- **Role of push funding** (and in general public-private partnerships) that are designed to reduce the entry barriers and speed up market entry particularly for emerging-market vaccine suppliers
- **Interaction between PAHO and GAVI/UNICEF**. This, in general, requires considerations of the scope for segmenting markets in ways that favour differential, tiered or 'equity' pricing. This we believe will have a significant impact on time to market entry of multinational vaccine suppliers in particular
- **Funding levels for vaccine supply to low-income countries with and without AMC intervention**. We considered this variable, given arguments that even without AMC intervention, in an ideal situation the level of funding for procurement should be no different from the funding when an AMC is available. Also, as noted earlier, the mere presence of an AMC affects 'demand' expressed by GAVI-eligible countries by altering vaccine introduction dates.

Given the model inputs and confounding (inhibiting or enabling) factors, it is imperative to subject our counterfactual models to a number of sensitivity analyses. We took the pragmatic approach of restricting our sensitivity analyses to demand realisation and vaccine prices. We selected these variables on the basis of our prior expectations *and* preliminary runs of our models with imputed and arbitrarily chosen values for the models' inputs that suggest that these parameters consistently had an impact on the models' outputs. Below is a summary of our initial thinking on what variables should be subject to sensitivity analysis.

One methodological difficulty in assessing the impacts of these confounding factors listed above is finding a robust quantitative measure of our selected confounding factors, i.e., identifying an appropriate unit for measuring the impact of push funding, or differences in funding levels, for example. Given this problem of finding a quantitative

scale for these confounding factors, we aimed to identify variables in our models that they might have an influence on.

We considered that the number of emerging-market suppliers and the time to market entry by these vaccine manufacturers could be enhanced if they receive some push funding from international and non-governmental organisations. Push funding/ subsidies will reduce barriers to market entry by lowering the sequence of fixed cost investments needed; holding all else constant, this should speed up time to market entry by emerging-market suppliers. In the case of multinational vaccine producers, we expect that a market environment favourable/conducive for differential pricing across high-, middle- and low-income countries should increase the willingness to supply low-income countries with needed vaccines. This in particular may affect their willingness to respond to vaccine supply bids issued by UNICEF in the first place.

We considered that the role of push funding will be captured through varying vaccine prices. We know, for instance, that it was thought that no vaccine manufacturer from the developed world could produce MenAfriVac® conjugate vaccine for less than $0.50 per dose and in 2004, PATH (with $70 million grant from the Bill and Melinda Gates Foundation) entered a sublicense and supply agreement with Serum Institute of India (SII) to develop the vaccine for a target price of $0.40 per dose. The effect of push funding to lower market entry costs is thus akin to paying higher prices in a situation without push funding to lower the sequences of costs involved.

Similarly, the effect of interaction between PAHO and UNICEF will be captured via 'price' as the main effect is to reduce the scope for differential pricing. So for example, in Counterfactual 2, given the tensions between PAHO and UNICEF, and the fact that charging lower prices to low- and middle-income countries may invite requests for price concessions from healthcare payers in high-income countries, vaccine suppliers may find it profitable to simply charge prices equal to those for the public sector in high-income countries rather than those usually charged to middle-income countries (as reported in Table 6).

Regarding the impact of differences in funding levels in the worlds with and without AMC intervention, recall that we assumed in our base case analysis that there is less funding in an environment without an AMC intervention and there is an 'AMC effect' on demand[14]. We considered that any differences in funding levels will be reflected in the forecasted demand expressed by GAVI-eligible countries for the pneumococcal vaccines. Since our base case already captures this 'demand effect', we aimed to explore in our sensitivity analysis varying degrees to which our 'counterfactual demand estimates' generated by AVI will be realised. We explore whether 100%, 75% or 50% of that demand will be realised and the impacts this will have on our model outputs.

[14] We followed this line of thought bearing in mind arguments that funding levels with or without AMC intervention should *ideally* be no different. It is clear, however, that more funding has been mobilized for vaccine purchase relative to past trends.

9 Baseline data collection and analysis

This section of the report reviews the data collection and analysis carried out during the baseline study. It discusses the contents of the indicator matrix outlined towards the end of Part I of this report, taking each indicator by AMC goal and objective and presents:

1. Justification of the indicator choice
2. Data sources used in the baseline and recommendations for future data collection where appropriate
3. Data analysis used in the baseline and recommendations for future data analysis where appropriate
4. Details of data presentation for the baseline results and relevant recommendations for future M&E activities

Lessons learnt from the data collection and analysis activities at baseline are discussed in Part IV of this report to assist future M&E activities.

9.1 AMC goal: Morbidity and mortality

To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030

Indicator 1: Cumulative number of cases of IPD averted due to TPP vaccines in GAVI-eligible countries

Indicator 2: Cumulative number of future deaths averted due to TPP vaccines in GAVI-eligible countries

a) Justification

Reducing morbidity and mortality is the overarching goal of the AMC. Pneumococcal disease is the leading cause of death among children under five in the world.

The indicators measuring morbidity and/or mortality due to pneumococcal disease are relevant to assessing the overall goal of the AMC strategy: 'to reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030'.

Many factors influence morbidity and mortality due to communicable diseases, ranging from changes in the infectious agent (e.g. virulence) to public health policies to prevent infection (e.g. vaccination).

The roles of modifiers and attribution will be examined. There are factors interfering (both positively and negatively) with the ‘ideal’ association between vaccination and disease incidence reduction seen, for example, in randomised control trials.

Furthermore, it will be hard to attribute changes observed to any single intervention, such as vaccination. However, by matching GAVI AMC deployment and changes in disease burden, it will be possible to make a plausible case for relating pneumococcal vaccination under AMC to mortality reduction.

b) Data sources

Pneumococcal disease incidence and mortality are not systematically reported by countries because they require microbiological confirmation, which is not routinely performed in all suspected cases. Therefore, aetiological data can only be inferred from cases that have an aetiological confirmation: either from records of the fraction of the suspected cases routinely seen in health services which have microbiological confirmation, or from research sites specifically looking at IPD. Both sources provide local data and the only way to get global figures, consistent with the GAVI AMC goal, is to elaborate estimates based on data from several sources and years.

At present, WHO has made available the country estimates of IPD, with totals and by syndrome (WHOd) and is planning to produce annual estimates that will be available to GAVI. This is the most reliable available source of global and country by country data on the burden of IPD.

There is ongoing work in The Gambia and Kenya that specifically looks at IPD prior to vaccine introduction. In November 2006, GAVI committed funds to supporting the initial two years of these studies. The goals are:

- to evaluate the health impact of pneumococcal vaccination in two early-adopter countries;
- to determine whether catch-up programs can 'front load" the prevention of pneumococcal disease and prevent illness among unvaccinated populations through herd immunity;
- to assess changes in the incidence of serotypes not included in the 7-valent vaccine (i.e. serotype replacement) and their impact on overall invasive pneumococcal disease rates.

However, these studies will produce the IPD data required to evaluate vaccine efficacy specifically in the areas in which they are undertaken. The estimates derived from these studies will be valuable in the future for the elaboration of national and global estimates, but they are not so appropriate for the current AMC evaluation, which is much wider in terms of geographical scope.

c) Data analyses

In this section we report some of the analytical results of the global estimates (WHOd and O'Brien 2009). In relation to pneumonia, the global estimates paper calculated:

- the number of pneumococcal pneumonia cases: applying the proportion of pneumonia attributable to *S. pneumoniae* to the estimated all-cause pneumonia cases;
- the number of pneumococcal deaths: applying the proportion of all-cause pneumonia deaths attributable to *S. pneumoniae* to the country-specific estimates of pneumonia deaths.

Some adjustments were made to account for HIV status. The proportion of pneumonia cases or deaths attributable to *S. pneumoniae* was estimated based on four efficacy trials of PCV (The Gambia 2005, Philippines 2009, South Africa 2003 and USA 2006)[15]. Data from trials was adjusted for serotype, coverage and efficacy against pneumococcal pneumonia.

O'Brien et al. (2009) state that the model may underestimate the contribution of pneumococcal disease in high-mortality areas, because the model is limited by all-cause pneumonia mortality data. They also acknowledge that the real ranges of the values estimated might be larger than the ones presented in their paper. They also mention discrepancies between their estimates and those from other sources, especially the calculations of the Sabin Vaccine Institute and the Pan American Health Organisation for Latin America (for example, 18,000 pneumococcal deaths in under-5s estimated by Sabin compared with the 33,000 estimated by O'Brien et al.), and discuss reasons for these. The estimated all-cause pneumonia cases and deaths were from the WHO Global Burden of Disease, 2004 update (WHO, 2004a).

d) Data Presentation

Data is presented sorting the number of cases and deaths to better ascertain the relative contribution of each GAVI-eligible country to the total burden of disease for GAVI-eligible countries.

Data is presented in two bar charts (see findings Part III, Section 11) plotting the estimated number of IPD cases and deaths. Countries are ordered by the absolute number of these indicators. The figures present the cumulative percentage of cases and deaths, which can be used to show how many countries account for half (or any other proportion) of cases and deaths.

The proportion of annual deaths to be averted over the total number of estimated deaths to achieve the goal of reducing the number of deaths by 7 million by year 2030 provides an indication of the magnitude of the effort involved in reaching this goal.

9.2 AMC objective 1: Vaccine development

To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP)

Indicator 3: Cumulative number of TPP candidates

a) Justification

Currently there are only a few candidates meeting the TPP. It is theorised that the AMC will encourage an increase in the number of candidates being developed, thus increasing the likelihood that TPP requirements will be met.

[15] Dates are year of publication.

The AMC mechanism is based on the premise that it will stimulate R&D activity in the area of pneumococcal vaccines, by increasing the resources spent on clinical development (Levine et al, 2005). This indicator aims to capture changes in pneumococcal vaccine R&D over time, focusing on the later stages of the R&D process, especially clinical development. The reason for this focus is three fold. First, the emphasis placed on the underlying premise that the AMC mechanism will mobilise product development especially in the later stages of the R&D process. Second, the importance of the cost and timelines of clinical development in raising the overall cost of pharmaceutical product development (DiMasi, 2006; Keyhani et al, 2006) Third, the difficulty of determining the number and type of activities taking place and defining suitable measurement points at the pre-clinical (Molvolti, personal communication).

This indicator will measure the total number of pneumococcal vaccine candidates meeting the TPP. In line with our reasoning above, our definition of a pneumococcal vaccine 'candidate' includes those products that are within:

- the clinical trial stage of product development (defined as between the lodging of an investigational new drug (IND) file[16]/ another national regulatory authority equivalent, or a first clinical trial registered on a clinical trial database should the former data not be available, and the submission of the Biological License Application (BLA) or New Drug Application (NDA)/ other national regulatory equivalent);[17]
- the approval phase (between BLA/ NDA submission and gaining of WHO prequalification status and AMC eligibility) or;
- those which are on the market and which meet the TPP (specifically, having WHO prequalification and AMC eligibility, which target *Streptococcus pneumoniae* in infants and work against serotypes 1, 5 and 14)

b) Data sources

Vaccine candidates[18] can be identified at various stages of the R&D process, since manufacturers have to register their R&D activities with various government agencies in different countries. These include the US Food and Drug Administration (FDA), other national regulatory authorities, the European Medicines Agency (EMA) and various clinical trials databases, most prominently, the US National Institutes of Health (NIH) (www.clinicaltrials.gov) and European Community (EudraCT) databases. A

[16] This is a US FDA procedure. Other countries have differing procedures as does the overarching European Medicines Agency (EMA).

[17] The BLA and NDA are US FDA procedures. Other countries have different procedures as does the overarching EMA.

[18] As outlined in Section 9.2., our definition of a vaccine candidate refers to vaccines within the clinical trial stage of product development (defined as between the lodging of an investigational new drug (IND) file/ other national equivalent or first clinical trial registered on a clinical trial database should the former data not be available and the submission of the Biological License Application (BLA) or New Drug Application (NDA)/ other national equivalent), those within the approval phase (defined as between submission of BLA/ NDA and WHO PQ and AMC eligibility status) and those being marketed having already received WHO PQ and AMC eligibility.

thorough search of these various sources was conducted, supplemented by a further web-based search including company websites, interviews and e-mail exchanges with vaccine manufacturer representatives, using the following step-wise process:

Initial data collection activities:

1. An initial general web search using various combinations of the keywords: 'R&D', 'clinical trials', 'early/ late stage', 'expenditure', 'plant investments', 'manufacturing capabilities', 'regulation', 'profitability', 'confidence', 'market demand', 'market supply', 'price'. These were associated as necessary with other keywords such as 'pneumococcal disease', 'vaccinology', 'AMC', 'GAVI'. Further searches were undertaken using various variations of these two sets of words and their combinations.
2. Exploratory discussions with GAVI personnel and analysis of 'grey literature'' related to the AMC to identify pneumococcal vaccine manufacturers.
3. Representatives of companies identified from activities 1 and 2 were interviewed by telephone, using a semi-structured questionnaire. The interview questions addressed the situation with respect to the pneumococcal vaccine industry prior to the introduction of the AMC. The question guide also focused on collecting data related to R&D and plant investments, licensing or production agreements and manufacturing levels in the pharmaceutical industry for pneumococcal vaccines. Furthermore it explored factors affecting company decisions in areas related to industrial R&D, production and distribution of pneumococcal vaccines. These questions were based on an initial set of indicators that were developed and subsequently changed to those outlined in the indicator matrix in Part I above, Table 5:. Discussions midway through the data collection process resulted in a change in the focus of data collection following a revisioning of the indicators that data collection was to focus on, as outlined above. The interview guide and list of companies interviewed are available in Annexe 3.
4. An initial e-mail was sent to all companies with vaccine candidates meeting the TPP (addressed to the representatives initially interviewed) outlining the data collected following the websearch and the interviews, and requesting confirmation of the data's accuracy.

After the finalisation of the indicator matrix, the following final data collection activities were carried out:

5. A specific web search of key websites. The web search identified vaccine candidates and their dates against agreed milestones. The websites used were the US NIH clinical trials website, the FDA website and Federal Register, the EMA website and the European clinical trials website, the websites of all the companies identified as having vaccine candidates, and two industry database websites (BioPharm Insight and Thomson Pharma).[19]

[19] The two industry websites required a subscription in order to be accessed fully. This was arranged during baseline data collection, but the need for a subscription may have implications for future data collection.

6. A final e-mail was sent to the same company representatives to gain final clarification of the data gained from the data collection and analysis activities based on the finalised indicator matrix.

Future data collection

Due to the change in emphasis of the data collection indicators that occurred during the baseline study, we believe that future data collection needs only to focus on activities 5 and 6 above. Although changes are unlikely to occur quickly within the R&D pipeline, it would be efficient to collect data on a yearly basis.

c) Data analysis

A data collection table was created for recording the data and identifying gaps in data availability

Table 7: Vaccine candidates

Company	Candidate	IND	P I	P II	P III	BLA/ NDA	WHO PQ	AMC Eligibility	Notes
Company X…	Product X…	Month-Year	Month-Year	Month - Year	Month - Year	Month – Year	Month - Year	Month - Year	Any additional information

The search of multiple websites provided a means of triangulation of vaccine candidate details, especially the dates when milestones were reached. The data table was then transformed to the format used in the Findings section of this report Part III, Section 11.

d) Data Presentation

We have presented the data for Indicator 3 in Section 11.2, using a narrative milestone history approach. This outlines details of each of the TPP candidates identified, with specific dates against key milestones. We then present a tabular analysis of the situation during the baseline years 2005 and 2009. This is feasible because of the small number of candidates involved, and provides an opportunity to include additional information on important clarification points required in the baseline study (i.e. dosage type). We recommend that future data should be recorded in the same way, so that results can be easily compared.

Indicator 4: Median time between key milestones in the development of TPP candidates

a) Justification

The AMC is concerned with accelerating the PCV development process. It is believed that the AMC will have an impact on the timeline for one or more phases of the development process.

The AMC mechanism is expected not only to mobilise product development but also to *accelerate* production and introduction of pneumococcal vaccines into GAVI-eligible countries. In particular, the AMC mechanism is expected to act as a financial incentive mechanism to manufacturers of pneumococcal vaccines to accelerate the production and availability of late stage candidates (Levine et al, 2005). Evidence from other pull funding mechanisms show that these mechanisms can speed up the regulatory process of new drugs (DiMasi et al, 2003; DiMasi, 2002) and potentially speed up the time for clinical trials if the regulatory framework allows this (see Milne, 2002).[20]

This indicator will provide a means to measure the changing median time between key milestones in the development of TPP candidates. The milestones have been chosen taking into account the issues raised in determining Indicator 3. They are as follows: application for IND status; application for BLA status, WHO prequalification and AMC eligibility. The latter two have been chosen as the main focus, rather than licensing by country specific regulatory authorities, because they are emphasised by the pneumococcal vaccine AMC TPP.

b) Data sources

This indicator used the data collected for Indicator 3 outlined above.

<u>Future data collection</u>

For practical reasons, we recommend annual data collection. However, due to the time frames involved, data analysis can be done every four years in line with the impact evaluation that will be conducted.

c) Data analysis

Following a literature review,[21] the following data analysis mechanism was developed based on the milestones used in previous studies:

1. For each identified candidate, a calculation (in months) of the length of the clinical trial phase (between submission of first IND submission/ other national equivalent or first clinical study registration to date of marketing application submission using BLA or NDA/ other national equivalent)
2. For each identified candidate, where applicable, calculation (in months) of the approval phase (between submission of BLA or NDA/ other national equivalent and WHO prequalification and AMC eligibility)[22]

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[20] This is with reference to the US Orphan Drugs Act which has been considered by some as an exemplary pull funding mechanism and used in comparisons of the AMC (Grace, 2006; Danzon, 2007)

[21] The majority of work conducted on timeframes (usually as a result of focusing on R&D costs) in pharmaceutical R&D pipelines is that by the Tufts Center for Study of Drug Development (c.f. DiMasi et al, 2003; DiMasi et al, 2002; Reichert, 2006). Although criticisms can be made of their data sources, their methodologies are robust (c.f. Consumer Project on Technology, n .d.).

[22] As previously stated, we are not using country based licensing approval as the final approval date due to the emphasis within the AMC TPP mechanism on the need for WHO prequalification and AMC eligibility.

3. For each phase, ranking of the total number of months (low to high) and calculation of the summation of the median figure.

Since this analysis does not include any indication of median times for preclinical activities, which were not considered, for reasons already stated above, we are not in a position to analyse the median times for the whole R&D development process for pneumococcal vaccines. The calculation by itself does not provide any indication of the number of vaccines that have not completed the vaccine development process. By using a median figure (rather than the mean) we mitigate against the effects that candidates dropping out would have on the calculation.

We have not compared the results of these calculations against development times for other vaccines, so we cannot assess how far the median times that this calculation produces fit with a 'normal' vaccine development timeline.

We were also not able to make a comparable calculation for the situation in 2005, at the start of the baseline study. As DiMasi et al.(2003) pointed out in relation to drug development, it is difficult to collect historical data, especially where clinical trials first take place in countries where an IND application is not required. For 2005, we found only one candidate had received WHO prequalification and none had received AMC eligibility. We discuss the implications of this for future data collection later in this report.

d) Data Presentation

The data should be presented outlining median months for the clinical and approval phases based on months between each key milestone.

Indicator 5: Cumulative number of AMC eligible TPP vaccines

a) Justification

This indicator will show how many of the TPP candidates meet the TPP as per IAC evaluation of eligibility.

A registered manufacturer of a pneumococcal vaccine can apply to GAVI for eligibility status. The appropriate GAVI committee will then review the manufacturer's application to determine whether a vaccine meets the pneumococcal vaccine AMC TPP.

As this is the final milestone prior to potential use of a candidate in a GAVI-eligible country under the AMC, the notion that the AMC will accelerate production and availability should result, over time, in a greater number of candidates meeting the TPP and becoming eligible for the AMC.

b) Data sources

This indicator used the data collected for Indicator 3 outlined in 8.1 above.

c) Data analysis

The baseline data analysis conducted a summation of candidates that met AMC eligibility using data from Indicator 3. Future data analysis is recommended on an annual basis after annual collection of data for Indicator 3.

d) Data Presentation

The data is presented for each of the baseline years with details of each eligible candidate, its name and the actual date on which eligibility was conferred. For the baseline study findings we have provided this in a narrative format.

9.3 AMC objective 2: Vaccine availability

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

Indicator 6: Total number of doses of TPP vaccine offered to UNICEF SD per year for GAVI-eligible countries

a) Justification

The aim of the AMC is to increase capacity of production to meet GAVI country demand. The number of offered doses is the best proxy for actual capacity availability. This indicator is needed in addition to doses contracted (see Indicator 7 below), since the number of offered doses may exceed contracted supply.

An indicator is needed to review the success of the supply offer process and which can be reviewed against Indicator 5 to assess progress. At the same time this indicator acts as a partial proxy for the production capacity of pneumococcal vaccine manufacturers which will provide another measure of the degree to which the AMC mechanism is accelerating vaccine production; this time in relation to manufacture and supply rather than production of initial candidate vaccines. The difficulty of accurately determining manufacturing capacity using quantifiable figures was noted in the 2008 report commissioned by the AMC M&E Subgroup of the AMC Donor's Committee. We have used the total number of pneumococcal vaccines meeting TPP offered to UNICEF SD per year for GAVI-eligible countries as a proxy for production capacity. This is also based on the knowledge that UNICEF is the world's largest vaccine buyer (WHO et al, 2009) and a sizeable percentage, if not all, childhood vaccines used in many GAVI-eligible countries are procured by, and delivered through UNICEF SD (UNICEF, 2003; Rosenbom, 2010). While this indicator does not capture total production capacity it will capture production capacity relevant to GAVI-eligible countries with a degree of accuracy. Obviously, it would be preferable also to be able to provide an indication of the percentage of total production that goes to GAVI-eligible countries (via UNICEF procurement processes). However at the time of the baseline

study this information was not available. In the recommendations in Part IV of this report we discuss future options to gain this data.

b) Data sources

This indicator used the data collected from UNICEF SD via GAVI based on the supply offers received from pneumococcal vaccine producing companies meeting AMC eligibility.

Future data collection is recommended yearly to enable regular review of this situation.

c) Data analysis

The baseline data analysis had minimal data points here and no formal analysis was conducted. The data provided by GAVI is presented for each baseline year in a simple table (see Findings section below).

d) Data Presentation

The data are presented for each baseline year outlining total number of doses of TPP vaccines that were offered to UNICEF SD by year (including offered doses for future years). We have presented this in a narrative format.

Indicator 7: Number of doses of TPP vaccine contracted under AMC by year

a) Justification

The AMC aims to improve availability in terms of increasing production of PCV meeting TPP for GAVI-eligible countries. It is necessary to measure the number of contracted doses, since the number of doses offered by manufacturers may not always be realistic.

Measuring total number of vaccine doses offered to UNICEF SD (Indicator 6) is not the same as knowing the number of vaccine doses contracted to be supplied to UNICEF SD. On receipt of supply offers, UNICEF SD reviews these against the demand forecasts, which were the basis of its supply call, to determine the final figures that will be procured. This indicator will enable a comparison to be made with Indicator 6 and subsequently Indicator 10 regarding number of vaccine doses shipped. As noted in the baseline findings section below, sometimes the data points against these indicators can be the same. However, we do not envisage this occurring all the time, especially as the AMC mechanism becomes more established.

b) Data sources

This indicator used the data collected from UNICEF SD via GAVI, based on the outcome of UNICEF's analysis of the supply offers and demand forecasts and subsequent decisions on numbers of doses required and contracted from pneumococcal vaccine producing companies meeting AMC eligibility.

Future data collection is recommended yearly to enable regular review of this situation.

c) Data analysis

The baseline data analysis had minimal data points here and no formal analysis was conducted. The data provided by GAVI is presented for each baseline year in a simple table (see Findings section below).

d) Data Presentation

The data is presented for each of the baseline years outlining total number of doses of TPP vaccines contracted by UNICEF SD by year broken down by company. We have provided this in a narrative format.

9.4 AMC objective 3: Vaccine uptake

To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after the AMC finance are used up.

Indicator 8: Cumulative number of countries that have applied for GAVI support for PCV

a) Justification

This gives an indication of country interest in introducing PCV. It is theorised that the AMC will lead to accelerated country demand due to the long term commitment to financing pneumococcal vaccine and the certainty on price.

This indicator quantifies the number of countries in different application status of support for PCV introduction: approval, conditional approval, request for clarifications and need for resubmission.

Apart from the number of countries in each submission phase, it is proposed to look at the number of children in those countries. There are great disparities in the total population and the percentage of children in GAVI-eligible countries. Therefore the number of countries in each submission phase will not necessarily correlate with the number of children affected. Since the target of the PCV is children, it is important to quantify the number of children and not only the number of countries.

b) Data sources

There are two main data sources for countries' demand indicators: GAVI, for the number of countries in each phase of application for support, and the UN statisticall division for the number of children in GAVI-eligible countries:

- GAVI-eligible countries submitting proposals for PCV introduction support: GAVI provides this information. GAVI issues quarterly one page reports. These reports reflect the approval activity during the quarter. Therefore, all reports have to be

taken into account, not the most recent ones, which would not reflect the demand / approval status of all countries over time.

- The number of children from GAVI-eligible countries is the cohort of targeted children in each country. These figures can be obtained from the UN (UNDATA). The UN Statistics Division provides data on the number of under-5s, by country and in five years periods. This is the most reliable and standard source of childhood population data given that this data is used as a denominator to compare countries.

c) Data analyses

To estimate indicators related to countries' demand, data from three sources has to be merged:

1. names of GAVI-eligible countries;
2. countries' demand for GAVI's support, by year;
3. UN population figures for children

To merge this data, some manual edition of countries names has to be performed, in order to ensure that all data points correspond to the same country-year dyad.

Countries are classified according to the status of their demands for support, as defined by GAVI:

- Approval
- Conditional approval
- Clarifications
- Resubmission

d) Data Presentation

Data is presented in a column chart, with one column per year and each column divided according to the number of countries at each submission stage; similarly, in a second chart with the number of children living in those countries in different submission stages. This will allow the observation of trends over years of each submission status and in the global number of applications. It would be expected that the AMC will produce changes in the rate of submission or approval of applications that could be translated into changes in those trends. A chart showing the cumulative number of countries at different stages of submission has also been included.

Indicator 9: Cumulative number of GAVI-eligible countries introducing TPP vaccines

a) Justification

Countries plan the introduction of PCV vaccine in advance. This has to be synchronised with the application process (previous indicator) and the actual shipment of vaccine (next indicator).

It is expected that AMC will lead to accelerated country demand due to the long term commitment to financing PCV and the certainty about the vaccine's maximum price.

Therefore, an indicator measuring the degree of countries' demand for GAVI's support would capture the effects of AMC on the events and processes that take place prior to the actual deployment of vaccines within countries, which are mostly dependent on vaccination programmes performance (immunisation systems).

Annual plans for the introduction of PCV by countries will provide an early overview of effects of the AMC strategy on countries' vaccination strategies and policies. Comparing the introduction plans year by year will allow the identification of postponements or premature introductions of PCV by countries. Furthermore, taking into account the calendars of introduction of other vaccines will allow consideration af how far the introduction of other vaccines may affect PCV introduction positively or negatively.

b) Data sources

The data to provide an overview of countries introducing PCV were obtained from WHO. This source also provides data related to the introduction of other vaccines, which are essential for determining the system requirements in the mid- and long-term; overall when considering the investments in cold chain infrastructure and equipment (see Section 11.4).

c) Data analyses

Data on the year of introduction of new vaccines do not require any special analysis.

d) Data Presentation

Data on the year of introduction of PCV, pentavalent and rotavirus have been plotted into a chart showing the time line in years, all GAVI-eligible countries and a data point for each vaccine introduction (see Figure 33). This chart shows how many countries introduce which vaccines in a given year; and which vaccines are introduced in each country each year. These data are used for the calculation of the cold chain requirements as well. The effects of the introduction of other vaccines on the introduction of PCV are beyond the scope of the AMC evaluation. However, to ease the presentation and interpretation of data, the calendars for the introduction of new vaccines have been unified into a single chart. See the calendar of introduction in the Findings section.

Indicator 10: Cumulative number of doses of TPP vaccine shipped to GAVI-eligible countries

a) Justification

This indicator enables the assessment of the AMC's effect on vaccine supply independent of the capacity of countries to distribute and administer PCV to the target population.

The immunisation system comprises the infrastructure and processes to acquire, distribute and administer vaccines to the target population. In the whole process of making vaccines available to the target population, from vaccine development up to vaccine administration to the population, the shipment of vaccines is the last step

before vaccines enter the national health systems of GAVI-eligible countries. Once vaccines arrive in a country, it is the country system which will guarantee that they are stored, managed, transported and administered to the target population. This latter phase is beyond the immediate effects that AMC can have in making PCV available.

b) Data sources

Data on the shipment of vaccines can be retrieved from the UNICEF site (UNICEFc) where data is available for West Africa, Central Africa, Eastern and Southern Africa, Eastern Mediterranean and Europe, and Southeast Asia and Western Pacific. This data is also sent to GAVI periodically. It has also been reported by UNICEF that GAVI has access to this data in MS Excel format.

c) Data analyses

Data on vaccine shipments is published in 'pdf' format and needs to be transformed into data management software for analysis. Shipments are presented in terms of doses and GAVI approval event; therefore, to obtain annual estimates by countries, shipments for each vaccine, shipments and submission status have to be combined.
Data presented here correspond to the most recent aggregated annual figures (2008) for DTP. It is anticipated that PCV will be available as it is progressively introduced in GAVI-eligible countries.

d) Data Presentation

Data on shipments is presented in a bar chart for DTP3 as an illustration. GAVI-eligible countries are sorted by the number of doses shipped.

Indicator 11: PCV3 coverage in GAVI-eligible countries

a) Justification

Coverage is the key indicator to determine what proportion of the target population ultimately receives the recommended number of doses of PCV.

Although AMC objectives are not directly related to increasing vaccination coverage, achieving the overall goal of the AMC is strongly dependent on vaccination coverage. Morbidity and/or mortality due to a vaccine-preventable disease cannot be reduced unless a certain level of vaccine coverage is attained. Secondly, this indicator is related to the countries' uptake of vaccine and will have an explanatory value to relate the levels and rates of vaccine uptake by countries with the observed changes in morbidity and/or mortality.

Furthermore, the key indicator to measure the performance of immunisation programmes is vaccine coverage. High vaccine coverage is the result of well functioning processes: from vaccine acquisition, delivery and transportation, up to the ensuring of access of the target population to vaccines. Coverage is the end point of the chain of events eventually leading to a measurable impact in terms of burden of disease.

Point estimates of national coverage figures (e.g. coverage at year x) are useful to assess whether a given country has reached a certain level or not. However, for a continuous monitoring of coverage, the time dimension is equally important because high levels of coverage cannot be reached instantly as soon as the vaccine is available in countries. Many factors will influence the attainment of high levels of coverage even when vaccines are available, which have to do with the preparedness of the system and its capacity to reach the target population, including those groups with poor social or geographical access. Measuring the number of years to attain certain levels of coverage will allow an early detection of delays and prompt action to address them.

b) Data sources

The data sources for PCV coverage will be captured by the WHO/UNICEF Data Estimates in the future. At present countries can already record the immunisation schedule including PCV in the Joint Reporting Form (JRF).

For this baseline, data on DTP3 and Hib coverage will be used; first, to show how future data on PCV coverage can be analysed; and second, to have a comparator of the range of changes in coverage that have occurred in the last 20 years. DTP3 coverage data is available through WHO in the WHO/UNICEF JRF. The JRF also provides information on the number of districts in each country which report certain levels of coverage.

c) Data analyses

In the absence of PCV data, we have used DTP3 as an illustration and reference. Data on coverage from WHO (JRF) is readily available in percentages and disaggregated by country; so no further analyses are required.

d) Data Presentation

Two sets of charts are presented: a bar chart, with one bar per country, showing a point estimate for a given year and column chart showing the cumulative number of countries reaching certain levels of vaccination coverage.

Indicator 12: Time to national peak coverage

a) Justification

Important indicator to assess the extent to which TPP vaccine is scaled up rapidly to reach the target population.

Point estimates of national coverage figures (e.g. coverage at year x) are useful to assess whether a given country has reached a certain level or not. However, for a continuous monitoring of coverage, the time dimension is equally important because high levels of coverage cannot be reached instantly as soon as the vaccine is available in countries. Many factors will influence the attainment of high levels of coverage even when vaccines are available, which have to do with the preparedness of the system and its capacity to reach the target population, including those groups with poor social

or geographical access. Measuring the number of years to attain certain levels of coverage will allow an early detection of delays and prompt action to address them.

b) Data sources

The data sources for PCV coverage will be captured by the WHO/UNICEF Data Estimates in the future. At present countries can already enter the immunisation schedule including PCV in the Joint Reporting Form (JRF).

For this baseline, data on DTP3 and Hib coverage will be used; first, to show how future data on PCV coverage can be analysed; and second, to have a comparator of the range of changes in coverage that have occurred in the last 20 years. DTP3 coverage data is available through WHO in the WHO/UNICEF JRF. The JRF also provides information on the number of districts in each country which report certain levels of coverage.

c) Data analyses

In the absence of PCV data, we have used DTP3 as an illustration and reference. Data on coverage from WHO (JRF) are readily available in percentages and disaggregated by country; so no further analyses are required.

d) Data Presentation

Two sets of charts are presented: a bar chart, with one bar per country, showing a point estimate for a given year, and a column chart showing the cumulative number of countries reaching certain levels of vaccination coverage.

PART III – BASELINE FINDINGS

This part of the report reviews the findings of the baseline study. It therefore discusses in more detail the model results and the findings of the baseline surveys.

10 Findings: counterfactual model

10.1 Base case analysis

10.1.1 Counterfactual 1

Figure 17 represents the demand-supply results of the model for Counterfactual 1 given the assumptions we made and data employed. It illustrates the discrepancies between demand and supply with successive entries into the market by multinational-1, multinational-2 and the emerging-market supplier. Figure 17 captures the following sequence of events. We have multinational-1 supplying a 10-valent PCV in 2008 using existing production plant capacity; in 2012, multinational-2 starts producing with its pre-build-out capacity production; in 2020, the emerging-market supplier arrives and starts producing directly with new plant as it does not benefit from a pre-build-out production capacity. These production/supply decisions are clearly represented on the graph by the different coloured bars: blue for multinational-1, yellow for multinational-2 and green for the emerging-market supplier.

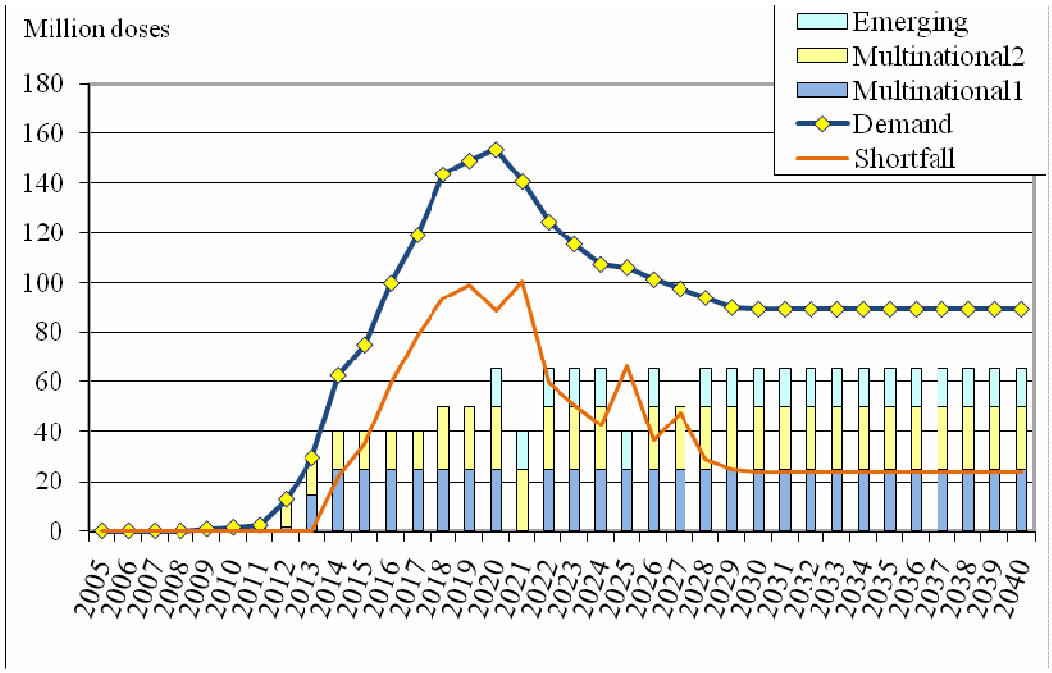
The variable labelled 'shortfall' represents the discrepancy between the demand and the supply. This 'shortfall' trend fluctuates according to the variation in demand and supply; in particular, it responds to market entry by the different vaccine manufacturers. Overall, we observe that demand never matches supply consistently. We also observe from Figure 17 that whenever demand matches supply, the shortfall is null. Conversely, the shortfall rises whenever demand exceeds supply. This is particularly evident whenever a plant shuts down and follows from our assumption that each new plant dedicated for supply to low-income countries shuts down once for one year 8 years after production starts. Indeed, the total supply drops at three different dates corresponding to whenever the new dedicated plant built by multinational-1, multinational-2 or the emerging-market supplier shuts down (in years 2021, 2025 and 2027).

Note that, in 2005, multinational-1 could possibly supply enough, using its existing production plants (built to meet high-income countries' demands) but does not, as demand expressed at that time is null. In 2009, multinational-1 uses its pre-build-out production capacity to produce 0.8 million doses for the aggregate market of GAVI-eligible low income countries. (Note that this is not easily visible in Figure 17) Within this short-run period, the market is characterised by one supplier (multinational-1) and

demand matches supply. In 2012, multinational-2 enters the pre-build-out period and starts producing 11 million doses for low-income countries with its production capacity dedicated to high-income countries.

Although this implies a preference for the 13-valent vaccine technology produced by multinational-2 relative to the 10-valent one produced by multinational-1, this preference is determined by supply available in any given period and thus changes over time. Note that the aggregate supply stemming from both multinational-1 and multinational-2 in 2012 is nearly matching the demand, the shortfall drops and it is close to zero until 2013. This, however, is a fortuitous outcome as demand at the time is yet to peak – since some GAVI-eligible countries are 'late adopters' either because introducing PCVs was not on their health priority list or because they are yet to get funding approval from the GAVI Board or because of bureaucratic delays in getting funding approval.

Figure 17: Demand and supply results for Counterfactual 1



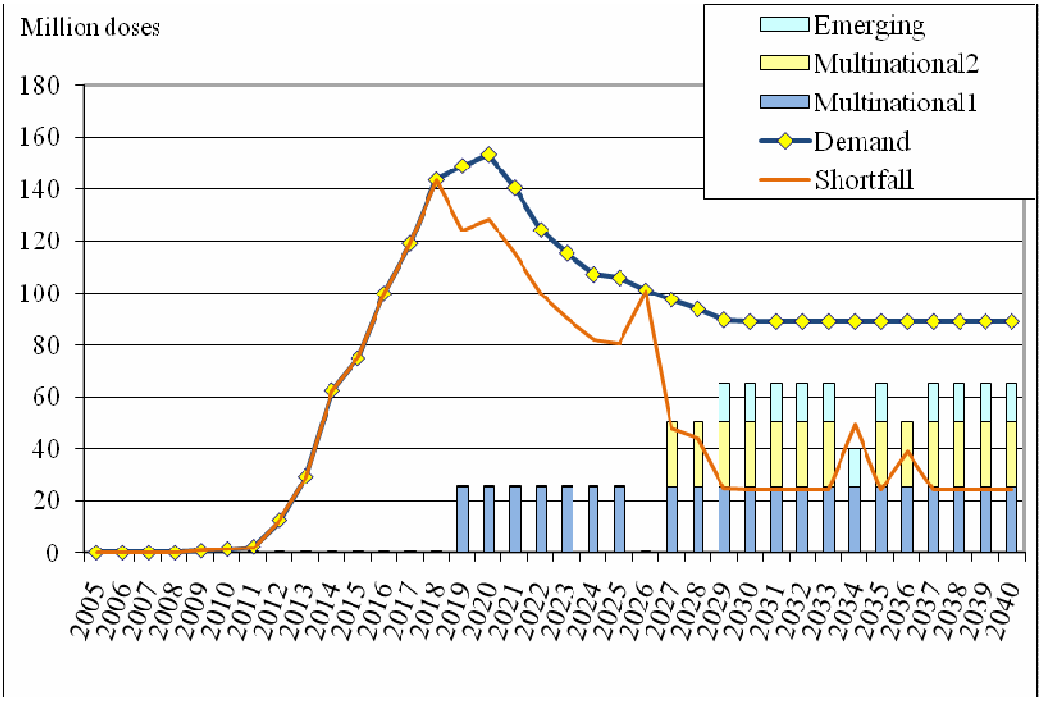
In 2014, multinational-1 starts supplying its product with the new dedicated plant and at that time supply does not match demand. In 2018, multinational-2 starts production with its new dedicated plant and supplies 25 million doses. This is illustrated by a higher aggregate supply as the short-run is characterised by two-supplier equilibrium. Note that even with entry by multinational-2, the shortfall curve still rises; this, however, has nothing to do with supply but simply reflects an increase in demand for the pneumococcal vaccines. In 2020, the emerging-market supplier enters the market and this leads to an increase in aggregated supply and a concomitant decline in the 'shortfall'. After 2028, the demand and supply trends remain constant and as a consequence the 'shortfall' curve is unvarying at 65 million doses.

10.1.2 Counterfactual 2

Figure 18 represents the demand-supply results of the Counterfactual 2 modeling. The supply and the shortfall trends vary according to successive entries into the market of multinational-1, multinational-2 and the emerging-market supplier. Given that the UNICEF procurement arrangement is assumed not to be operative, there is initially no supply as the pre-build-out period for multinational-1 starts in 2010. After this date, the shortfall equals demand until multinational-1 enters the market with the new plant in 2019. This is because at $10.00 per dose, demand is nearly zero given our assumed demand function. In 2019, multinational-1 starts producing using the new dedicated plant capacity supplying 25 million doses and the shortfall generally falls albeit in 2020 there is a temporal increase because demand is still increasing.

The shortfall curve then moves continuously away from the demand curve with occasional increases in shortfall whenever the new plants of multinational-1, multinational-2 or the emerging-market supplier shut down. The new dedicated plant built by multinational-1, multinational-2 and the emerging-market supplier respectively shut down in years 2026, 2034 and 2036. Again, these different periods are clearly visible on the graph and are represented by a sharp 'shortfall' increase.

Figure 18: Demand and supply results for Counterfactual 2



In 2026, multinational-1's plant suffers a shutdown and aggregate vaccine supply drops sharply with the shortfall curve rising to match demand. This is because multinational-2 is still in a pre-build-out period, the UNICEF procurement arrangement is temporarily out of operation (vaccine suppliers with new dedicated plant capacity enter the market much later) and because vaccines prices charged during the pre-build-out period are 'higher' with an associated lower demand. One year later, in 2027,

multinational-2 starts producing and the shortfall declines, in 2029. At the same time, the emerging-market supplier enters the market. In 2034, multinational-2's plant shuts down; aggregate supply decreases as the shortfall curve rises only to fall by a disproportionate amount one year later (since the market by then is characterised by three suppliers). In 2036, the emerging-market supplier's production plant shuts down and the shortfall increases. After 2036, the demand and supply movements remain constant and the shortfall trend remains stable until the end of the model's time frame.

10.1.3 Health impacts

Given the supply and demand patterns observed, we estimated the health impacts by calculating the cumulative number of DALYs averted. As discussed, this exercise is based on a very simplified assumption that for each dose of vaccine supplied a number of DALYs will be averted. In other words, we are assuming rather simplistically that we have a linear dose response (treatment-effect) curve and the efficacies of the vaccines supplied (10-valent technology for multinational-1, 13-valent technology for multinational-2 and 10-valent technology for emerging-market supplier), are at least equal to the 7-valent pneumococcal conjugate vaccine produced by Wyeth (now Pfizer). We had to make these assumptions since the literature we identified only provided clinical and cost effectiveness data for the 7-valent PCV.

We estimated the cumulative number of DALYs averted in Counterfactual 1 as **365.05** million, and the number of DALYs averted annually over the model's time horizon is **10.43** million. We estimated the cumulative number of DALYs averted for Counterfactual 2 as **231.16** million, and the number of DALYs averted annually over the model's time horizon is **6.6** million.

As an alternative measurement of health impact, we estimated the cumulative number of deaths in the worlds described by Counterfactual 1 and Counterfactual 2. As discussed, this exercise is based on the assumption that for every 1000 children, 7.4 deaths will be averted (source: GAVI). In this case, we need not assume a linear dose response (treatment-effect) curve and but we have to assume that the efficacies of the vaccines supplied (10-valent technology for multinational-1, 13-valent technology for multinational-2 and 10-valent technology for emerging-market supplier) are at least equal to that of the 7-valent pneumococcal conjugate vaccine.

We estimated the cumulative number of deaths averted in Counterfactual 1 as **3.57** million, and the number of deaths averted annually over the model's time horizon is **0.10** million. We estimated the cumulative number of deaths averted for Counterfactual 2 as **2.26** million, and the number of deaths averted annually over the model's time horizon is **0.06** million[23].

[23] Given that the DALYs is a composite measure of years of life lost to mortality and years of life lived with disability, there is some inconsistency between the estimated cumulative numbers of deaths and DALYs averted as a result of taking data from different/unrelated sources.

10.1.4 Confirming market entry

In Counterfactuals 1 and 2, an implicit assumption is made that the vaccine manufacturers (multinational-1, multinational-2 and the emerging-market supplier) will enter the market. However, it is important to test this assumption given the other assumptions we have made in these models, and given the data available to us. That is, we need to ensure 'internal consistency' of the model.

To do this, we estimated the net present value (NPV) of investing in production capacity to supply our aggregate market of GAVI-eligible countries. We employ NPV as a measure of the economic feasibility of investing in a new project: an indicator of market entry by the different vaccine suppliers. Theoretically, vaccine producers will enter the market when the NPV is positive and greater than the NPV of the next feasible investment. The estimated NPV thus does not only have to be greater than zero. However, for our purposes and for simplicity, we assume that market entry will be observed if the computed NPV for the different vaccine manufacturers in our models is positive and greater than zero.

We carried out NPV calculations with respect to the pre-build-out period and the time frame within which a new production plant dedicated solely to supply for low-income countries is in operation.

Table 8 shows the estimated NPV under the assumptions made in the model for Counterfactual 1. So based on the values of the model inputs defined in the base case, all vaccine suppliers will probably consider it worthwhile and profitable to enter the market during and after the pre-build-out period. We say probably because even if the NPV is positive, shareholders of the respective vaccine suppliers may choose to pursue production and supply of another vaccine (in another clinical category) that offers a higher return on investment.

Table 8: NPV results for Counterfactual 1

		Multinational 1	Multinational 2	Emerging
Pre Build-out	**NPV of profits**	33	107	n/a
New Plant	**NPV of operating profits**	266.99	93.64	44.58
	NPV of capital costs	59.45	53.40	31.79
	NPV of profits net of capital costs	**207.53**	**40.23**	**12.80**

Table 9: below shows the estimated NPV under the assumptions made in the model for Counterfactual 2. This means that within the pre-build-out period multinational-1 will find it attractive to supply using existing plant capacity. For multinational-2, the estimated NPV is negative but not far from breaking even. This most likely reflects the differences in cost in producing and supplying a 13-valent technology compared to a 10-valent version. However, this might not affect the decision to supply using existing plant capacity, since multinational-2 makes profit from investing in a new plant, and this potentially means it makes a positive overall profit over the model's time horizon. In sum, our assumptions about market entry in Counterfactual 1 and Counterfactual 2 are appropriate.

Table 9: NPV results for Counterfactual 2

		Multinational 1	Multinational 2	Emerging
Pre Build-out	**NPV of profits**	0.59	-0.26	n/a
New Plant	**NPV of operating profits**	151	30	13
	NPV of capital costs	35	21	12
	NPV of profits net of capital costs	**115.59**	**9.31**	**0.94**

10.2 Sensitivity analysis

10.2.1 Counterfactual 1

Below in Table 10 are the results of the selective sensitivity analysis we conducted for Counterfactual 1; the selected parameters tested are as previously described. The parameters varying in this analysis are the firm prices (during and after the pre-build-out period) and the demand realisation percentage. We used the following firm prices: $4.20, $5.90, $6.20, $6.60 and $8.00. We chose these price levels to illustrate the following cases: where the NPV is negative for all suppliers, where the NPV is positive for multinational-1 only, where the NPV is positive for multinational-1 and multinational-2 only and finally, where the NPV is positive for all suppliers. Our sensitivity analysis suggests that with a 50% forecasted demand realisation and a firm price of $4.20, the NPV result is negative for all vaccine suppliers. In other words, at the price of $4.20 and 50% of demand realised, we have the undesirable case of zero supply. However, given the limitations highlighted previously, the results presented are mainly illustrative.

Note that there is no difference between the NPV estimates for a 100% demand realisation and a 75% demand realisation. This, we believe, is a result of instances where the demand for the PCVs exceeds the (total) maximum production plant capacity available. For that reason, moving from 100% to 75% demand realisation

does not add to or take away from the profitability of the investment made. At 50% demand realisation we have more instances where demand is less than the (total) maximum capacity available. (This can be verified by checking the accompanying Excel spreadsheets.)

Whilst the base case NPV analysis confirms our assumptions about market entry, the sensitivity analysis conducted tells us to pay attention to market environment if vaccine supply to low-income countries is to be assured. Even then the base case results hold only under the assumptions and the values of the parameters employed. These can easily change with changes in the underlying assumptions or values of the parameters used in the model. By selecting particular values, one can easily translate our model into a one- or two-supplier equilibrium. Our results are, however, consistent with historical evidence and with the general notion that the number of vaccines at any point will be determined by the market environment.

We know for example that the meningitis vaccine market was characterised by a three-supplier equilibrium (two WHO pre-qualified multinational producers and one WHO pre-qualified emerging-market supplier) in 2005, and this three-supplier equilibrium persisted until 2005. On the other hand, the hepatitis B vaccine market, in 2005, was characterised by a six-supplier equilibrium (one WHO pre-qualified multinational producer and five emerging-market suppliers). By 2010, the market was characterised by nine suppliers; one multinational producer as before and eight emerging-market suppliers. (Note that this includes suppliers of Hepatitis-B-containing polyvalent vaccines.)

In contrast, the market for Hib vaccines was characterised in 2005 by four suppliers, all of whom were multinational firms. In 2010, the market for Hib vaccines was characterised by eight suppliers with the entrance of four emerging-market suppliers in addition to the incumbent multinational firms. (Note here also that this includes suppliers of Hib-containing polyvalent vaccines.)[24]

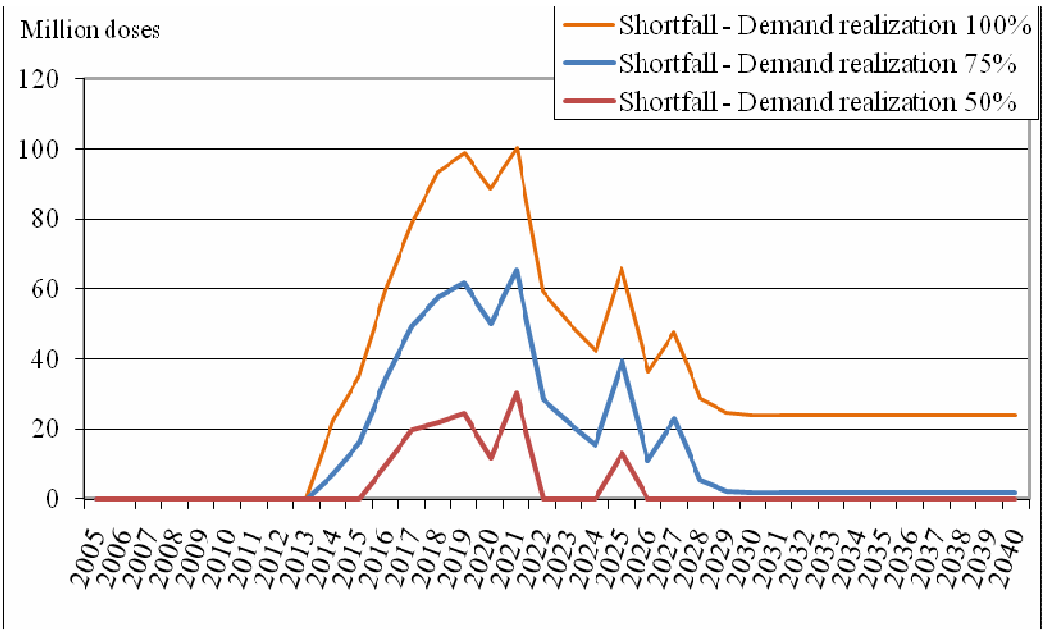
[24] Note that the data we received challenge our expectations that vaccine markets tend to be characterised by one-, two- or few-supplier equilibria. We find it unusual that in some cases there are eight/nine vaccine suppliers albeit these numbers refer to total number of producers supplying monovalent/single *and* polyvalent/combination products.

Table 10: Counterfactual 1 sensitivity analysis results

		100% forecasted demand realisation					75% forecasted demand realisation					50% forecasted demand realisation				
		Firm prices					Firm prices					Firm prices				
		$4.20	$5.90	$6.20	$6.60	$8.00	$4.20	$5.90	$6.20	$6.60	$8.00	$4.20	$5.90	$6.20	$6.60	$8.00
Pre Build-out	NPV of profits															
	Multinational 1	10.07	26.39	29.27	33.11	46.55	5.91	15.38	17.05	19.28	27.08	2.20	5.59	6.19	6.98	9.78
	Multinational 2	30.18	84.36	93.92	106.67	151.30	28.81	80.80	89.97	102.20	145.01	26.99	76.01	84.66	96.20	136.57
	Emerging	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
New Plant	NPV of profits net capital costs															
	Multinational 1	-3.71	145.92	172.33	207.53	330.76	-3.71	145.92	172.33	207.53	330.76	-61.70	56.33	77.16	104.94	202.14
	Multinational 2	-94.10	1.05	17.84	40.23	118.59	-94.10	1.05	17.84	40.23	118.59	-99.35	-10.24	5.49	26.46	99.85
	Emerging	-51.02	-5.82	2.16	12.80	50.02	-51.02	-5.82	2.16	12.80	50.02	-53.43	-9.51	-1.76	8.58	44.75

Figure 19 below depicts results of analyses that show the differences in 'shortfall' depending on how much of the forecasted demand is realised. There are two things to note here. First, a 'perceived' shortage in vaccine supply depends very much on the accuracy of the forecasted demand for pneumococcal vaccines. Given current aggregate supply, policy makers will be less worried if actual demand for pneumococcal vaccines is only 50% of what is forecasted. Secondly, vaccine suppliers will be faced with 'demand risks' if forecasted demand exceeds what is realised. In such situations, one needs to readjust the NPV estimates presented above to reflect these demand risks: it is possible that though our simulations in the base case confirm market entry, one may not observe entry at all.

Figure 19: Shortfall sensitivity analysis results for Counterfactual 1



10.2.2 Counterfactual 2

Table 11 shows the results of the sensitivity analysis conducted for Counterfactual 2. As before, the parameters varied in this analysis are the firm prices (during and after the pre-build-out period) and the demand realisation percentage. Contrary to Counterfactual 1 in which the price during the pre-build-out period equal the price accepted for supply with the new dedicated plant, prices in Counterfactual 2 are different during and after the pre-build-out period. This is captured in Table 11 that integrates the different prices envisaged.

We used the following possible vaccine prices in public sectors of GAVI-eligible countries, presented in PneumoADIP/Applied Strategies (2009), for the pre-build-out period: $5 (low income countries), $10 (middle income countries) and $50 (high income countries). Concerning the firm prices for the new plant we used the same set as those for Counterfactual 1: $4.20, $5.90, $.40, $6.60 and $8.00.

Table 11: Counterfactual 2 sensitivity analysis results

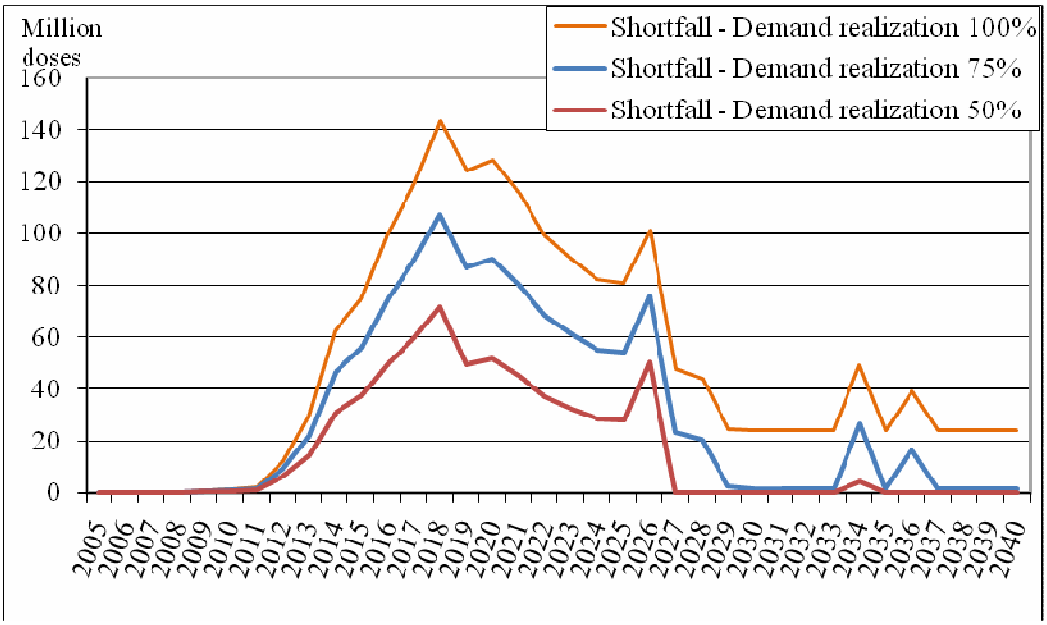
	100% forecasted demand realisation					75% forecasted demand realisation					50% forecasted demand realisation				
Pre Build-out	Firm prices					Firm prices					Firm prices				
		$5.00	$10.00	$50.00			$5.00	$10.00	$50.00			$5.00	$10.00	$50.00	
NPV of profits															
Multinational 1		-4.01	0.59	0.03			-4.01	0.59	0.03			-4.00	0.59	0.03	
Multinational 2		-5.64	-0.26	0.01			-5.64	-0.26	0.01			-5.64	-0.26	0.01	
Emerging		n/a	n/a	n/a			n/a	n/a	n/a			n/a	n/a	n/a	
New Plant	Firm prices					Firm prices					Firm prices				
	$4.20	$5.90	$6.40	$6.60	$8.00	$4.20	$5.90	$6.40	$6.60	$8.00	$4.20	$5.90	$6.40	$6.60	$8.00
NPV of profits net capital costs															
Multinational 1	-4.02	80.71	105.63	115.59	185.37	-4.02	80.71	105.63	115.59	185.37	-24.91	48.44	70.02	78.65	139.05
Multinational 2	-34.59	-3.50	5.65	9.31	34.92	-34.59	-3.50	5.65	9.31	34.92	-39.45	-13.93	-6.42	-3.42	17.59
Emerging	-18.84	-4.83	-0.71	0.94	12.48	-18.84	-4.83	-0.71	0.94	12.48	-21.64	-9.12	-5.44	-3.97	6.34

From Table 11 above, it is clear that depending on the market environment in terms of vaccines prices offered and what proportion of demand is realised, the number of vaccine suppliers will change accordingly. This in turn will have a significant bearing on how one can ensure that supply matches demand and/or hedge against vaccine supply interruptions, by having alternative sources of vaccine supply.

As with the results for Counterfactual 1, there is no difference between the NPV estimates for a 100% demand realisation and a 75% demand realisation. This is a result of instances where the demand for the PCVs exceeds the (total) maximum production plant capacity available. For that reason, moving from 100% to 75% demand realisation does not add to or take away from the profitability of the investment made. At 50% demand realisation we have however more instances where demand is less than the (total) maximum capacity available – and the NPV estimates change accordingly.

Figure 20 below illustrates the shortfall trends according to the different demand realisation percentages (100%, 75% and 50%) entered in the model. The trends are exactly the same but at different levels. The higher the demand realisation percentage is, the higher is the trend in the graph. Note that this effect of demand takes into consideration 'demand expressed by India' which is determined by the demand realisation percentage in our Excel spreadsheets. One can easily carry out further sensitivity analysis, by varying demand expressed by India (in the accompanying Excel spreadsheets).

Figure 20: Shortfall sensitivity analysis results for Counterfactual 2



As before, a 'perceived' shortage in vaccine supply depends very much on the accuracy of the forecasted demand for pneumococcal vaccines. One will be less worried about vaccine supply shortages if actual demand for pneumococcal is only

50% of what is forecasted. But vaccine suppliers will be faced with 'demand risks' if forecasted demand exceeds what is realised. In such situations, one needs to readjust the NPV estimates presented above to reflect these risks: it is possible that, though our simulated exercise suggests market entry, one may not observe entry at all if the risk-adjusted NPV estimate is zero or less. This applies particularly to building new production plants dedicated for supply to low-income countries.

We deduce from the analyses carried out that, even within the simplified worlds we have modelled, the supply of beneficial vaccines (and rate of diffusion of expected health benefits) will be determined by a number of interacting issues and factors. The set of interacting factors we have considered, however, does not include events that happen at the health system level. We also did not consider any potential effects on R&D investments decisions – either in new vaccine products or in line extensions of existing vaccine products or in the development of 'biosimilars' as is often the case for emerging-market suppliers.

It is clear that outcomes in Counterfactual 1 are better than those in Counterfactual 2 in that supply matches demand more closely over different time periods. This situation, however, can be improved via policy interventions that incentivise vaccine suppliers to scale up their production capacity. As an illustrative example, if multinational-1 and multinational-2 were to invest in new production plant capacity of 40 million doses, the shortfall observed would be much lower as supply fits demand more closely. This is depicted in Figure 21 and Figure 22 below.

Figure 21: Demand and supply in Counterfactual 1 with higher plant capacity

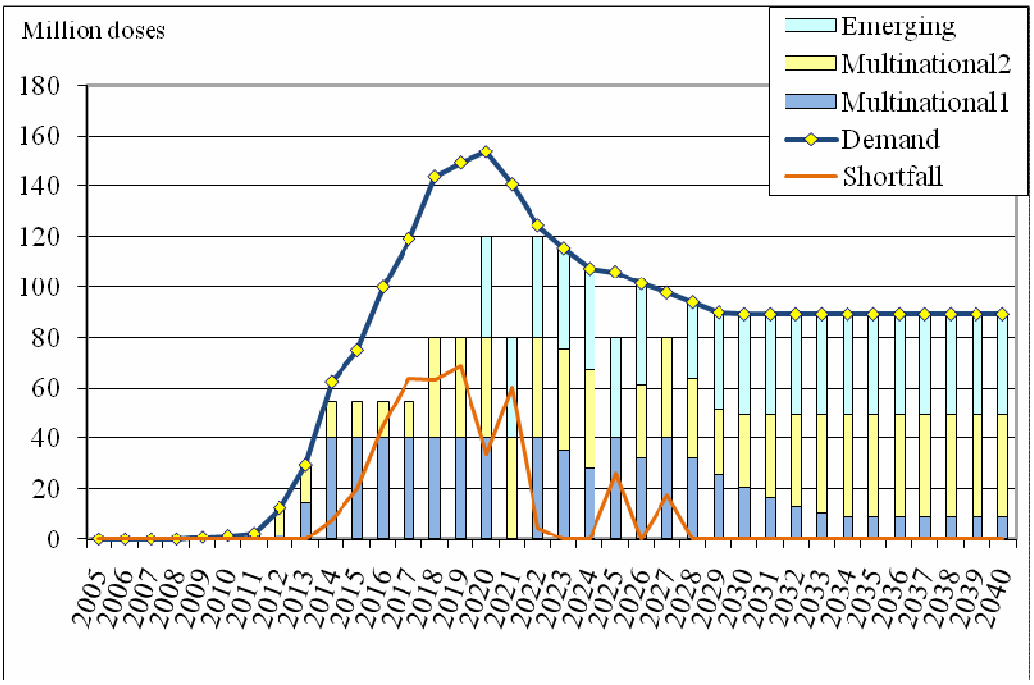
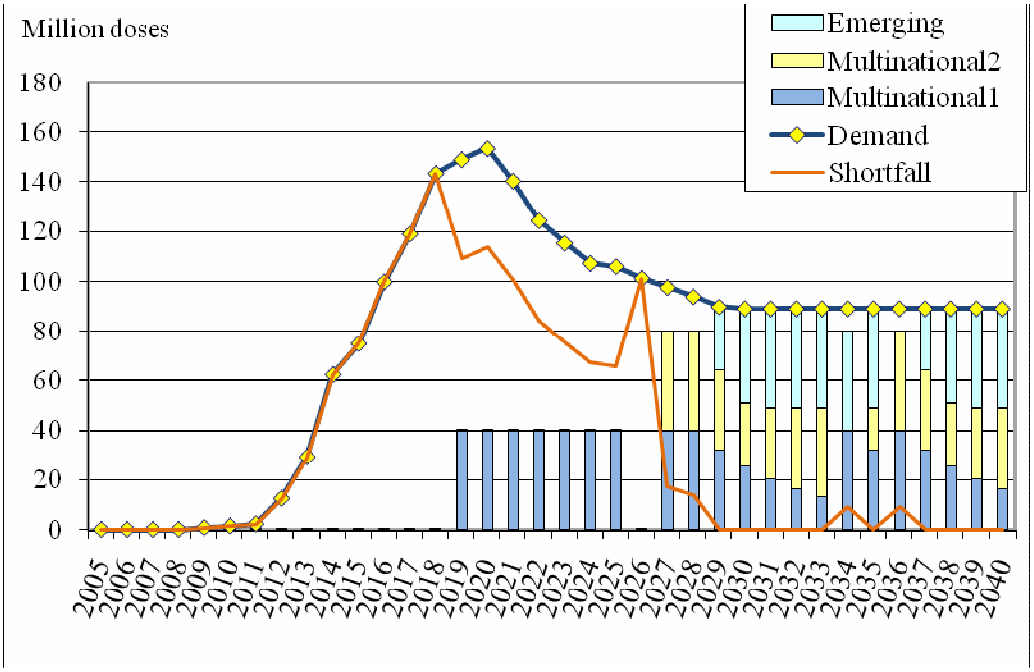


Figure 22: Demand and supply in Counterfactual 2 with higher plant capacity



Our analysis indicates that getting the 'price' right is important. We note from our sensitivity analysis that the single lowest price that offers a positive investment return for all vaccine suppliers is $6.60 per dose irrespective of what proportion of forecasted demand is realised. It is also the minimum price that would support a vaccine market with alternative sources of supply as an insurance protection against plant failures. We can call this a 'sustainable' price if it can be afforded given resources available whilst maintaining the structure, conduct and performance of the vaccine market in ways that ensure access and security of supply. If the price is too low, as a result of aggressive bargaining for instance, we may not have a market that supplies the desired quantities of vaccines to match demand.

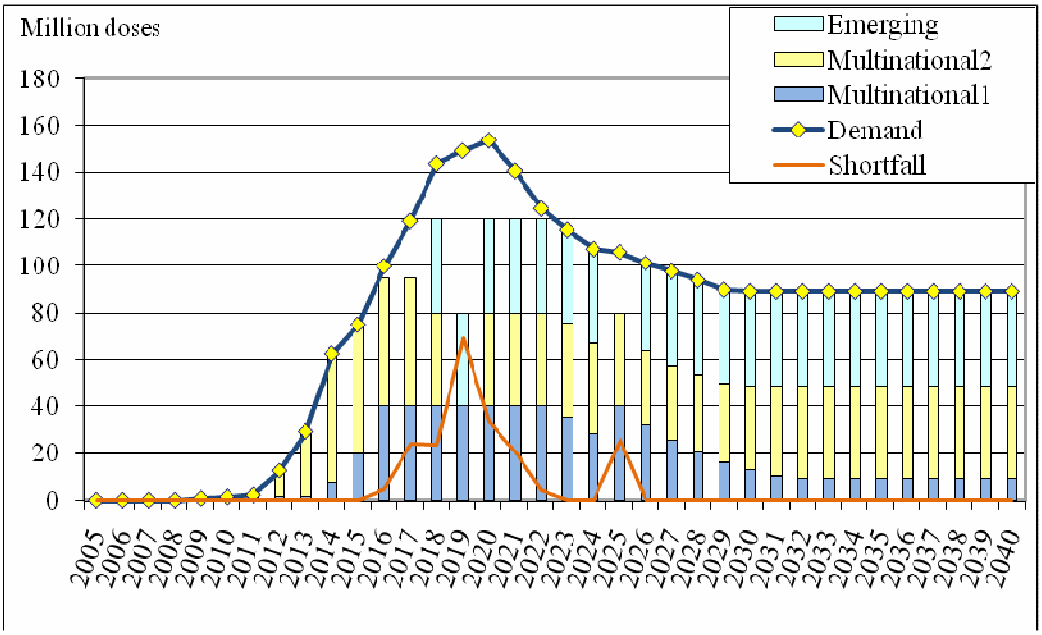
Note, however, that even if $6.60 per dose is the 'right' price we still have to deal with the fact that faced with diverse sources of financial risk, including that arising from inaccuracies in forecasted demand, vaccine suppliers may be reluctant to invest in dedicated production plants as we have assumed in our counterfactual models. The required 'hurdle', i.e. the expected return that will satisfy a risk-adjusted NPV, will be higher and for that matter the sustainable price would be higher. A potential offsetting factor to having a 'high' sustainable price might come from the fact that the demand expressed in Counterfactual 1 and Counterfactual 2 is less than what a properly informed demand might be. However, such an informed demand will not be part of the world without an AMC intervention.

Notwithstanding, $6.60 per dose is the 'right' price as long as the assumptions underlying our counterfactuals models and the supporting data are 'right'. Needless to say our analysis is illustrative and can easily be adapted once more appropriate data, especially data on vaccine production and supply costs, are available. It is worth

mentioning that a necessarily higher 'sustainable' price can be implemented indirectly via push funding supports to multinational and emerging-market suppliers to defray the costs of plant investments.

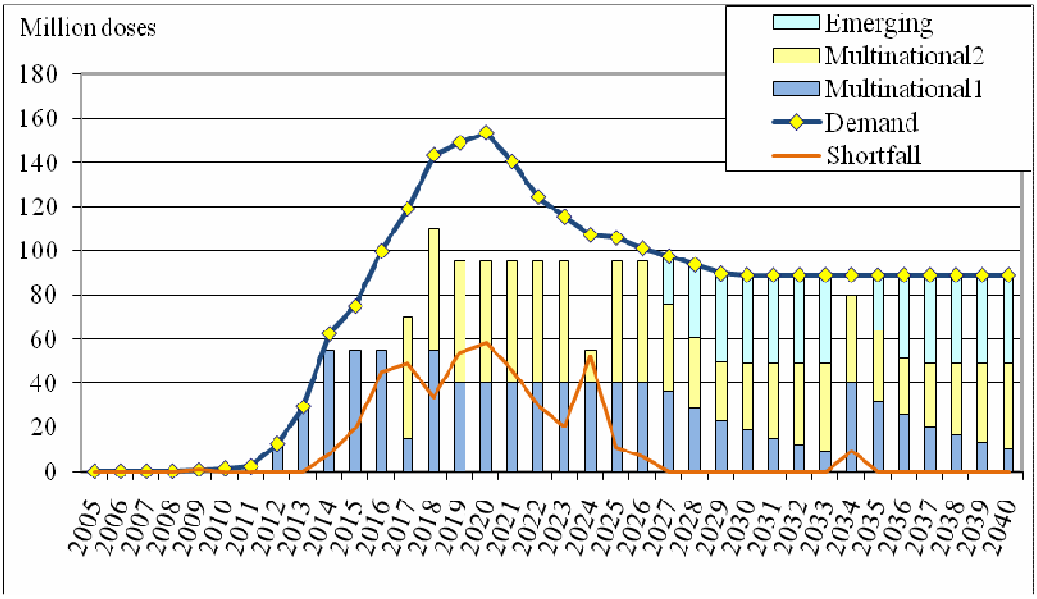
We note the critical role of the UNICEF procurement arrangement in ensuring vaccine supply to low-income countries – as shown by the differences in results between Counterfactual 1 and Counterfactual 2. Results for Counterfactual 1 are always better than those for Counterfactual 2. However, even if the UNICEF procurement arrangement is up and running all the time, this will not necessarily accelerate diffusion of clinically beneficial vaccines to low-income countries once they become available elsewhere. If the vaccine suppliers in our models could be incentivised to build dedicated production plants much earlier this would accelerate diffusion of the vaccines as well as lowering any shortfall between demand and supply. This is illustrated in Figure 23 and Figure 24[25].

Figure 23: Demand-and supply in Counterfactual 1 with earlier building of a new dedicated plant (capacity of 40 million doses)



[25] This analysis can be easily replicated in the accompanying Excel spreadsheets by (1) setting the active pre-build-out period to NO (2) increasing the capacity of the new plant for multinational-1, multinational-2 and the emerging-market supplier to 40 million doses, and (3) equating the start dates for the new plants to the beginning of the pre-build-out period.

Figure 24: Demand and supply in Counterfactual 2 with earlier building of a new dedicated plant (capacity of 40 million doses)



Note that we conducted a number of sensitivity analyses to gather some idea of which model parameters are most 'relevant' to the outputs observed and hence of greater policy significance. From this initial set of sensitivity analyses, we focused our attention on the model parameters that we judged to have significant effects on the models' outputs. For example, for Counterfactual 2, we found that varying the length of time during which the UNICEF procurement arrangement is not operative had no significant effects on the model results. We therefore did not consider this parameter any further.

10.3 Conclusions and limitations

In sum, the market structure that will satisfy the desired objectives of vaccine availability (through scaling up production capacity) and accelerated uptake will be determined by how various factors interact. The analyses conducted identify the crucial role of 'price', which means establishing a delicate balance between concerns about 'affordability' as well as security of supply. We note that particular attention should be focussed on demand risks via better forecasting techniques to reduce the 'risk premium' necessary for vaccine producers to supply under conditions of demand uncertainty.

We note that UNICEF plays a key role in the procurement of vaccines for low-income countries, and if, for one reason or the other, there are interruptions in its operations, even temporarily, any shortfall in vaccine supply worsens. But even if UNICEF's procurement arrangement is up and running all the time, one still has to deal with the problem of delayed vaccine introduction and inadequate numbers of vaccine suppliers. An external policy intervention is needed to alter such undesirable market outcomes.

It is important to highlight that our analysis and the results presented in this report are illustrative and subject to the underlying model assumptions and the (imputed) data used in the models – not to mention the fact that our defined counterfactuals describe a predefined sequence of events with the dates on which these events occurs being largely hypothetical. The latter applies specifically to our assumptions about market entry decisions of the three vaccines suppliers considered.

However, we believe that our work provides some indications as to what needs to be considered if access and security of supply of vaccines to GAVI-eligible low-income countries is to be assured. The results of our analyses hold as long as the assumptions and data employed here are 'true'. For this reason, we have built the models to be as 'flexible' as possible so as to leave enough scope for future work (refinements) based on our models and using 'richer' sources of data and improved methodology.

11 Baseline country and industry findings

This part of the report reviews the findings of the baseline study. We discuss each indicator by AMC goal and objective. The table below summarises findings of the baseline study by goal and objectives. Findings are described in detail below.

Table 12: Overview of pneumococcal vaccine AMC baseline study findings

Indicators	Results
Goal: To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030	
1. Cumulative number of cases of IPD averted due to TPP vaccines in GAVI-eligible countries	2005 = 0 2009 = 0
2. Cumulative number of future deaths averted due to TPP vaccines in GAVI-eligible countries	2005 = 0 2009 = 0
Objective 1: To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP)	
3. Cumulative number of TPP candidates	2005 = 3 2009 = 5
4. Median time between key milestones in the development of TPP candidates	Insufficient data
5. Cumulative number of AMC eligible TPP vaccines	To September 2010 = 2
Objective 2: To bring forward the availability of effective pneumococcal vaccines for developing countries by guaranteeing the initial purchase price, for a limited quantity of the new vaccines, that represents value for money and incentivises manufacturers to invest in scaling-up production capacity to meet developing country vaccine demand.	
6. Total number of doses of TPP vaccine offered to UNICEF SD per year for GAVI-eligible countries	2005 = 0 2010 = 7.2 million
7. Number of doses of TPP vaccine contracted under AMC by year	2005 = 0 2010 = 7.2 million
Objective 3: To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after AMC finance is used up.	
8. Cumulative number of countries that have applied for GAVI support for PCV	2005 = 0 2009 = 33
9. Cumulative number of GAVI-eligible countries introducing TPP vaccines	2005 = 0 2009 = 0
10. Cumulative number of doses of TPP vaccine shipped to GAVI-eligible countries	2005 = 0 2009 = 0
11. PCV3 coverage in GAVI-eligible countries	2005 = 0 2009 = 0
12. Time to national peak coverage	2005 = 0 2009 = 0

Note: We use ***TPP vaccine*** to denote a pneumococcal conjugate vaccine meeting TPP criteria

11.1 AMC goal: Morbidity and mortality

To reduce morbidity and mortality from pneumococcal diseases and, specifically, to prevent an estimated 7 million childhood deaths by 2030

Indicator 1: Cumulative number of cases of IPD averted due to TPP vaccines in GAVI-eligible countries

Indicator 2: Cumulative number of future deaths averted due to TPP vaccines in GAVI-eligible countries

Table 13, Figure 25, Figure 26 and Figure 27 summarise information on cases of pneumococcal disease and number of deaths in different countries.

The paper by O'Brien et al. (2009) provides worldwide estimates for different types of pneumococcal disease incidence and mortality for the year 2000.

Table 13: Pneumococcal pneumonia global estimates

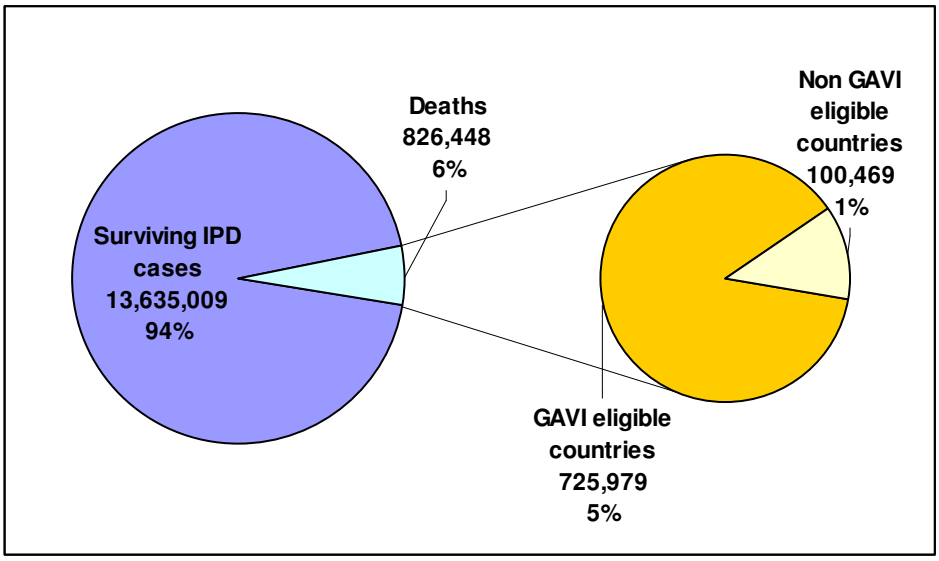
Indicator	Subgroup	No. of cases
Global incidence, children under 5 (in millions)		13.8
	Africa	3.8
	Americas	0.6
	Southeast Asia	5.3
Percentage in relation to clinical pneumonia cases from all causes		8.6%
Deaths (in thousands)		741
	Africa	406
	Americas	24
	Southeast Asia	169

Source: O'Brien 2009.

In 2000, the global under-5 population was 620,422,370.
There were 826,448 deaths due to IPD, of which 725,979 (88%) occurred in GAVI-eligible countries.

Figure 25 shows the number of cases and deaths in GAVI-eligible and non-eligible countries.

Figure 25: IPD cases and deaths in GAVI and non-GAVI-eligible countries.



Source: WHOd

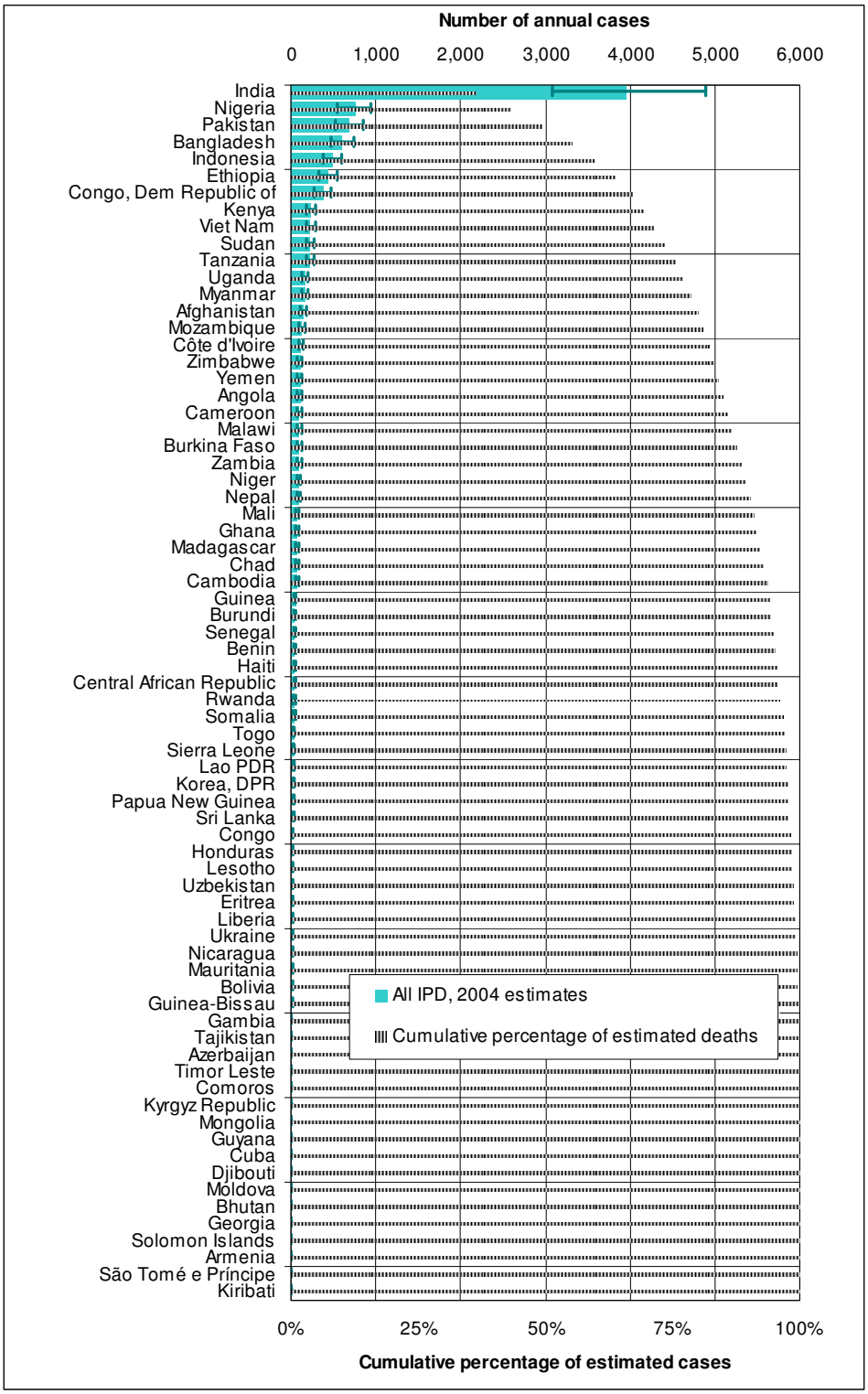
Figure 26 shows the annual number of cases in GAVI-eligible countries in 2004.

Figure 27 shows the estimated deaths in these countries, due to IPD in number and cumulative percentage, in the same year, and the annual target of averted deaths to reach the target of 7 million averted deaths in year 2030.

A total of 725,000 annual deaths due to IPD were estimated to occur in year 2004. Five GAVI-eligible countries accounted for 50% of those deaths: India (142,000 deaths, 20%), Nigeria (85,000 deaths, 12%), Ethiopia (55,000 deaths, 8%), Democratic Republic of Congo (50,000 deaths, 7%) and Afghanistan (31,000 deaths, 4%).

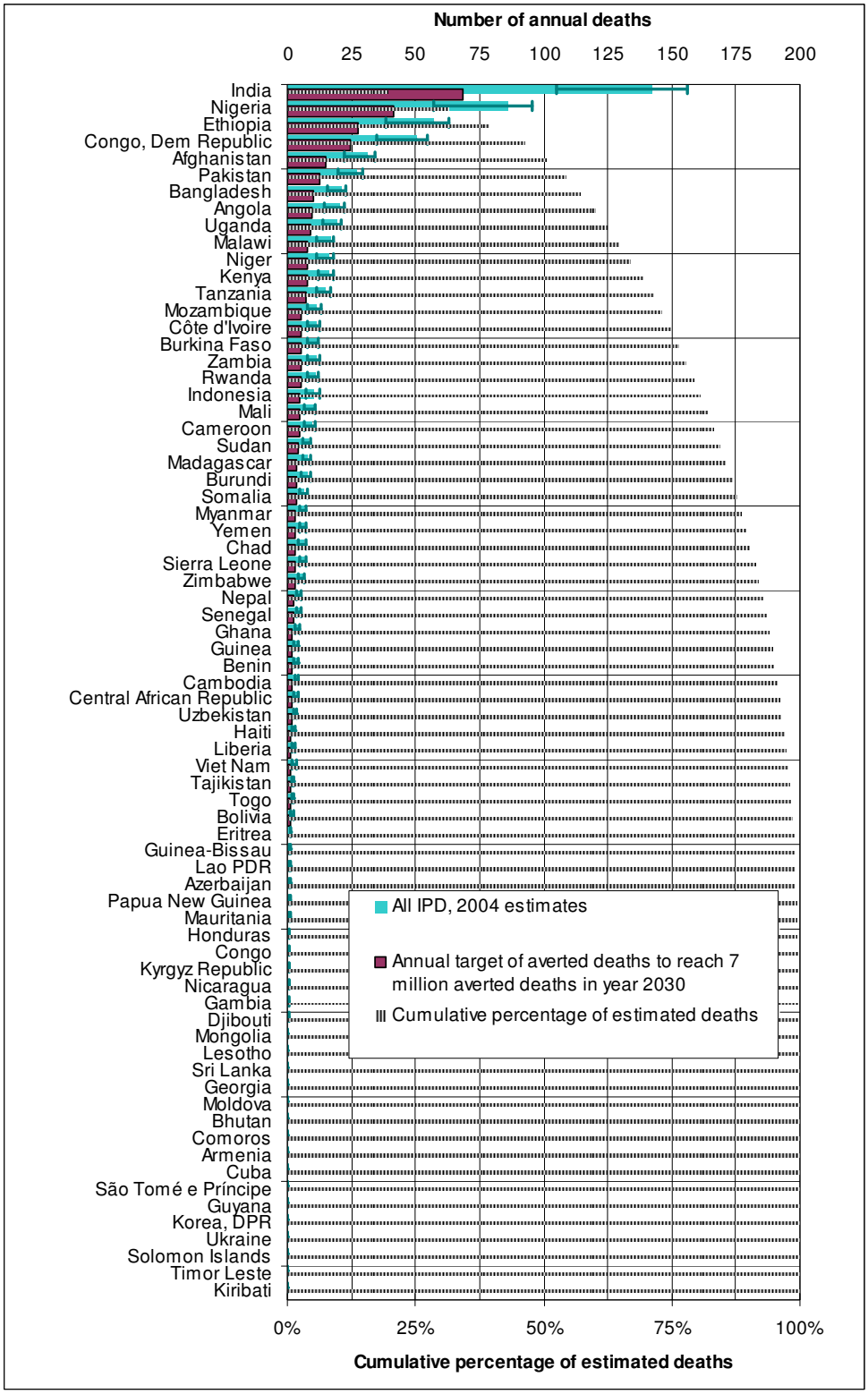
In order to achieve the AMC goal of averting 7,000,000 deaths due to IPD by year 2030, approximately half of the annual deaths have to be averted in each country. Given that the distribution of deaths is clustered in a small number of countries, a substantial proportion of deaths in those countries need to be averted.

Figure 26: Estimated IPD cases (2004) in number and cumulative percentage, in GAVI-eligible countries



Source: WHOd

Figure 27: Estimated deaths (2004) due to IPD in number and cumulative percentage, and annual target of averted deaths to reach the target of 7 million averted deaths in year 2030, in GAVI-eligible countries



It has to be taken into account that uncertainty boundaries of epidemiological indicators limit the usefulness of these indicators for monitoring pneumococcal vaccine impact on health outcomes, especially at early stages of vaccine introduction where changes of health outcomes are small. However, there is an explicit WHO recommendation that countries are encouraged to survey pneumococcal disease to provide baseline data and to monitor the impact of vaccination (WHO, 2004b)[26].

11.2 AMC objective 1: Vaccine development

To accelerate the development of pneumococcal vaccines that meet developing country needs (TPP)

Indicator 3: Cumulative number of TPP candidates

The search of clinical trial databases and various websites, as outlined in the methodology section above, found clinical trials data linked to a number of different vaccine candidates in clinical development or already launched. However, few matched the TPP or were actively progessing through a milestone during 2005 and 2009. Therefore, below we list all the vaccine candidates meeting the TPP from 1995 to the present and provide details of their progress through the key milestones (Table 14). We have then extrapolated the data relevant to 2005 and 2009 as the baseline years for this study (Table 15 and Table 16). No preclinical candidates have been included at this stage, owing to the difficulty in obtaining accurate details of the true state of this field. Current estimates of the number of preclinical programmes in existence are in the region of 20 (AMC Donor Group, 2008). We discuss the implications of this for future data collection in the next section of this report.

[26] This is particularly important in those developing countries that are among the first to introduce the vaccine into their national programmes; and in countries where there is a high prevalence of HIV infection or where other conditions known to increase the risk of pneumococcal disease exist.

Table 14: Situational review of vaccine candidates meeting TPP[27]

Company	Candidate	Milestone History
Wyeth Vaccines (now Pfizer) - UK	Prevnar-13[28]	♦ Phase I clinical trials started in 2004. This year also saw the start of a phase I/II clinical trial. ♦ The first phase III trial took place in 2006 and reported in December 2008. ♦ BLA submission finally completed (rolling submission started early 2008) March 2009. ♦ EMA approval was received in September 2009 ♦ FDA approval was received in February 2010
	9vPnC[29]	♦ A Phase III trial started in South Africa in 1998 and reported in 2003 ♦ A further Phase III trial in The Gambia started in 2000 and reported in 2005. ♦ This product was discontinued by Wyeth in 2004.
GSK - Belgium (In 2010 GSK and Fiocruz started a technology transfer deal to enable future production in Brazil)	Synflorix[30]	♦ Phase I interim formulation trial took place in 1997 ♦ Phase II interim formulation trial took place in 1999 ♦ Phase III interim formulation trial took place in 2000 ♦ Phase III of the final formulation took place in 2005 ♦ Synflorix is manufactured in three different presentations: mono-dose vial, two-dose vial and pre-filled syringe. ♦ Synflorix submitted for marketing approval from EMA in December 2007. EMA approval was received in March 2009 for all three presentation formats ♦ WHO PQ was received in October 2009 for the mono-dose vial and in April 2010 for the two-dose vial presentation ♦ AMC eligibility received April 2010 for the two-dose vial
	new generation *S pneumoniae* vaccine (pediatric)	♦ Entering Phase II clinical development February 2010
Intercell - Austria with Novartis (in association with PATH)	IC-47	♦ First Phase I trial started in March 2009 with results reported in February 2010. ♦ Further trials are now being planned
Sanofi Pasteur - France	*Streptococcus pneumoniae* protein vaccine	♦ Phase I studies were in process in February 2010 ♦ A previous Phase I study of this or a similar candidate was also conducted in 2007.
(in association with the Finnish Public Health Institute)	11-PCV[31]	♦ Phase II trials occurring from 1995. ♦ Further trials conducted from 2000 – 2004. ♦ Since 2005 no further development reported. ♦ This candidate discontinued by Sanofi Pasteur in 2008.
	Streptococcus pneumoniae vaccine (conjugate)	♦ This candidate was expected to enter clinical trials in 2006. No evidence of clinical trials taking place of this candidate has been found. ♦ In March 2008 the company confirmed it was moving its attention to *S. pneumoniae* protein vaccine development

[27] As mentioned in the methodology section above, this refers to candidates which have reached clinical development or beyond in the pipeline, are targeted *at Streptococcus pneumoniae* in infants and work against serotypes 1, 5 and 14.
[28] also known as 13vPnC; PCV-13; Prevnar 13; Prevenar 13
[29] also known as 9vPnC-MnCC, PncCMR9
[30] also known initially as Streptorix, and at times appears in clinical trials as GSK-1024850A/ GSK-1024805A, GSK 2189242A, 11Pn-PD-DiT, 10Pn-PD-DiT, GSK-513026 (all interim formulations)
[31] also known as 11PncDT, Pn-PD, PncDT, PncDT11 and PncOMPC

Table 15: Status of the pneumococcal vaccine candidate pipeline in 2005

Company	Candidate	Phase I	Phase II	Phase III	WHO PQ	AMC eligibility
Wyeth (now Pfizer)	Prevnar-13		X			
GSK	Synflorix			X		
Sanofi-Pasteur (with the Finnish Public Health Institute)	11-PCV		X			

Note: Sanofi-Pasteur's 11valent PCV was not in on-going Phase II trials in 2005 but was still an 'active' candidate within the company pipeline, as it was not discontinued until 2008 (although no further development was reported from 2005 onwards).

Table 16: Status of the pneumococcal vaccine candidate pipeline in 2009

Company	Candidate	Phase I	Phase II	Phase III	WHO PQ	AMC eligibility
Wyeth (Pfizer)	Prevnar-13			X		
GSK	Synflorix				X	
GSK	New generation *S. pneumoniae* vaccine (paediatric)	X				
Intercell/ Novartis	IC-47	X				
Sanofi-Pasteur	*S. pneumoniae* protein vaccine	X				

Note: GSK's and Sanofi-Pasteur's new generation vaccines were not in on-going Phase I trials in 2009 but were still 'active' candidates within the company pipeline with trials scheduled for 2010.

Indicator 4: Median time between key milestones in the development of TPP candidates

Measurement of the median times was to take place using the information collected for Indicator 3. However, as outlined in the methodology section of this report (Part II), we found that there are insufficient data to enable us to generate a reasonably sound estimate of median times between milestones. For example, we do not have a starting date for all Phase I trials or submission of IND or other national equivalent, which makes it impossible to gauge the starting point for the clinical trial phase for some candidate vaccines. We only have a single data point for a vaccine candidate in the

clinical trial phase, i.e. the Phase III trial of the candidate 9vPnC from Wyeth (now Pfizer). This makes it impossible to gauge the time it took to go from Phase I or II to Phase III. Few of the products have completed WHO PQ or AMC eligibility and therefore we are unable to conduct any meaningful analysis of the marketing phase. This has implications for future data collection which we discuss in the next section of this report.

Therefore, in Figure 28 below we outline, for illustration only, the approximate years between milestones for Prevnar 13, based on the limited data we were able to collect. In Table 17 we provide only a graphical illustration of the timelines based on the data available for all the candidates listed in Table 14.

Figure 28: Approximation of years between milestones for Prevnar 13

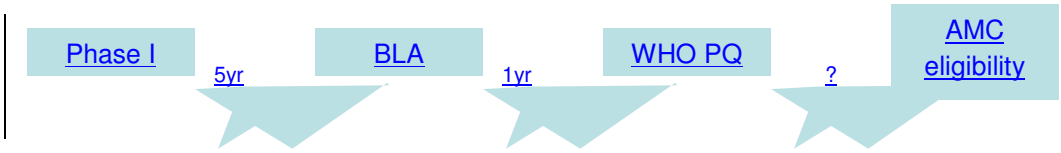


Table 17: Illustration of timelines for pneumococcal vaccine development

		Year															
Company	**Candidate**	**95**	**96**	**97**	**98**	**99**	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**
Pfizer (formerly Wyeth)	Prevnar-13[32]										PI		PIII				F
															BLA		
																F	
	9vPnC[33]				PIII												
							PIII										
GSK	Synflorix[34]					PI	PII					PIII			F		
																P	
	new generation *S pneumoniae* vaccine (paediatric)																PII
Intercell/ Novartis (in association with PATH)	IC-47															PI	
Sanofi Pasteur	*Streptococcus pneumoniae* protein vaccine														PI		PI
(in association with the Finnish Public Health Institute)	11-PCV[35]	PII						P?									
	Streptococcus pneumoniae vaccine (conjugate)	No development activity found.															

E = EMA; F = FDA; P = WHO PQ; PII/ III… = trial result date not known

[32] also known as 13vPnC; PCV-13; Prevnar 13; Prevenar 13

[33] also known as 9vPnC-MnCC, PncCMR9

[34] also known initially as Streptorix, and at times appears in clinical trials as GSK-1024850A/ GSK-1024805A, GSK 2189242A, 11Pn-PD-DiT, 10Pn-PD-DiT, GSK-513026

[35] also known as 11PncDT, Pn-PD, PncDT, PncDT11 and PncOMPC

Indicator 5: Cumulative number of AMC eligible TPP vaccines

As of June 2010, one TPP vaccine, GSK's Synflorix, had received AMC eligibility. This is the final AMC-related pipeline milestone for a vaccine and follows receipt of WHO prequalification. Synflorix has also received WHO prequalification (for its mono-dose and two-dose vial formulations).

11.3 AMC objective 2: Vaccine availability

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

Indicator 6: Total number of doses of TPP vaccine offered to UNICEF SD per year for GAVI-eligible countries

In March 2010 GSK and Pfizer offered to UNICEF SD 30 million doses from January 2012 and in January 2013 respectively. In addition GSK and Pfizer offered to provide a total of 7.2 million doses, 24.2 million doses and 20 million doses for the years 2010, 2011 and 2012 respectively, as part of the AMC Capacity Development Period.

Indicator 7: Number of doses of TPP vaccine contracted under AMC by year

On 23rd March 2010 GSK and Pfizer were contracted to supply 30 million doses annually. GSK will start provision of these doses from January 2012 and Pfizer from January 2013. In addition GSK and Pfizer have agreed to provide a total of 7.2 million doses, 24.2 million doses and 20 million doses for the years 2010, 2011 and 2012 as part of the AMC Capacity Development Period.

11.4 AMC objective 3: Vaccine uptake

To accelerate vaccine uptake by ensuring predictable vaccine pricing for countries and manufacturers, including binding commitments by participating companies to supply the vaccines at low, long-term and sustainable prices after the AMC financing has been used up.

Indicator 8: Cumulative number of countries that have applied for GAVI support for PCV

Figure 29 shows the number of countries at the stage of being approved, asked for clarification or with conditional approval increased from 2, 1 and 1 in 2007 up to 5, 4 and 7 in 2009, respectively. One country was asked to resubmit in 2009 (Nigeria).
Figure 30 presents the same data but shows the cumulative number of countries at each level of application status over the years.

Figure 29: Number of GAVI-eligible countries by PCV demand status and year.

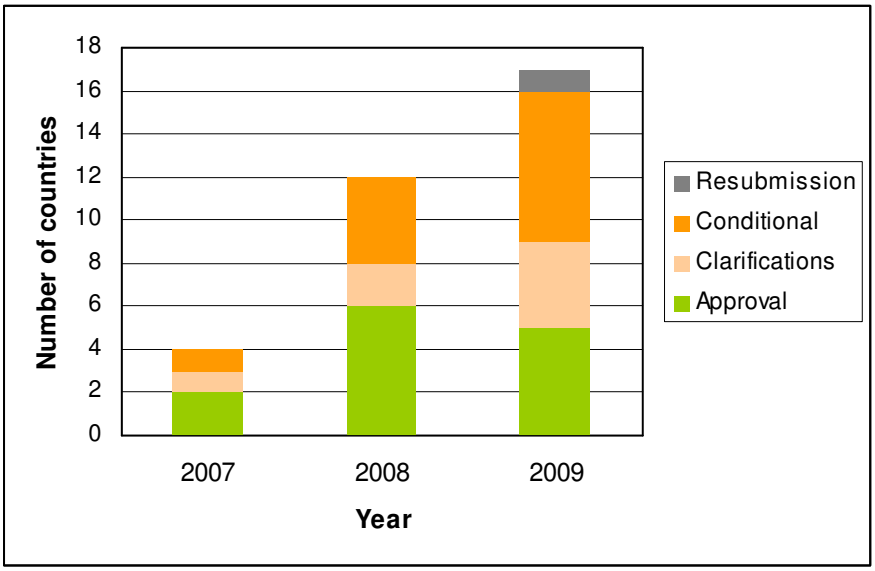


Figure 30: Number of GAVI-eligible countries by PCV demand status and cumulative by year.

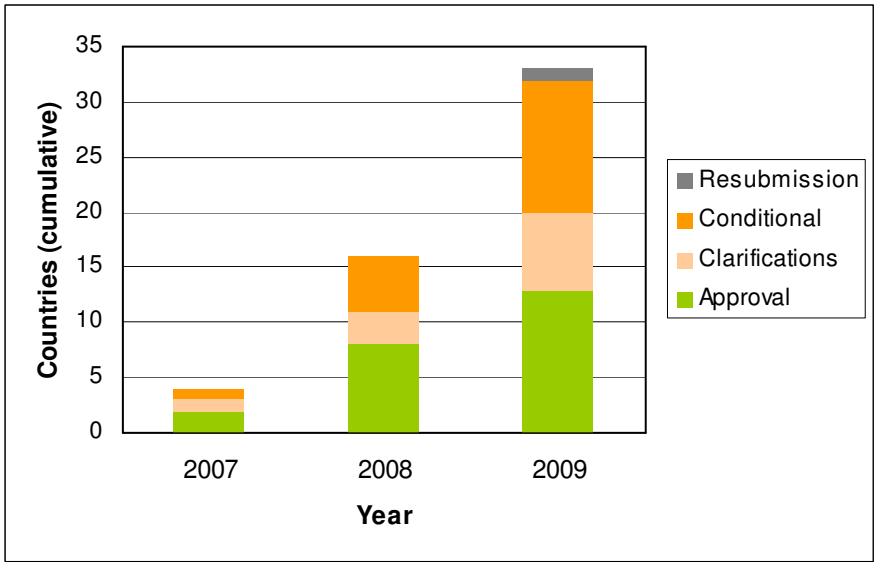


Figure 31 relates PCV demand status to the number of children under five in GAVI-eligible countries. It is interesting that when this figure is compared with Figure 29:, the differences between years are larger in Figure 29: suggesting that the countries applying later on (in 2009) had larger under-five populations than those applying earlier.

Figure 31 shows that in 2009, 114 million children were living in countries that applied for GAVI support to introduce PCV vaccine (almost one third of the children living in GAVI-eligible countries).

Figure 31: Number of children in GAVI-eligible countries by PCV demand status and year.

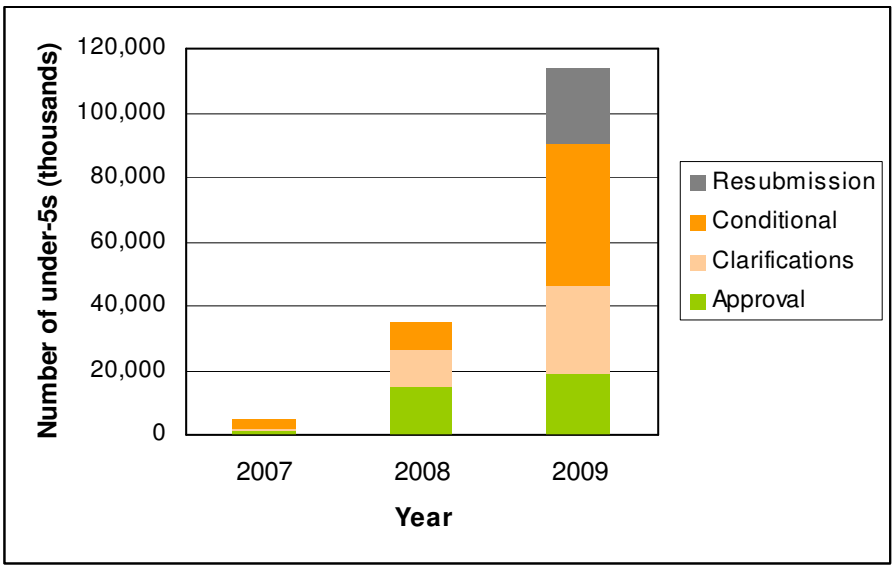
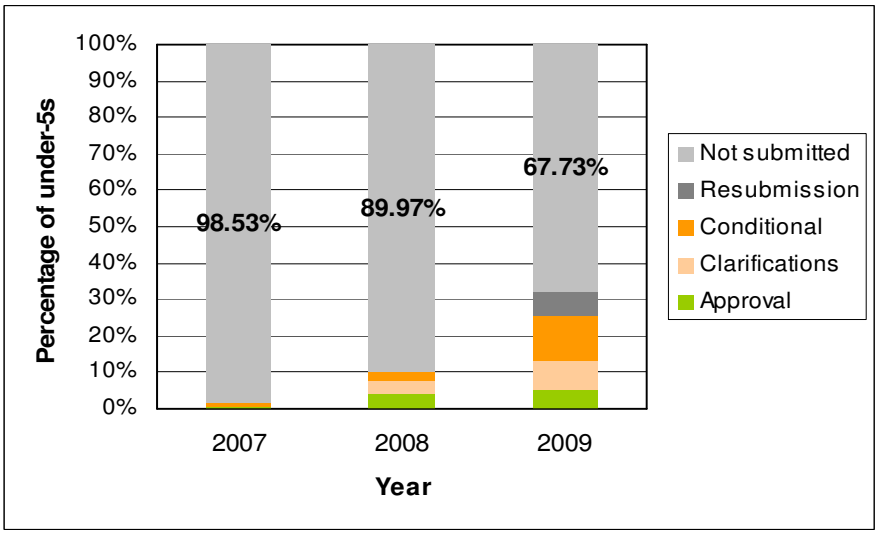


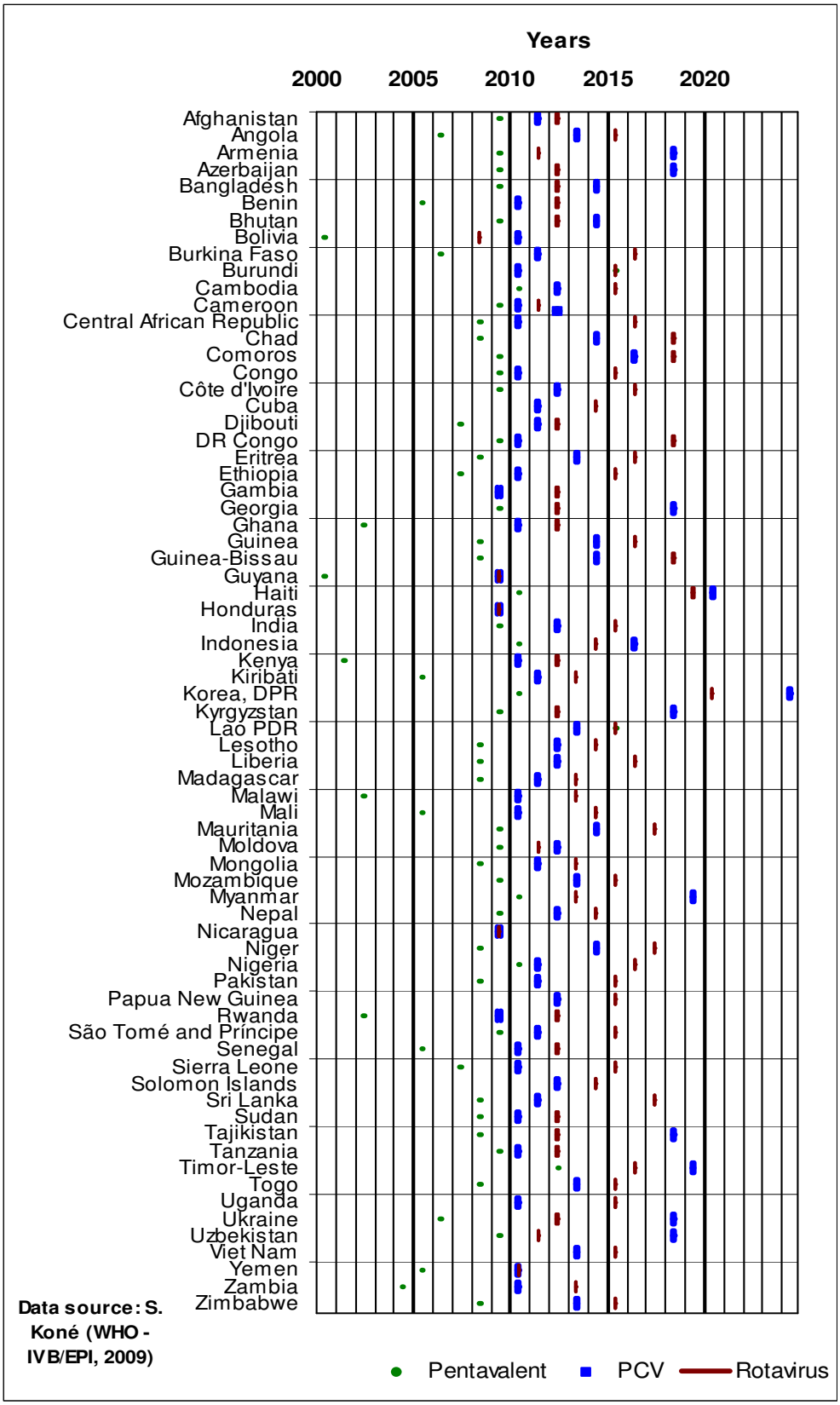
Figure 32: Percentage of children in GAVI-eligible countries by PCV demand status and year.



Indicator 9: Cumulative number of GAVI-eligible countries introducing TPP vaccines

The year of introduction of new vaccines provides an overview of the efforts that each GAVI-eligible country will have to make to take up any new vaccines. It is relevant to look at other vaccines, as well as TPP vaccines, because the demands for support from countries for the introduction of TPP vaccines cannot be considered in isolation from other events that may influence this demand, such as the introduction of other vaccines. Certainly, those countries where other vaccines are being introduced will have to make a substantial additional effort.

Figure 33: Forecast calendar for the introduction of new vaccines (2000 to 2025).

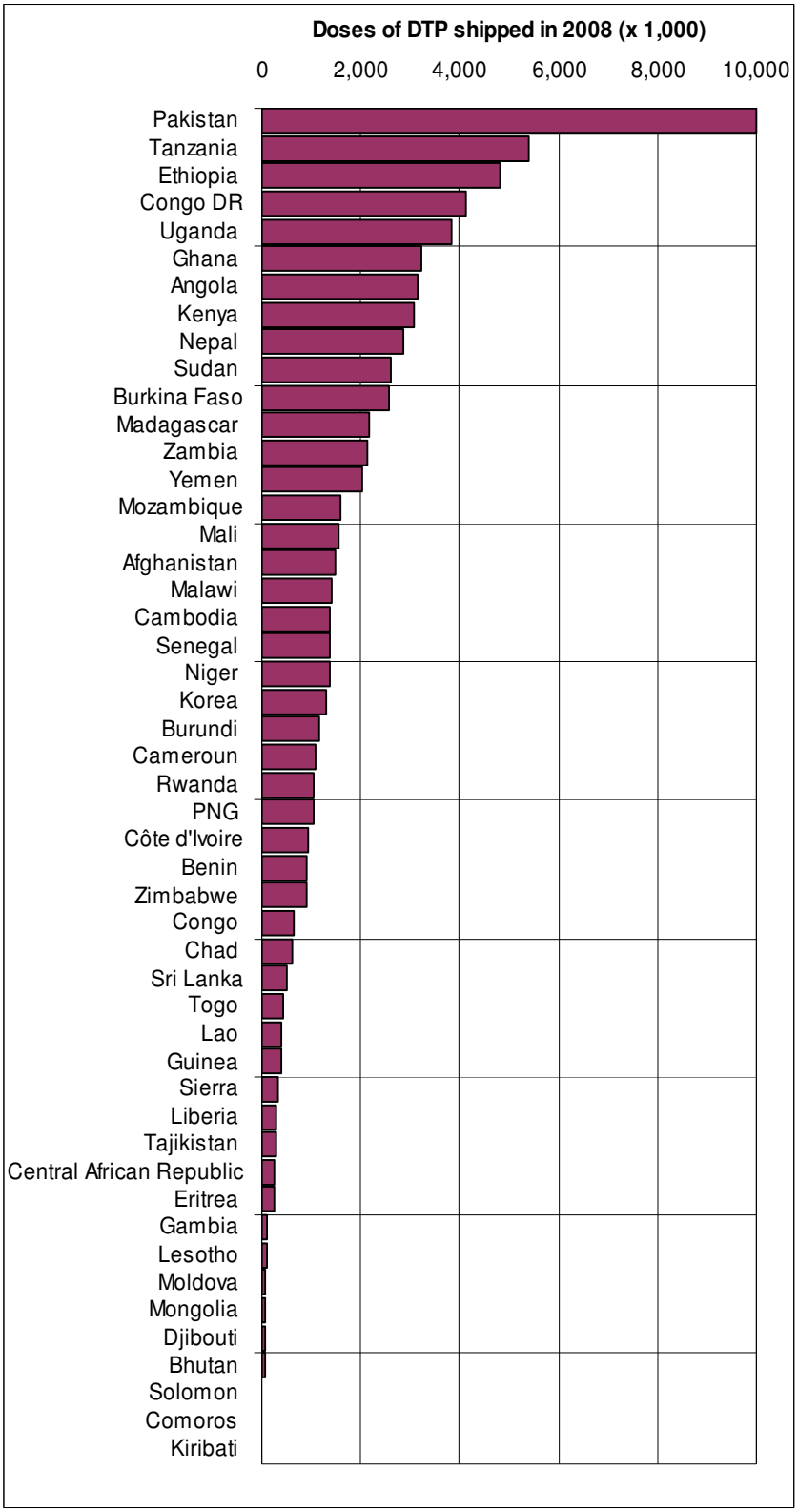


Indicator 10: Cumulative number of doses of TPP vaccine shipped to GAVI-eligible countries

Figure 34 illustrates graphically how the number of doses of vaccine shipped can be related to countries, using the shipment of DPT in 2008 as an example. In 2008, almost 76 million doses of vaccine were shipped into GAVI-eligible countries (excluding Latin American Countries), led by Pakistan (10 million), Tanzania (5.4 million), Ethiopia (4.8 million) and DR Congo (4.1 million).

A similar chart can be elaborated for PCV when data becomes available.

Figure 34: DTP shipped in selected GAVI-eligible countries (2008)



Source: UNICEFc

Indicator 11: PCV3 coverage in GAVI-eligible countries

Indicator 12: Time to national peak coverage

In 2008, WHO only reported PCV coverage from Luxemburg, Palau and San Marino (WHOc).

We therefore considered DTP3 and Hib3 data as examples for indicators 11 and 12: DTP3 because it is the reference vaccine to monitor coverage across countries, and the one for which data are available for the longest period of time; Hib3 because it is a vaccine of recent introduction, with a reasonable amount of data, and can serve as an approximate comparison with what could be expected to happen with the introduction of TPP vaccine. We also looked at Rotavirus data, but these were available only for 2008 and in a very limited number of countries.

Figure 35 compares estimates of DTP3 coverage by GAVI-eligible countries at one time-point (2005), sorted by decreasing coverage. Most countries had coverage above 80% and all but 8 countries had coverage below 60%.

Figure 36 and Figure 37 show the distribution of the number of countries with different levels of coverage, for DTP3 and Hib, respectively. These charts can show:

- how many GAVI -eligible countries have reached a certain level of coverage by year x , and
- how many years it has taken for a certain number of countries (e.g. half of them) to reach a certain level of coverage.

An example of the former is that in 1992, 30 GAVI-eligible countries reached 80% DTP3 coverage; of the latter, that for the first time in 2005 at least half of these countries reached DTP3 coverage of 80%.

In the case of DTP3, while the number of countries with DTP3 coverage of 80% or above increased exponentially from 0 (1980) up to 30 (1991), it took 13 years for this to happen in half of the GAVI-eligible countries (37 countries in 2004). In 2008, 55 countries had coverage of 80% or above (or conversely, 17 of the 72 countries had values below 80% in 2008).

The case of Hib3 is similar. In the first years of introduction, there was an exponential increase in the number of GAVI-eligible countries with coverage of 80% or above: from one country in 1998 up to 29 in 2008, 10 years later. This is a similar pattern to the one observed in the case of DTP3, where 24 countries reached 80% coverage of DTP3 in the first 10 years after 1980.

It is not surprising that introduction of Hib led to a rapid increase in coverage, owing to the fact that GAVI was supporting its introduction. GAVI supports the introduction of new vaccines in countries where DTP3 coverage is more than 50% (GAVI). This is

consistent with the pattern seen and with the small number of countries with Hib coverage below 50%, as compared with DTP3, that can be observed in the figures.

Recognizing that the introduction of new vaccines depends on many and complex factors, the threshold of 50% in DTP3 coverage may have been the main factor for the relatively small number of countries with Hib coverage above 80%. However, the number of countries with DTP3 coverage below 50% decreased from 16 in 1998, to 9 in 2002, and only 1 or 2 countries have remained below 50% in the last three years.
Therefore, in 2002, 62 countries already had DTP3 coverage acceptable for GAVI support in introducing Hib.

Figure 35: DTP3 coverage in GAVI-eligible countries (2005)

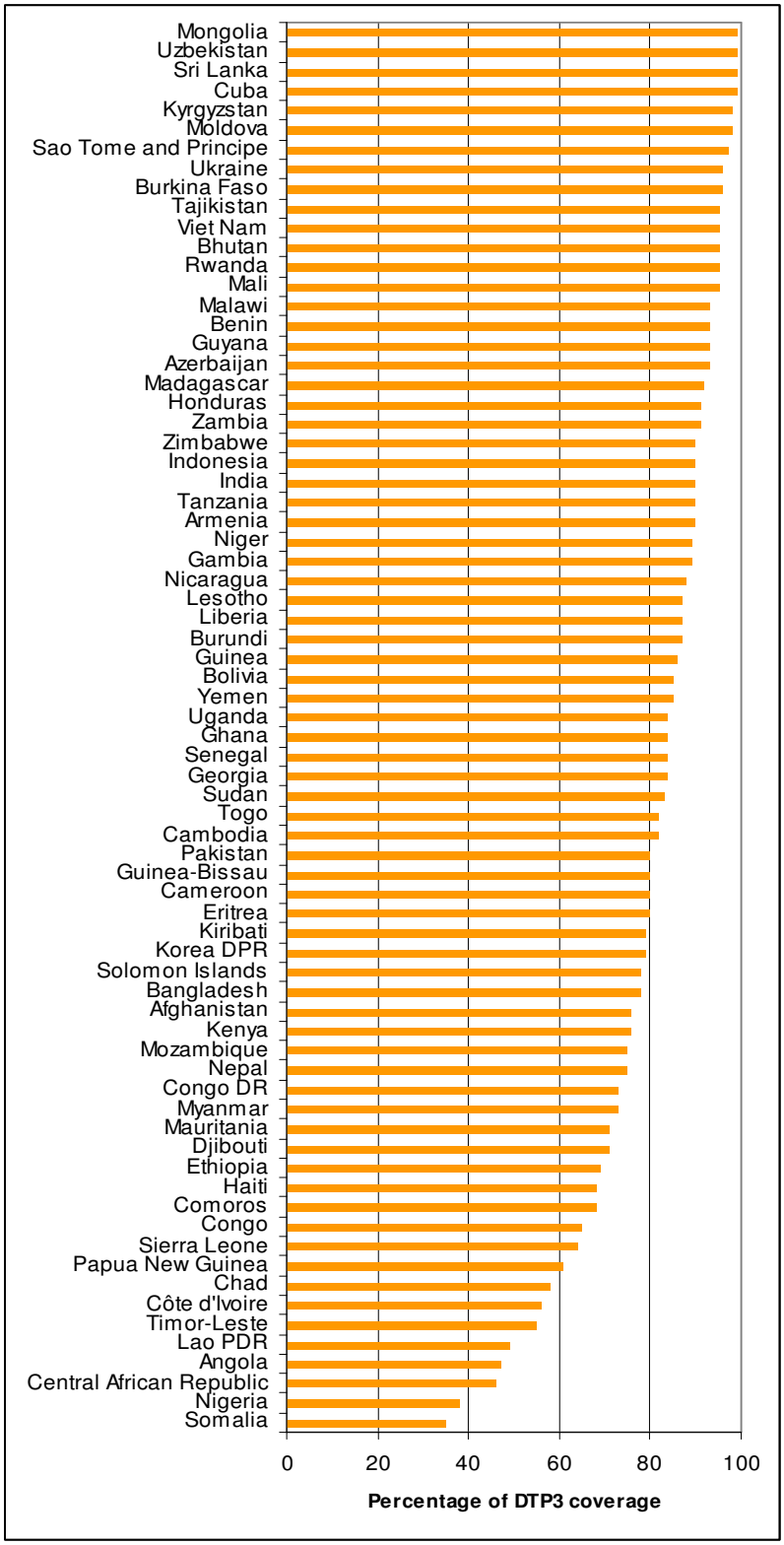


Figure 36: Number of GAVI-eligible countries with different ranges in DTP3 coverage (1980 to 2008)

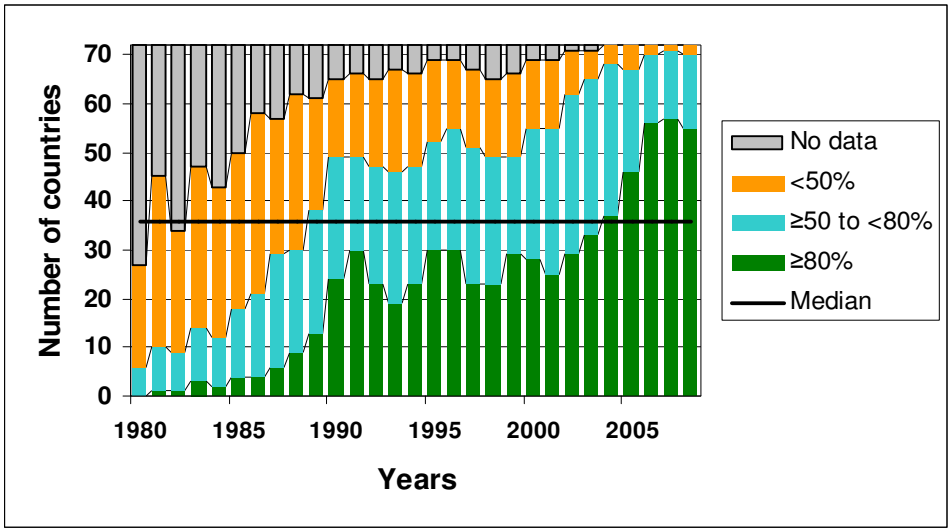
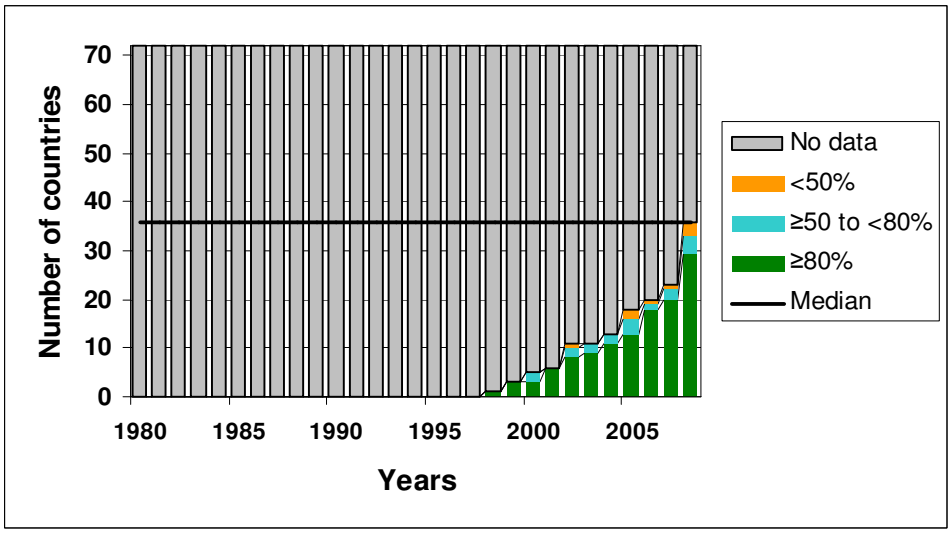


Figure 37: Number of GAVI-eligible countries with different ranges in Hib coverage (1998 to 2008).



PART IV – LESSONS LEARNT AND WAY FORWARD

12 Study process: lessons learnt

This baseline study was a dynamic process that evolved over the study period from January 2009 to July 2010. We continuously integrated findings that came up as we searched for and gathered information, and accumulated experience as we collected data and defined the counterfactuals. As there was no set or standard methodology for the study, the identification and development of tools and indicators, data sources and data analysis was a lengthy process. A major challenge was the fact that the baseline was set in 2005. The need for retrospective data collection led to difficulties in finding and accessing the data and information necessary to populate the indicators and the model. Another problem was that data from the vaccine-producing industry were essential, but there were issues of confidentiality and transparency, and the willingness of manufacturers to disclose strategic information varied greatly.

The baseline study did not represent a linear process of design, data collection and results. It rather consisted of a systemic process within a rapidly changing and complex environment in terms of epidemiology, economics and vaccine technology causing enabling, inhibiting and unintended effects that affected the study setting from 2005 to 2010.

The definition of counterfactuals, based both on academic analysis of the vaccine industry and perceptions and validation of key informants, was another endeavour that required substantial input. It became increasingly clear over the study time that the counterfactual model is the core element of this baseline and for future monitoring of the AMC impact.

Finally, the integration of the various components – industry dynamics and behaviour, infectious disease epidemiology in low income countries, and counterfactual definition and quantitative modelling, which required quite distinct expertise and methodologies, into a comprehensive and consolidated baseline study and body of knowledge required close collaboration and exchange within the team.

13 Counterfactual model: specific lessons learnt

Our models were designed to simulate the world without an AMC intervention for the introduction of PCVs. From the quantitative estimation work conducted, we see that reproducibility and assumptions are important challenges to empirical estimations of outcomes in any such model. The quality and availability of data will determine the

relevance of the policy implications that can be drawn from any quantitative modelling work. Although there are limitations to the validity of the models' outputs, we believe that general policy implications hold as long as the underlying assumptions and data assumed or imputed are 'reasonable'. However, for meaningful real-life decision making, it will be appropriate to make use of the best available data. For this reason, it is advisable to build 'flexible' quantitative models that can be easily adopted and adapted to accommodate new data and/or policy insights whenever they become available.

14 Country level indicators: specific lessons learnt

The baseline study and the counterfactuals required country-level data for populating indicators, as described in Section 6.7 above. During the process of definition of indicators and data collection we came to the following conclusions. The comments below concern country level indicators 1,2,8,9,10,11,12, as described in Table 5:.

- Global estimates of the burden of pneumococcal disease are of limited value for monitoring the impact of PCV, mainly because they may not be carried out frequently enough, and data generated in global estimates may not be sensitive enough to changes in PCV coverage, especially at the beginning of PCV introduction.

- The appropriateness of the IPD indicators should be considered. They have to be specific enough to allow the monitoring of disease-related indicators and to permit the attribution of changes in incidence to PCV vaccination status. They should also be feasible to collect. Studies able to demonstrate pneumococcal aetiology (e.g. through body fluids cultures) are the ideal. Such studies to monitor changes in disease incidence and mortality are being conducted in The Gambia and Kenya. However, they are not always feasible in countries with limited resources. Pneumonia diagnosed by X-rays is easier to monitor and reasonably sensitive to changes in IPD incidence, as shown in randomised clinical trials (RCT), but the diagnosis is less specific for pneumococcal pneumonia.

- Continuing the production of data in sentinel sites already looking at IPD (PneumoADIP) should also be considered. This might need some inputs in order to include vaccine coverage monitoring in those sites, if this is not already being done.

- IPD surveillance and health impact should take into account:
    - the need to assess the potential impact of new PCVs covering more serotypes, especially those more prevalent in low- and middle-income countries (LMIC);
    - concerns about serotype replacement, especially related to vaccines with 10 to 13 serotypes;

  - the need to investigate what is the impact of catching up on vaccinating older children, and of booster doses administered to young children.

- A similar coverage analysis to the one conducted for this report should be undertaken as PCV is introduced and data become available in the WHO/UNICEF JRF.

- Future monitoring of PCV coverage should not only be based on national figures, but also include the number of districts with coverage below a certain level (e.g. 80%). This data for PCV may not be routinely captured in the future, in the JRF. However, data for DTP3 could be used as a proxy.

- Special attention needs to be paid to the issue of additional cold chain capacity when planning PCV introduction. Many countries may have to increase their cold chain capacity at national level; substantially in some cases. Readiness of the cold chain may easily become a critical limiting factor. Planning for additional capacity for the cold chain must take into account the possible introduction of other new vaccines.

- WHO have no plans to report stock-outs of specific vaccines other than DTP in the JRF. DTP stock-outs can be used as a proxy in the future.

- Financial indicators as reported in the JRF at present cannot be used to monitor government spending share in relation to PCV, since data is not disaggregated by the type of vaccine or immunisation activity. The AMC is a funding mechanism, and the detailed financial monitoring it requires will need much more detailed data, where spending specifically on TPP vaccines can be tracked down.

15 Industry level indicators: specific lessons learnt

The collection of industry level data is subject to a number of constraints, many of them due to issues of confidentiality and transparency, and the varying willingness of manufacturers to disclose strategic information. The identifying of data sources was also time-consuming, and various lessons for the future were learnt during the process. The comments below concern industry level indicators 3, 4, 5, 6, 7 as described in Table 5: in Section 6.7 above.

- The sources of data

The search strategy used to populate indicators was outlined in the methodology chapter of this report. However not only was the search strategy time consuming, but the best source of data was found to be industry intelligence websites, especially Thomson-Pharma.com and not clinical trial sites such as clinicaltrials.gov. Access to the industry intelligence website was possible due to a time-limited purchase of access

rights by the Open University for another project. Future monitoring of the vaccine candidate pipeline would benefit greatly from access to this or an equivalent database.

- Gaining a picture of the *whole* development process (Indicator 3)

Baseline findings for Indicator 3 currently only outline details of candidates at the stage of clinical development for human use, or beyond it. Gaining an accurate picture of preclinical activity is difficult. Without such information, it is not possible to review the complete situation, but as the emphasis of the AMC is on the promotion of later state development of vaccines rather than early stage activities, it may be sufficient for future M&E activities to continue to concentrate on more 'downstream" R&D related activities.

- Quantitative data collection (Indicator 4)

Gaps in the data found for Indicator 3 made it impossible, at this time, to conduct an analysis of the median time between milestones for the calculation of Indicator 4. The search strategy used with the sources available was comprehensive, so access to further sources of data will be needed in order to perform the median calculation measurement foreseen for Indicator 4.

- Production times (Indicators 6 & 7)

Finally, in order to provide information related to manufacturing capacity, we had to use a proxy indicator, namely doses supplied to UNICEF SD. This was due to the market-sensitive nature of manufacturing production data. GAVI may wish to consider specific negotiations with companies to gain such data directly, particularly if it is found, in the future, that more countries start direct procurement of vaccines, which will reduce the validity of the proxy.

16 Conclusion

The key lessons learnt with respect to the datasets of the baseline study relate primarily to access to and availability of data (particularly industry data), and the reliability of the data. Another issue encountered during baseline data collection related to the matters of accuracy for all three components, sensitivity to change (mainly for the country component) and specificity (also for epidemiological data).

Finally, with regard to the counterfactual models, reproducibility and assumptions were and remain important challenges to empirical estimations of outcomes in any model designed to simulate the world without an AMC intervention for the PCVs. The quality and availability of data will determine the relevance of the policy implications that can be drawn from any quantitative modelling work.

In conclusion, although this study was designed as a stepwise process, in reality the baseline study became an iterative process with two major points of reorientation. These points of reorientation resulted from the recognition of the need to focus more

attention on the counterfactual model and from problems encountered during data collection. This process required close collaboration and exchange within the baseline study team in order to ensure integration of the various components of the study into a comprehensive and consolidated baseline study and body of knowledge.

The result has been the development of a number of recommendations or lessons learnt for future M&E activities of the AMC pilot. These are in addition to the provision of a technical tool for future M&E of the pneumococcal AMC with defined indicators, and a counterfactual model to monitor the impact of the AMC.

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18 Annexes

Annexe 1: Counterfactual definition: expert interviews

18.1.1 Introductory note

Dear…

GAVI's Mission is to save children's lives and protect people's health by increasing access to immunisation in poor countries.

I am writing to ask for your assistance with an important study which the GAVI Alliance has recently commissioned. The work is related to a new financial mechanism we are piloting, the Advance Market Commitment (AMC) scheme for a pneumococcal vaccine.

The objective of the study is to compare the AMC pilot with other strategies for vaccine introduction regarding development, manufacturing and uptake of vaccines in low-income countries. The other strategies will be represented by two counterfactual scenarios which will estimate what would have happened if no AMC had been implemented.

As part of the counterfactual analysis, the Office of Health Economics consulting (OHE), London is undertaking an interview programme with experts in the field to discuss their views on some possible scenarios showing what could have been achieved in the pneumococcal disease area if an AMC did not exist.

Given your knowledge and expertise in this area, we would greatly value your advice /input on these topics. The interview will last for one hour and will be conducted by phone. If you are interested in participating in the interview programme, we will send you a brief summary of the work on counterfactuals and the list of questions we would like to discuss.

Ideally, we would like to arrange a telephone interview with you next week (week beginning 6th July). I appreciate that this is an extremely tight schedule; however, I would be grateful if you could let us know if you would be available during the next few days. Depending on your availability the call would involve from the OHE either Martina Garau or Ebenezer Tetteh.

I would be grateful if you could liaise with them to let us know if you are willing to take part in the interview programme.

Please do not hesitate to contact me if you have any queries or require any further information on the project.

I look forward to hearing from you

18.1.2 List of interviews for the first interview programme

Non-governmental organisation
Tido von Schoen-Angerer (MSF Campaign for Access to Essential Medicines)

International organisation
Patrick Zuber (WHO)

Academic
Paul Wilson (Columbia University)

ADIP
Kate O'Brien (John Hopkins, Centre for Global Health; previously PneumoADIP)

Other
John Boslego (PATH)

AMC donor
Saul Walker (DFID; Department for International Development, UK)

18.1.3 Questionnaire for the first interview programme

Defining the counterfactuals

Purpose of the interview

To elicit experts' views on appropriate counterfactual scenarios representing possible states of the world were the advanced market commitment (AMC) not launched (i.e. the counterfactual scenarios). Prior to the introduction of the AMC concept in 2005, there was only one available pneumococcal vaccine (a 7-valent pneumococcal conjugate vaccine (PCV) licensed by Wyeth) and two in advanced stage of development (a 10-valent PCV produced by GSK and a 13-valent by Wyeth). Around 20 vaccine candidates were detected in different stage of development.

In this interview, we would like to discuss with you what are the main factors related to the pneumococcal vaccine environment that should be considered when developing the counterfactuals (i.e. the 'without policy intervention' scenarios) and what is the available data that should be used to populate the scenario model.

Part 1 – Demand side in a 'no-AMC' scenario

1. Without the introduction of an AMC, which funding arrangement would be established to supply the PCVs in poor (GAVI-eligible) countries?

   a) Conventional procurement model (e.g. via UNICEF, GAVI fund) where volumes and price are determined through a centralised competitive bid;
   b) Country-by-country negotiations where part of the funding can come from national budgets, GAVI funds, and/or companies' donations;
   c) Others.

   Are these options mutually exclusive?

The following questions refer to the no-AMC scenarios identified in the previous question. i.e., option a), option b), or others and aim at understanding key differences in the vaccine demand environment between these and an AMC scenario.

2. Would policy initiatives such as the PneumoADIP have an impact on access to the vaccines?

3. Would the recipient countries be 'ready' to adopt the vaccines (e.g. would they have appropriate infrastructures)?

4. What would be the main barriers for the uptake of the vaccines (e.g. technology characteristics)?

5. Which price would be guaranteed to the vaccine manufacturer/s?

6. When would the vaccines in question be available to GAVI-eligible countries?

7. Do the factors discussed in part 1 represent the key elements influencing the demand side of a pneumococcal vaccine in a no-AMC scenario? Do you have any other suggestions?

Part 2a – Supply side in a 'no-AMC' scenario

8. Without the introduction of an AMC, which manufacturer/s would expand the production capacity to supply GAVI-eligible countries with the available vaccines (i.e. the 7-valent, the 10-valent and 13-valent PCV)?

    a) Vaccine manufacturers serving high income countries (i.e. original developers);
    b) Local vaccine manufacturers (i.e. emerging-market suppliers) producing follow-on versions of existing PCVs;
    c) Others.

For each of the two available vaccines:

9. How many competitors would enter the market?

10. Which level of vaccine supply would be ensured by the vaccine manufacturer/s (given the expected demand, which level of coverage would the manufacturer/s able to offer)?

11. How long would it take the manufacturer/s to make scale-up decisions and build new production plants?

12. Do the factors discussed in part 2 represent the key elements influencing the supply side of a pneumococcal vaccine in a 'no-AMC" scenario? Do you have any other suggestions?

Part 2b – Supply side pre-AMC

13. Do you think that the pre-AMC scenario of the supply side considered in the analysis (i.e. 7-valent PCV in the market plus the 10-valent and the 13-valent PCVs in advance stage of development) is a good approximation of the state of the world in 2005? Can you provide any other insights?

Part 3 – Examples

The AMC Framework report identified two potential examples which could be used to populate the counterfactual scenario model: the rotavirus vaccine (for which GAVI created an ADIP similar to that for the pneumococcal vaccine) and the Hib vaccine.

14. Do you think that the indicated vaccines should be used as benchmark to assess the AMC performance, as they represent examples where an AMC was not introduced? What are the similarities and differences as compared with the pneumococcal vaccine environment and technology characteristics?
    Do you have any other suggestions?

18.1.4 List of interviews for second interview programme

Recipient Country
Rehan Hafiz (Ministry of Health, Pakistan)

AMC Implementation
Susan McAdams (World Bank)

Non-governmental Organisation
Rohit Malpani (Oxfam America)

International Organisation
Shanelle Hall (UNICEF Supply Division)

ADIP
Mark Alderson (Pneumococcal Vaccine Project, PATH)

Investment Cases
Lew Barker (Aeras Global TB Vaccine Foundation)

Other Experts
Sandy Wrobel (Applied Strategies)

Academic
Jonathan Levin (Stanford University)

18.1.5 Questionnaire for the second interview programme

Validating the counterfactuals

Counterfactual 1 - Early conventional procurement

Without an AMC, one possible market setting on the demand side could be:

- The funding arrangements: they are established through a conventional procurement model where: UNICEF solicits bids; firms bid; UNICEF accepts a bid or bids (trying whenever possible to procure from multiple manufacturers) and issues contracts. GAVI participates in the process through the 'procurement reference groups". Contracts have typically been for three years, although perhaps only the first year is guaranteed.
- Timing: funding arrangements are finalised in the short run, i.e. in the next 2-3 years.
- The total level of funding: donor money raised to fund PCVs is less than that raised with the AMC.
- Local decision makers in GAVI-eligible countries: they endorse the UNICEF agreement and introduce PCVs, subject to funding support from GAVI.

On the supply side, the market could present:

- Number and type of manufacturers entering the low-income country market:
    - One multinational company (GSK) responding to the UNICEF bid and expanding capacity for developing countries.
    - Another multinational company (Wyeth) needing more support, given its limited experience with low-income country markets.
    - An Indian manufacturer beginning its R&D programs on a pneumococcal conjugate vaccine (PCV) to pursue the local market.
    - Entry decisions of other emerging manufacturers following standard timelines and procedures: they would watch and monitor the market (number of countries buying PCVs and total demand volumes) and based on that they would make their investment decisions. Upfront funding directly supporting one or more emerging manufacturers may accelerate the process. They are not able to enter the market before 2013-2014.

Counterfactual 2 - Late conventional procurement

The other possible no-AMC scenario could present less favourable assumptions as opposed to Counterfactual 1.

On the demand side, we could have:

- The funding arrangements: there is a failure of a centralised and coordinated action to provide funds and to determine the purchasing price in developing

countries. This is mainly due to issues concerning difficulties for manufacturers in adopting a differential pricing policy (i.e. sell at different prices in different geographical regions of the world). As in the case of the 7-valent PCV, the manufacturer may prefer to donate vaccine doses to specific countries instead of responding to an invitation to bid due to its agreement with PAHO.

- Timing: conventional UNICEF procurement system is not successful in the short term as no supplier put a bid. Only after prolonged negotiations some kind of solution are found to allow the firms to offer these vaccines to GAVI countries at a lower-than-PAHO price.
- The total level of funding: donor money raised to fund PCVs is less than with the AMC;
- Local decision makers in GAVI-eligible countries: they prefer to wait and purchase from their own local suppliers.

On the supply side, there could be:

- Number and type of manufacturers entering the low-income country market:
    - Only one multinational company willing to supply GAVI-eligible countries in the short term (most likely GSK);
    - The other multinational company initially targets middle-income countries and private markets in poor countries;
    - Emerging manufacturers' strategic behaviour is not fundamentally different from that outlined in Counterfactual 1, i.e. market penetration following standard timelines.

Based on the key conditions of the vaccine environment outlined above, we have identified the following indicators for the counterfactuals:

d) The overall timescale for access

e) Level of coverage

f) Distributed PCVs and their technical characteristics

Questions:

1. In your view, are the two counterfactual scenarios outlined above plausible?

2. Is there any element on either the demand and the supply sides of the counterfactuals which is missing?

3. One of the purpose of the study is to populate the scenarios with some estimate points of the three indicators (a, b, and c). Data can include real life data and, when this is not available, projections which can be used in the model simulation. The two examples of existing vaccines suggested in the AMC Framework report were rotavirus and *Haemophilus Influenzae* Type B (Hib) vaccines. The former represents a new vaccine which has been launched but still needs to be introduced and widely used in developing

countries; thus it should be used as a benchmark to assess the AMC performance in the future, as data on uptake and other indicators would need to be collected alongside data on the pneumococcal vaccine. The latter is an older vaccine which can provide some historical data on vaccine uptake in poor countries.

As there is not one single obvious example that can be applied to the pneumococcal vaccine, the examples of Rotavirus and Hib can be used to populate the counterfactual scenarios of PCV only with some adjustments reflecting the key differences between the vaccine environments.

For indicator a, the overall timescale for access, what is the example that should be used? Please indicate what of the following should be used for Counterfactuals 1 and 2:

- Less than Hib, e.g. 2/3 or 1/3 of the timescale observed for Hib?
- More than Hib, e.g. 4/3 or 5/3 of the timescale observed for Hib?
- Same as Hib?

- Less than Rotavirus, e.g. 2/3 or 1/3 of what you would expect for Rotavirus?
- More than Rotavirus, e.g. 4/3 or 5/3 of what you would expect for Rotavirus?
- Same as Rotavirus?

Please motivate your choice.

For indicator b, the level of coverage, what is the example that should be used? Please indicate what of the following should be used for Counterfactuals 1 and 2:

- Less than Hib, e.g. 2/3 or 1/3 of the coverage observed for Hib?
- More than Hib, e.g. 4/3 or 5/3 of the coverage observed for Hib?
- Same as Hib?

- Less than Rotavirus, e.g. 2/3 or 1/3 of what you would expect for Rotavirus?
- More than Rotavirus, e.g. 4/3 or 5/3 of what you would expect for Rotavirus?
- Same as Rotavirus?

Please motivate your choice.

For indicator c, the distributed PCVs and their technical characteristics, please indicate which PCV is more likely to be distributed under counterfactuals 1 and 2:

- 10-valent PCV?
- 13-valent PCV?
- Both 10- and 13- valent PCVs?

Please motivate your choice.

18.1.6 Summary of second Interview programme

General comments

The general consensus from the second round of interviews was that the counterfactuals defined in Section 7 were a reasonable and plausible depiction of what the state of affairs could be if AMCs were not made available for the production and supply of pneumococcal vaccines.

Some interviewees did not like Counterfactual 2, as they considered the failure of Wyeth (now Pfizer) to respond to UNICEF's bids to be a one-off event. Their view is that it happened because UNICEF proposed a one-year bid for small quantities of the vaccine. This was a deviation from the conventional procurement process for large quantities (reflecting aggregated country demands) over a three-year period.

Counterfactual 2 is, however, a description of what happens with country-specific procurement arrangements, which is a disaggregated demand model. Such a counterfactual scenario could be brought about by a number of events. A lack of bids is only one of them. Lack of funding for GAVI is another. The important factor is that the rationale we put forward is plausible.

Another criticism levelled at Counterfactual 2 was that it ignored the role of information (research) and policy advocacy. One cannot ignore important factors such as disseminating the results of research evidence (for example, information on the magnitude of clinical demand/need), and how much WHO support can be exerted to get developing countries to prioritise the introduction of pneumococcal vaccines (or indeed, any vaccine), and the priority developing countries place on these vaccines irrespective of external influences.

However, we maintain that Counterfactual 2 is a credible scenario of events that might follow when the conventional (aggregated demand) procurement system used by UNICEF fails to work as planned. We believe the role of disseminating research evidence and WHO recommendations in creating or fostering appreciable demand (and hence encouraging market entry decisions) can be captured by the appropriate choice of historical examples for quantitative estimation of this counterfactual.

In what follows, we want to highlight comments from the experts interviewed that have important implications for the estimation of our counterfactuals. Some of these comments, in our opinion, are not specific to the counterfactuals defined for the pneumococcal vaccines *per se,* but are rather a criticism of the AMC concept. For example, an argument was made that the time it takes to negotiate an AMC will have a bearing on how the counterfactuals, considering a scenario without AMC, can be compared with AMC intervention. Conventional procurement arrangements with UNICEF may be faster, and allow for more rapid delivery of the pneumococcal vaccines, if a lot of time has to be spent designing an AMC intervention and generating interest from donors. If it is felt to be correct, this possibility can be taken account of in the counterfactuals in the time-sequencing of events.

We present below more specific comments and perspectives on the counterfactuals defined.

Counterfactual 1 – early conventional procurement

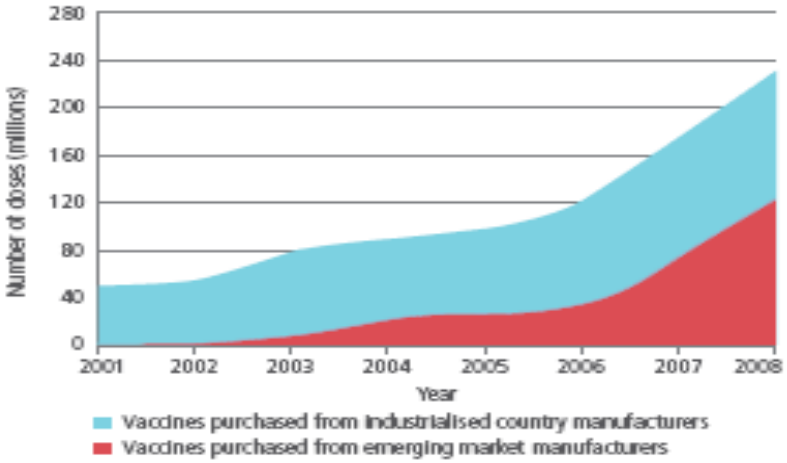
Although Counterfactual 1 is 'right' and describes 'business as usual', it might be useful to collect views on (and 'collective expectations' of) variables such as pricing for pneumococcal vaccines and probability of uptake before the AMC was announced. This is one possible source of confounding that we aware of, but it is difficult to deal with. Indeed, that the presence of the AMC can lead to changes in the behaviour of vaccine suppliers and national/international procurement agencies is evident from the recent deal between GSK and Brazil for the supply of Synflorix®. It is clear that the GSK-Brazil deal (of €1.5 billion, starting with an agreed volume and price of €11.50 falling to €5 in future years) reflects the 'path' carved out by the implementation of the AMC for pneumococcal vaccines. See Jack (2009) for details of the deal between GSK and Brazil.

Although it is not clear how different players will behave without an AMC, it may be that the commitments and obligations that an AMC places on manufacturers will reduce their willingness to supply vaccines under the AMC, notably because of the lack of price flexibility above the price ceiling set under the AMC. Depending on the importance attached to price flexibility by suppliers, pneumococcal vaccine supply may be higher in one of the counterfactuals.

The effect of price inflexibility (and other obligations and commitments set under the AMC) is more likely to affect emerging-market vaccine suppliers. In contrast to multinational companies, they do not have appreciable access to markets in high-income countries and are likely to have to share the pot of AMC funds and aggregated demand with multinational companies. Almost all the experts interviewed expressed concerns about the potential for market entry by vaccine suppliers from emerging and low-income countries on technical grounds. Compared, for example, to the monovalent conjugated Hib vaccine, PCVs are polyvalent and relatively more complex and technically more challenging to produce. (The same however cannot be said of a comparison between polyvalent Hib-containing vaccines and PCVs.)

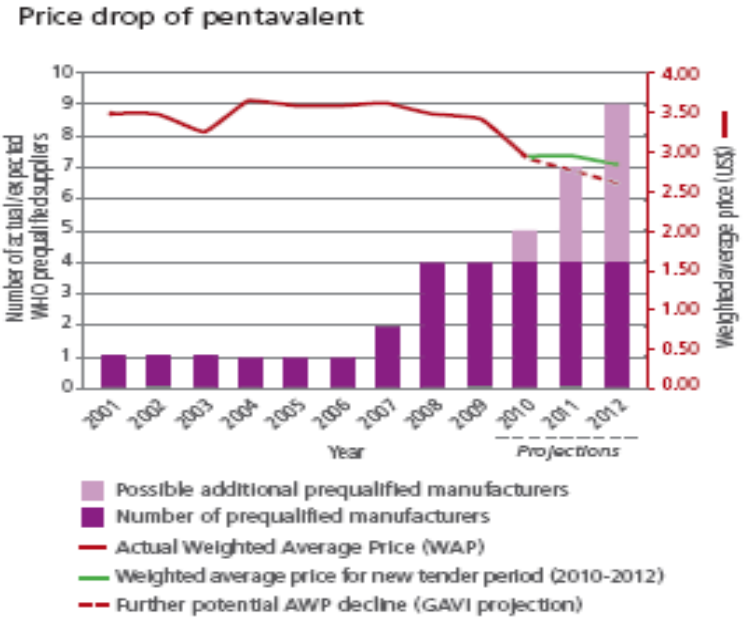
Vaccine suppliers from developing countries may find it difficult to produce pneumococcal vaccines that meet the target product profile specified under the AMC. Notwithstanding these technical challenges, a small number of vaccine suppliers from developing countries will enter the market for the production of pneumococcal vaccines (a scenario of no market entry is unlikely). Some developing country vaccine manufacturers have already expressed interest in producing the PCVs. The Serum Institute of India and the Chengdu Institute of Biological Products (a subsidiary of the China National Biotech Group) have been exploring the possibility of producing vaccines. And we also know that the pneumococcal AMC has received offers from four vaccine suppliers albeit the identities of these suppliers are confidential and we do not know whether the offers received are valid.

Figure 1: GAVI consolidation of demand for vaccines ensures security of supply



Source; GAVI (2009b)

Figure 2: Price competition on pentavalent Hib-containing vaccines



Source: GAVI (2009b)

With appropriate levels of funding, vaccine suppliers from low-income countries can be expected to respond if they have the technical capability to do so. With certainty of funding and certainty of receiving supply bids, emerging-market vaccine producers will respond to the invitation to supply pneumococcal vaccines even without an AMC intervention. The problem still remains that the pneumococcal AMC may not generate adequate incentives for emerging-market vaccine manufacturers if the available pot of AMC funds is largely taken up by GSK and Wyeth (now Pfizer). Evidence from GAVI's

operations (see Figure 1 and Figure 2 above) confirms the potential importance for volume and price of engaging emerging-market suppliers.

One interviewee argued that contrary to our assumptions, the level of funding will not necessarily be greater with an AMC intervention because other sources such as the International Finance Facility (IFF) can be used to generate adequate funds. The impact of such an alternative assumption needs to be modelled as part of the counterfactual analysis.

Counterfactual 2 – late conventional procurement

Counterfactual 2 was generally considered a good representation of recent developments and conflicts between PAHO, on the one hand, and UNICEF/GAVI, on the other. The effect these conflicts will have on Counterfactual 2 will depend on whether the tensions between PAHO and UNICEF can be resolved. The validity of the counterfactual will also depend on how countries graduating from GAVI-eligible status to middle-income status will be treated under the PAHO and UNICEF vaccine procurement arrangements.

The problem is that if PAHO applies and enforces its MFN clauses in its procurement agreements (which will enable them to extract the lowest price available), vaccine suppliers (especially multinational companies) will be less inclined to supply low-income countries, as price (discount) spillovers will lead to loss of sales revenues from purchases made by high- and middle-income countries at relatively higher unit prices). The outcome will be higher GAVI prices.

Of course the decisions and behaviour of vaccine manufacturers cannot always be predicted. For example, the general expectation is that GSK will be the main player with marginal involvement of Wyeth (now Pfizer). This may change if Wyeth, for altruistic reasons, decides to participate. In fact, it was brought to our attention that it was relatively easy for Wyeth to donate Prevnar® (the 7-valent pneumococcal vaccine). Wyeth had accrued surpluses of this product, and it was soon to be superseded by a therapeutically superior one. Wyeth donations were a way of avoiding holding an excess stock of vaccines, and at the same time developing its experience of working in low-income countries and also demonstrating corporate social responsibility. The donations from Wyeth were intended to show that polyvalent pneumococcal conjugate vaccines could be used in low-income settings. See also Lee (2009).

It is important to note that although Wyeth itself has no extensive experience of doing business in developing countries, as it is now part of Pfizer (which previously had no vaccines in its products portfolio) it could tap into Pfizer's experience of doing business in developing countries.

Indicators for the counterfactuals

In this section, we present what are essentially guesstimates from the experts interviewed as to how pneumococcal vaccines would have fared without an AMC. This

was done in comparison to what the expert interviewees expected (or knew) of rotavirus vaccines and the historical evidence on Hib vaccines. We want to emphasise that not all of the interviewees felt 'comfortable' and capable of providing such guesstimates. The main purpose of this exercise was to draw out some quantitative sense of how the world would have been without a pneumococcal AMC – to help create a proper well-scoped quantitative estimation of our counterfactuals.

Three indicators were used as the basis for comparison. These were:

- Timescale for access,
- Level of coverage, and
- How the technical characteristics of the different pneumococcal vaccines will affect their distribution and supply to low-income countries.

The consensus was that these three indicators were the right ones to use. However, it was suggested to us that a more appropriate set of indicators might have been: (1) the degree and speed of tiered pricing for low-income countries (2) the degree and speed of supply to these countries and (3) the degree and speed of uptake in these countries. No reason was given for this view, nor was any justification given for considering our list of indicators to be less appropriate. In fact, the second and third indicators suggested by the interviewee are not different from what we proposed, i.e. level of coverage and timescale of access. However, we agree that the degree and speed of tiered pricing to accelerate access in low-income countries is a useful indicator for evaluating what will happen with the counterfactuals.

In the following subsections, we provide a summary what the interviewees thought about the counterfactuals defined for pneumococcal vaccines with respect to the selected indicators provided in the questionnaire.

Timescale for access

Whether the timescale for access to pneumococcal vaccines without an AMC will be roughly similar to, or different from, that for Hib and rotavirus vaccines will depend on the interaction between various factors. On one hand, the pneumococcal vaccines are technically more complex and difficult to produce; which means entry by emerging-market vaccine suppliers, to meet an excess demand that GSK and Wyeth (now Pfizer) are not able or willing to meet, will be delayed. Looking at this factor alone will suggest that the timescale of access to pneumococcal vaccines without an AMC will be longer than that for Hib and rotavirus vaccines.

However, pneumococcal vaccines may be introduced much faster than Hib or rotavirus vaccines. The reason is: Hib vaccines and rotavirus vaccines have not received the same global health priority and health priority placed on these vaccines by developing countries was 'low'. This shorter timescale for pneumococcal vaccines will be boosted by information and evidence building. Furthermore, developing countries now have a better understanding and have gained greater appreciation of the value of vaccines.

One reason why the timescale of access for pneumococcal vaccines may be shorter than for rotavirus vaccines is because demand creation for rotavirus vaccines was

delayed by rolling (region by region) recommendations by the WHO's SAGE (Strategic Advisory Group of Experts). In addition, the work of PneumoADIP was focused more on demand creation whilst the efforts of Rotavirus ADIP were focused more on ensuring that the appropriate clinical trials were conducted, because of observed side-effects.

The comparison with Hib vaccines is more subtle than it appears. The timescale for uptake and access to Hib vaccines before the Hib Initiative and revised WHO recommendations for Hib vaccines was very slow. However, if you look at adoption of Hib vaccines after these events, it was extremely quick. The timescale for pneumococcal vaccines will therefore be shorter if there is adequate vaccine supply capacity and if there is active education and advocacy.

There is a risk that this might not be the case since PneumoADIP has been replaced by another initiative, Accelerated Vaccine Introduction (AVI), which some have perceived to be slow in getting up to speed. A possible outcome is that there will be no large differences in timescale for access; according to some of the interviewees, any decrements in timescale of access will be no more than 50% of what was observed for Hib vaccines. Nevertheless even taking 2 years off the time taken for the introduction of Hib vaccines will have significant health impacts (unless administrative and health system capacity problems may negate such access-time benefits).

Level of coverage

Once a country adopts a vaccine, it usually takes 2-3 years to achieve full coverage depending on health system infrastructure and available financing. It is plausible however that the level of coverage may be lower in larger countries such as India and Sudan. An alternative view is that uptake of pneumococcal vaccines (and the level of coverage) may be higher than that for Hib and rotavirus vaccines. This is because, over time, developing countries have become more informed and familiar with discussions about the value of national immunisation programs.

Specifically, developing countries have become more informed about pneumococcal disease (mainly as a spillover from the introduction of Hib vaccines into national immunisation programmes). Another reason why the level of coverage could be higher for pneumococcal vaccines (relative to Hib and rotavirus vaccines) is that the pneumococcal vaccines cover more serotypes of the causative organism and there is less controversy about the efficacy safety profile of pneumococcal vaccines compared to rotavirus vaccines, for example. Hence, clinical adoption in national immunisation programs will, therefore, probably be faster for pneumococcal vaccines.

Technical characteristics and vaccine distribution

With regards to this indicator, it was stated that there was a marginal difference between the 10-valent and 13-valent pneumococcal vaccines when one looks at the global serotyping of the disease-causing agent. There is however a significant gap in clinical utility when one moves from the 7-valent to the 10-valent.

There are 'extreme' differences in the business models of the two main vaccine manufacturers (GSK and Wyeth, now Pfizer) and this will have implications as to which

vaccine is distributed in low-income countries. Wyeth had traditionally employed a business model that focuses on major markets (i.e. high-income countries) and is likely to view the AMC (and markets in low-income countries) as less lucrative. GSK, on the other hand, has a well established business model of recouping revenues from low-income countries. The 10-valent vaccine is therefore more likely to be distributed in low-income countries; the 13-valent vaccine may become the most widely used product in high-income countries.

The choice between the 10-valent and 13-valent vaccines may depend on a trade-off between coverage of three additional serotypes and coverage of non-typable strains of *Haemophilus influenzae* (NTHi). In the 10-valent vaccine, GSK has conjugated the polysaccharide elements to a protein from NTHi; this in theory may offer some additional conferred immunity against NTHi. This theoretical expectation has not, at the moment, been validated through additional clinical studies.

Overall, whilst it seems the 13-valent vaccine may be more clinically appealing than the 10-valent vaccine, whether the 13-valent vaccine will be the most widely distributed depends on other factors such as:

- Purchase prices (in particular the dynamics of the relationship between PAHO and UNICEF),
- Clinical preferences that translates into differences in purchasing choices. This will in part be influenced by donors' preferences, WHO recommendations on which vaccines are therapeutically superior, and how well-informed low-income countries are with respect to the differences in technical characteristics of the vaccines
- Technical supply constraints and strategic behaviour of the vaccine suppliers. If, as expected, GSK becomes the main player in the pneumococcal vaccine market, then one would expect the 10-valent vaccine to be widely distributed and used. This will also be the case if Wyeth (now Pfizer) chooses not to participate.

Annexe 2: Counterfactuals Excel spreadsheet guide

Counterfactual 1

1. Demand and supply tab:

a. Demand

Base: demand trend => to enter figures

India: demand trend => to enter figures

India adjusted base: Base – (1 - India demand included[36]) * India

Demand forecast: India adjusted base* Demand realisation

b. Supply

i. Industry

Capacity: capacity adjusted multinational1 + capacity adjusted multinational2 + capacity adjusted emerging

Quantity sold: quantity sold multinational1 + quantity sold multinational2 + quantity sold emerging

Quantity sold (cumul): quantity sold cumul multinational1 + quantity sold cumul multinational2 + quantity sold cumul emerging

Gross revenue: gross revenue multinational1 + gross revenue multinational2 + gross revenue emerging

Average sale price: if(quantity sold, gross revenue/quantity sold,)

- ⇨ If the quantity sold is >0 your average sale price will be = gross revenue/quantity sold, if not it will be 0 (if you do not sell anything).

Shortfall: demand forecast-quantity sold

ii. Pre build out period

Multinational 1 - Active in pre build out period: if(and(active in pre build out period=YES, current year < end pre build out period multinational1), 1, 0)

- ⇨ If the option pre build period in activated (in 'assumptions' tab) and you are in a pre build out period (the current year is situated before the end date of the pre build out period) you will write 1 and if not (if you are not before the end of the pre build out period) you will write 0.

Multinational 2 - Active in pre build out period: if(and(active in pre build out period=YES, current year < end pre build out period multinational2), 1, 0)

36 See 'assumptions' tab

iii. Multinational-1

Capacity: pre build out capacity multinational1 + outage adjusted capacity multinational1

Capacity adjusted = capacity

Quantity sold: min(capacity adjusted multinationa1, demand forecast – quantity sold multinational2 – quantity sold emerging)

Quantity sold cumul$_n$: Quantity sold$_n$ + Quantity sold cumul$_{n-1}$

Quantity sold in first 5 years$_n$: Quantity sold in first 5 years$_{n-1}$ + quantity sold$_n$ * active in pre build out period$_n$

Average sale price: if(quantity sold = 0, 0, if(and(active in pre build out period = YES, current year< multinational pre build-out period end), pre-build-out price multinational 1, if(and(active in pre build out period = NO, current year< multinational pre build-out period end),0, supply price multinational 1) * inflation adjustment))

- ⇨ If you sell something (quantity sold>0), the pre-build-out period is activated and you are in a pre-build-out period you will report the pre build out price for multinational1. If your sell something but the pre-build-out period is not activated and you are in a pre-build-out period you will report 0. If your sell something but the pre-build-out period is not activated and you are in a pre-build-out period you will report 0. If you sell something but the pre-build-out period is not activated and you are not in a pre-build-out period you will report the supply price for multinational1

Gross revenue: average sale price * quantity sold

iv. Multinational-2

Quantity sold: min(capacity adjusted multinational2$_n$, demand forecast$_n$ – quantity sold emerging$_n$ – (1 – switching rate) * quantity sold multinational1$_{n-1}$)

v. Emerging

Capacity: outage adjusted capacity emerging[37]

Quantity sold$_n$: min(capacity adjusted emerging$_n$, demand forecast$_n$ – (1 – switching rate) * (quantity sold multinational1$_{n-1}$ + quantity sold multinational2$_{n-1}$)

vi. Adjustments

Firm discount factor$_n$: Firm discount factor$_{n-1}$ * 1 / (1 + firm discount rate[38])
Inflation adjustment$_n$: Inflation adjustment$_{n-1}$*(1+inflation indexing)

Cost adjustment$_n$: Cost adjustment$_{n-1}$ * 1 / (1 + annual cost growth)

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37 See 'cost&revenue'

38 See 'cost&revenue' tab supply/industry

2. Cost&Revenue tab:

c. Multinational-1/2 and emerging-market supplier

Pre build out period. Incremental production cost per dose: incremental cost per dose * cost adjustment * inflation adjustment

Quantity sold**: quantity sold in 'demand' tab

Average price: average sale price in 'demand' tab

i. Pre build out

Pre build out capacity: if(current year >= end pre build out period multinational1, 0, if(current year >= beginning pre build out period, number of doses in pre build out period, 0))

- ⇨ If you are in a pre build out period (between starting date and ending date) you will report the number of doses in pre build out period, if not (if you are not in a pre build out period) you will report 0.

Pre build out sales: max(0, quantity sold – outage adjusted capacity)

Pre build out profits: pre build out sales * (average price - Pre build out period.incremental production cost per dose)

ii. New plant

Capacity: if(current year >= beginning of new plant, number of doses for the new plant, 0)

Outage adjusted capacity: if(and(year of operation = plant outage year (8), unplanned outages = YES), 0, capacity)

- ⇨ If in the row 'year of operation' your value equals 8 (plant outage year in 'assumptions' tab) and if in your 'assumptions' tab your option 'unplanned outages' is activated (=YES) you will write 0, if not you will report the value in 'capacity".

Quantity sold: min(outage adjusted capacity, quantity sold**)

Capital cost: if(beginning of new plant = current year, cost of the number of doses for the new plant, 0)

- ⇨ If the current year is when you begin to produce with your new plant you will report the cost associated to the number of doses.

Capital build up$_n$: (capital cost$_{n+1}$ * 5 year capital buildup schedule year 5 + capital cost$_{n+2}$ * 5 year capital buildup schedule year 4 + capital cost$_{n+3}$ * 5 year capital buildup schedule year 3 + capital cost$_{n+4}$ * 5 year capital buildup schedule year 2 + capital cost$_{n+5}$ * 5 year capital buildup schedule year 1) * cost adjustment

Year of operation$_n$: if(capital cost$_n$ > 0, 1, if(year of operation $_{n-1}$>0, year of operation$_{n-1}$+1,0))

- ⇨ It is a year meter starting counting (1) when the new plant is built.

Semivariable costs$_n$: if(quantity sold$_n$+ quantity sold$_{n-1}$ > 0, semivariable cost per plant multinational1, 0) * cost adjustment

Variable costs: quantity sold * Variable cost per dose multinational1 * cost adjustment

Total cost: Semivariable costs+ Variable costs

Gross revenue: quantity sold * average price

Net revenue: gross revenue – (Semivariable costs+ Variable costs)

3. Assumptions tab:

d. Firm parameters

i. Discount rate

Used for the NPV calculation for the firms ('opportunity cost" notion).

ii. Unplanned outages

This is an indicator variable (Yes or No) for whether the firm experiences 'unplanned outages' resulting in shutdown of operations for one year while still incurring fixed costs. This input is set as Yes and the outage occurs 8 years after the plant has been set up.

e. Demand parameters

i. Demand realisation

This is a sensitivity parameter that determines how much of the demand forecast is actually realised.

ii. India demand included

This is a sensitivity parameter that determines the degree to which India is included in the demand forecast (proportion of people in India receiving the vaccine. 100%=India's forecast demand is fully realised).

f. Firm prices

i. Pre build out price

This is the price the firms would receive for one dose if they sell before the dedicated capacity comes on line (with the old plant for high income countries but producing for low income countries).

In Counterfactual 1 the pre build out price is equal to supply price as Unicef negotiates it (allowing the countries to get a price per dose not more expensive during the pre

build out period) whereas in Counterfactual 2 we have a country by country negotiation without Unicef procurement system.

ii. Supply price

This is the price the firms would receive for one dose once the new plan is built.

g. Costs for new plant

i. Variable cost per dose

This is the cost of production that changes with the quantity sold (eg: ingredients in the drug …).

ii. Semivariable cost per dose

This is the fixed cost of production that must be incurred before any quantity sold (eg: staff, machines …). These costs are not per year but happen just once until the production is decided to be increased or decreased.

h. Supply commitment

i. Date

These are the dates indicating the beginning of the pre build-out period and when the new plant has been set up (therefore the end of the pre build out period).

ii. Doses

This is the number of doses sold in million during the pre build out period and with the new plant.

iii. Capital costs

This is the cost in million dollars of setting up the new plant.

i. Firm assumptions

The annual cost growth is the increase of cost producing doses.

j. Other assumptions

i. Start date

This is the date when our model starts.

ii. Switching rate

This is the percentage of demand that can be shifted between suppliers in each year.
(from multi1 to multi2 or em,
from multi2 to multi1 or em,
from em to multi1 or multi2)

iii. Inflation indexing

This reflects the inflation rate (affects the selling price).

iv. Plant outage year

If capacity outages are on, plant is offline eight years after having being set up. The production is set to zero and factory costs are still paid.

k. 5 years capital buildup schedule

Year1: 20% of the costs of capital cost is paid
Year2: 20% of the costs of capital cost is paid
Year3: 20% of the costs of capital cost is paid
Year4: 20% of the costs of capital cost is paid
Year5: 20% of the costs of capital cost is paid

l. Incremental cost per dose

This is the cost of producing vaccines for supply to low income countries using existing plant capacity that has been built for supply to high income countries. This is the incremental cost of supplying in pre build out period.
Note that the existing production plant may have been existence prior to our reference year (2005)

m. NPV calculation tab:

Pre build-out:

NPV of profits: sumproduct(firm discount factor, pre build out profits multinational1, 1/inflation adjustment)

New plant:

NPV of operating profits: sumproduct(firm discount factor, gross revenue new plant multinational1, 1/inflation adjustment) – sumproduct(firm discount factor, total cost new plant multinational1, 1/cost adjustment)

NPV of capital costs: max(0, sumproduct(firm discount factor, capital buildup new plant multinational1, 1/cost adjustment)

NPV of profits net of capital costs: NPV of operating profits - NPV of capital costs

Counterfactual 2

1. Demand and supply tab:

a. Demand

Base: demand trend => to enter figures

India: demand trend => to enter figures

India adjusted base: Base – (1 - India demand included[39]) * India

39 See 'assumptions' tab

Demand forecast: India adjusted base* Demand realisation

Actual demand facing Multinational1/2: if(current year<beginning of pre build out period, ' ', if(and(current year>=beginning of pre build out period, current year<new plant set up), Actual demand facing Multinational 1/2, demand forecast)))

b. Supply

i. Industry

Capacity: capacity adjusted multinational1 + capacity adjusted multinational2 + capacity adjusted emerging

Quantity sold: quantity sold multinational1 + quantity sold multinational2 + quantity sold emerging

Quantity sold (cumul): quantity sold cumul multinational1 + quantity sold cumul multinational2 + quantity sold cumul emerging

Gross revenue: gross revenue multinational1 + gross revenue multinational2 + gross revenue emerging

Average sale price: if(quantity sold, gross revenue/quantity sold,)

- ⇨ If the quantity sold is >0 your average sale price will be = gross revenue/quantity sold, if not it will be 0 (if you do not sell anything).

Shortfall: demand forecast-quantity sold

ii. Pre build out period

Multinational 1 - Active in pre build out period: if(and(active in pre build out period=YES, current year < end pre build out period multinational1), 1, 0)

- ⇨ If the option pre build period in activated (in 'assumptions' tab) and you are in a pre build out period (the current year is situated before the end date of the pre build out period) you will write 1 and if not (if you are not before the end of the pre build out period) you will write 0.

Multinational 2 - Active in pre build out period: if(and(active in pre build out period=YES, current year < end pre build out period multinational2), 1, 0)

iii. Multinational-1

Capacity: pre build out capacity multinational1 + outage adjusted capacity multinational1

Capacity adjusted = capacity

Quantity sold: min(capacity adjusted multinationa1, demand forecast – quantity sold multinational2 – quantity sold emerging, Actual demand at $50 per dose Multinational1)

Quantity sold cumul$_n$: Quantity sold$_n$ + Quantity sold cumul$_{n-1}$

Quantity sold in first 5 years$_n$: Quantity sold in first 5 years$_{n-1}$ + quantity sold$_n$ * active in pre build out period$_n$

Average sale price: if(quantity sold = 0, 0, if(and(active in pre build out period = YES, current year< multinational pre build-out period end), pre-build-out price multinational 1, if(and(active in pre build out period = NO, current year< multinational pre build-out period end),0, supply price multinational 1) * inflation adjustment))

- ⇨ If you sell something (quantity sold>0), the pre-build-out period is activated and you are in a pre-build-out period you will report the pre build out price for multinational1. If your sell something but the pre-build-out period is not activated and you are in a pre-build-out period you will report 0. If your sell something but the pre-build-out period is not activated and you are in a pre-build-out period you will report 0. If you sell something but the pre-build-out period is not activated and you are not in a pre-build-out period you will report the supply price for multinational1

Gross revenue: average sale price * quantity sold

iv. Multinational-2

Quantity sold: min(capacity adjusted multinational2$_n$, demand forecast$_n$ – quantity sold emerging$_n$ – (1 – switching rate) * quantity sold multinational1$_{n-1,}$ Actual demand at $50 per dose Multinational2)

v. Emerging

Capacity: outage adjusted capacity emerging[40]

Quantity sold$_n$: min(capacity adjusted emerging$_n$, demand forecast$_n$ – (1 – switching rate) * (quantity sold multinational1$_{n-1}$ + quantity sold multinational2$_{n-1}$)

vi. Adjustments

Firm discount factor$_n$: Firm discount factor$_{n-1}$ * 1 / (1 + firm discount rate[41])

Inflation adjustment$_n$: Inflation adjustment$_{n-1}$*(1+inflation indexing)

Cost adjustment$_n$: Cost adjustment$_{n-1}$ * 1 / (1 + annual cost growth)

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40 See 'cost&revenue"

41 See 'cost&revenue" tab supply/industry

2. Cost&Revenue tab:

c. Multinational-1/2 and emerging-market supplier

Pre build out period.incremental production cost per dose: incremental cost per dose * cost adjustment * inflation adjustment

Quantity sold**: quantity sold in 'demand" tab

Average price: average sale price in 'demand" tab

i. Pre build out

Pre build out capacity: if(current year >= end pre build out period multinational1, 0, if(current year >= beginning pre build out period, number of doses in pre build out period, 0))

- ⇨ If you are in a pre build out period (between starting date and ending date) you will report the number of doses in pre build out period, if not (if you are not in a pre build out period) you will report 0.

Pre build out sales: max(0, quantity sold – outage adjusted capacity)

Pre build out profits: pre build out sales * (average price - Pre build out period.incremental production cost per dose)

ii. New plant

Capacity: if(current year >= beginning of new plant, number of doses for the new plant, 0)

Outage adjusted capacity: if(and(year of operation = plant outage year (8), unplanned outages = YES), 0, capacity)

- ⇨ If in the row 'year of operation' your value equals 8 (plant outage year in 'assumptions' tab) and if in your 'assumptions' tab your option 'unplanned outages' is activated (=YES) you will write 0, if not you will report the value in 'capacity".
- ⇨

Quantity sold: min(outage adjusted capacity, quantity sold**)

Capital cost: if(beginning of new plant = current year, cost of the number of doses for the new plant, 0)

- ⇨ If the current year is when you begin to produce with your new plant you will report the cost associated to the number of doses.

Capital build up$_n$: (capital cost$_{n+1}$ * 5 year capital buildup schedule year 5 + capital cost$_{n+2}$ * 5 year capital buildup schedule year 4 + capital cost$_{n+3}$ * 5 year capital buildup

schedule year 3 + capital $cost_{n+4}$ * 5 year capital buildup schedule year 2 + capital $cost_{n+5}$ * 5 year capital buildup schedule year 1) * cost adjustment
Year of $operation_n$: if(capital $cost_n$ > 0, 1, if(year of operation $_{n-1}$>0, year of $operation_{n-1}$+1,0))

- ⇨ It is a year meter starting counting (1) when the new plant is built.

Semivariable $costs_n$: if(quantity $sold_n$+ quantity $sold_{n-1}$ > 0, semivariable cost per plant multinational1, 0) * cost adjustment

Variable costs: quantity sold * Variable cost per dose multinational1 * cost adjustment

Total cost: Semivariable costs+ Variable costs

Gross revenue: quantity sold * average price

Net revenue: gross revenue – (Semivariable costs+ Variable costs)

3. NPV calculation tab:

d. Multinational-1/2 and emerging-market supplier

Pre build-out:

NPV of profits: sumproduct(firm discount factor, pre build out profits multinational1, 1/inflation adjustment)

New plant:

NPV of operating profits: sumproduct(firm discount factor, gross revenue new plant multinational1, 1/inflation adjustment) – sumproduct(firm discount factor, total cost new plant multinational1, 1/cost adjustment)

NPV of capital costs: max(0, sumproduct(firm discount factor, capital buildup new plant multinational1, 1/cost adjustment)

NPV of profits net of capital costs: NPV of operating profits - NPV of capital costs

4. Assumptions tab:

e. Firm parameters

i. Discount rate

Used for the NPV calculation for the firms ('opportunity cost" notion).

ii. Unplanned outages

This is an indicator variable (Yes or No) for whether the firm experiences 'unplanned outages' resulting in shutdown of operations for one year while still incurring fixed costs. This input is set as Yes and the outage occurs 8 years after the plant has been set up.

f. Demand parameters

i. Demand realisation

This is a sensitivity parameter that determines how much of the demand forecast is actually realised.

ii. India demand included

This is a sensitivity parameter that determines the degree to which India is included in the demand forecast (proportion of people in India receiving the vaccine. 100%=India's forecast demand is fully realised).

g. Firm prices

i. Pre build out price

This is the price the firms would receive for one dose if they sell before the dedicated capacity comes on line (with the old plant for high income countries but producing for low income countries).

In Counterfactual 1 the pre build out price is equal to supply price as Unicef negotiates it (allowing the countries to get a price per dose not more expensive during the pre build out period) whereas in Counterfactual 2 we have a country by country negotiation without Unicef procurement system.

ii. Supply price

This is the price the firms would receive for one dose once the new plan is built.

h. Costs for new plant

i. Variable cost per dose

This is the cost of production that changes with the quantity sold (eg: ingredients in the drug …).

ii. Semivariable cost per dose

This is the fixed cost of production that must be incurred before any quantity sold (eg: staff, machines …). These costs are not per year but happen just once until the production is decided to be increased or decreased.

i. Supply commitment

i. Date

These are the dates indicating the beginning of the pre build-out period and when the new plant has been set up (therefore the end of the pre build out period).

ii. Doses

This is the number of doses sold during the pre build out period and with the new plant.

iii. Capital costs

This is the cost of setting up the new plant.

j. Firm assumptions

The annual cost growth is the increase of cost producing doses.

k. Other assumptions

i. Start date

This is the date when our model starts.

ii. Switching rate

This is the demand that can change suppliers in each year.
(from multi1 to multi2 or em,
from multi2 to multi or em,
from em to multi1 or multi2)

iii. Inflation indexing

This reflects the inflation rate (affects the selling price).

iv. Plant outage year

If capacity outages are on, plant is offline eight years after having being set up. The production is set to zero and factory costs are still paid.

l. 5 years capital buildup schedule

Year1: 20% of the costs of capital cost is paid
Year2: 20% of the costs of capital cost is paid
Year3: 20% of the costs of capital cost is paid
Year4: 20% of the costs of capital cost is paid
Year5: 20% of the costs of capital cost is paid

m. Incremental cost per dose

This is the cost of producing vaccines for supply to low income countries using existing plant capacity that has been built for supply to high income countries. This is the incremental cost of supplying in pre build out period.
Note that the existing production plant may have been existence prior to our reference year (2005)

Annexe 3: Initial industry data collection

18.1.7 List of companies interviewed

Merck	Shanta Biotechnics
Wyeth/ Pfizer	Serum Institute of India
GSK	Panacea Biotec
Sanofi	Chengdu Institute of Biological Products
Novartis	BioManguinhos/ Fiocruz
Crucell	Centro de Química Biomolecular

18.1.8 Initial interview guide

AMC Baseline Study – Industry level

Interview Guide

1. In your firm's opinion, what are the main obstacles for getting vaccines to poor people in developing countries?

2. What is your preferred option for encouraging vaccine development for the poor in developing countries?

3. Has there ever been any arrangement similar to this AMC before? If yes, please tell us about it. Agreement might be similar in principle but differed in practise.

4. In the past was your company part of any other arrangement similar to AMC? What is the status of the arrangement now?

5. Do you think in future your company strategy will change either in regard to pneumococcal vaccines or in more general towards vaccine discovery, production and/or manufacture?
- What factors do you think would drive this?
- What role might an AMC play in these changes?

Industry Structure

1. What long term impact do you foresee the AMC having on the vaccine industry?
- Does your company foresee any positive impact of this AMC on the production and distribution of pneumococcal vaccines such as increase in vaccine production capacity, increase in number of firms?
- Does your company foresee any detrimental impact of AMC on development and distribution of pneumococcal vaccines such as monopoly creation and saturation of resources in one area only?

2. Do you see major structural changes in the vaccine industry in the more immediate term?
- What do you think will drive these?
- What is the contribution of the AMC to this change?
- Will AMC change things for some firms and not others?

3. Will these changes impact differently on firms in emerging markets on the one hand and advanced markets on the other? Will the AMC impact differently on firms in emerging or advanced markets?
- What would explain the differences?
- How will this affect your company?

Research & Development

1. What is your opinion about the current status of pneumococcal vaccine R&D within the industry as a whole? Has this changed since 2005?

2. What is current status of vaccine R&D in your company?
- How much of the total R&D budget is spent on vaccine R&D in your company?
- Has this changed since 2005?
- If so, what has led to these changes?

3. What is the focus of vaccine R&D in your company?

4. When did your company commence pneumococcal vaccine research and development?
- What drove this decision?
- How much R&D funding is directed to pneumococcal vaccines research in your company?
- Where are the R&D projects in your pipeline?
- What clinical trials of your pneumococcal vaccines have been conducted (including phase, geographical location, and enrolment numbers)?
- When were the IND applications lodged? When were the dossiers submitted to which regulatory authorities?

5. What factors will have an impact on your investments in pneumococcal vaccine R&D?
- What role will the AMC have in these changes? Why?
- Did the 2007 initial announcement of the AMC by Finance Ministers and world leaders have any effect on you companies spending decisions? [i.e., did the expectation that the AMC would be formalised and signed have any effect?]
- Has the AMC changed your clinical development plans for your pneumococcal vaccine/s?
- Has the AMC changed your registration plans for your pneumococcal vaccine/s?

6. If you had been able to design an incentive to stimulate pneumococcal vaccine R&D, what would you have preferentially chosen? For example, AMC, direct grant funding, patent extensions, PDP partnering, Priority Review Voucher etc

Production facilities

1. What is current status of pneumococcal vaccine manufacturing capacity in your company?
- How many doses of pneumococcal vaccines are produced annually?
- If you outsource manufacturing, who to, why and for how much?

2. Are you planning to change your investment into production facilities dedicated for pneumococcal vaccine?
- What are the reasons for this?
- If you are planning new plant for pneumococcal vaccines, where will this be?
- If you are not planning new plant for pneumococcal vaccines, how do you plan to manage increased production volumes?

3. Do you think the AMC will lead to increased investment in production facilities for pneumococcal vaccine?
- If yes, what proportion?
- What other options do you think could stimulate increased investment into pneumococcal vaccine plant?

4. If you had been able to design an incentive to stimulate production, what would you have preferentially chosen? For example, AMC, direct subsidy, GAVI procurement fund etc

Market

1. What is your company's view on the impact the AMC will have on vaccine markets?
- Will the AMC create a more appealing market environment for pneumococcal vaccines?
- Do you think it will foster competition by improving investments from more firms in pneumococcal vaccine market?
- Do you think the AMC will improve the availability of pneumococcal vaccines in general, and specifically in countries that are not GAVI-eligible?

2. What other alternatives do you see? Is the AMC your preferred option?

3. Currently, which are main markets for your company's vaccine business? Can you give specific percentages in each region?

4. Are you supplying vaccines to UNICEF/WHO?
- If yes, what percentage of sales of vaccines in your company does this represent? How does this compare with 2005?

Outcome mapping questions

Questions below in the outcome mapping section are designed to encourage interviewees to think about what sort of behaviour change would be necessary in order to supply poor people in developing countries with pneumococcal vaccines. This is to encourage a move away from narrow input/output models and to establish some baseline assessment of what sort of behaviour change might contribute to GAVI's overall goal

1. What are the necessary/ good/ fantastic changes you would like to see in different stakeholders to improve the availability of vaccines in developing countries?

2. What are the necessary/ good/ fantastic changes you would like to see in different stakeholders to improve R&D investment in vaccines?

3. What are the necessary/ good/ fantastic changes you would like to see in different stakeholders to improve vaccine production capacities or no of doses manufactured?

4. If it were up to you, what would be your preferred policies to support your pneumococcal vaccine R&D programme?

5. If it were up to you, what would be your preferred policies to support your pneumococcal vaccine manufacturing plans?

4. In your opinion will AMC provoke any or all of changes you would like to see to improve availability of and access to vaccines for poor people? What other initiatives could stimulate changes? Who should introduce these changes?

5. What role could your company play in stimulating change? Under what conditions might your company play this kind of a role?