GROUP B STREPTOCOCCUS VACCINE

FINANCIAL ANALYSIS

World Health Organization

FULL VALUE OF VACCINE ASSESSMENT

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Group B streptococcus vaccine: full value of vaccine assessment. Financial analysis

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Acknowledgements

Executive summary

As part of the development of a value assessment for a group B streptococcal (GBS) vaccine, an assessment was conducted on the return on investment and financial sustainability for vaccine manufacturers of developing and commercializing a GBS vaccine.

The assessment indicated that the development of a GBS vaccine could be finalized by 2028 with a total cost of some US$ 226–378 million for completion of the clinical development and building a dedicated manufacturing plant. After achieving the first registration and WHO prequalification the vaccine could be rolled out globally as of 2029 based on countries' burden of disease, strength of immunization programme and maternal immunization platform.

Subject to different assumptions on vaccination schedules and target populations, the number of introducing countries and the strength of competition, the vaccine could generate up to US$ 8 billion in sales over the period 2029–2040. This turnover could increase to US$ 16 billion with a two-dose schedule with priming in adolescence and boosting during pregnancy or could be lowered to US$ 1.9 billion if two competitors are in the market.

As a result, the net present value (NPV) of the initiative is US$ 742 million in the base case, providing vaccine manufacturers with a significant return on the initial investment and hence making the vaccine development enterprise financially viable. The NPV can range up to US$ 1.6 billion for two-dose scenarios. Importantly, the NPV remains positive under the most aggressive competition or most conservative clinical development scenarios. Of all pessimistic scenarios (lack of Gavi support, higher COGS, stronger competition, need for full efficacy trial) the NPV turns marginally negative (US$ -34 million) only under the most conservative clinical development scenario (i.e. the need for a full efficacy trial). The results of these more pessimistic scenarios are evidence of an acceptable level of risk of the initiative that can absorb most unexpected deterioration of the assumptions of the base case.

On the basis of the simulated plan and market forces, the business case for the development of a GBS vaccine can be considered financially sustainable. It is likely to guarantee a sizeable return on investment without the need for any incentive beyond the market. These results should encourage manufacturers to focus their efforts on the development of a GBS vaccine that can have not only a solid public health value assessment but also a commercial one. Nonetheless, the role of donors or financers can still prove very important in de-risking the development of the GBS vaccine that, especially at this stage, is still affected by many levels of uncertainty.

1. INTRODUCTION

Globally, group B streptococcal (GBS) disease is estimated to cause at least 409 000 (UR, 144 000–573 000) cases of serious infections in mothers, their fetuses or infants and 147 000 (UR, 47 000–273 000) stillbirths and infant deaths annually *(1)*. Because of the high burden of disease and the technical feasibility of development, GBS was identified as a priority for the development of a vaccine for maternal vaccination by the WHO Product Development for Vaccines Advisory Committee *(2, 3)*.

Several vaccines have been and continue to be in development through large multinational pharmaceutical companies as well as smaller companies supported by donor funding *(4)*. In the past, several programmes have failed or have been discontinued and none of the vaccines currently in clinical development have yet progressed beyond Phase II. They are therefore facing large investment decisions prior to realization of a licensed vaccine.

This report describes the potential financial outcomes that can be expected from successful development of a GBS vaccine that can attain global registration. The report also assesses whether specific additional financing is required to support the clinical development activities. It builds on previous work that described potential scenarios of demand for a GBS vaccine. The report should be read in conjunction with the other workstreams that will contribute to describing the full public health value assessment (FPHVP) – which includes the full health, economic and societal value of a vaccine to a broad range of global stakeholders, including from the perspective of low- and middle-income countries – and aims to explain the full direct (individual) and indirect (population) effects of a GBS vaccine.

2. OBJECTIVES

This report aims to assess the return on investment and financial sustainability for vaccine manufacturers of developing and commercializing a GBS vaccine delivered by maternal immunization. The assessment, which is based on a set of assumptions about prices, potential revenue and likely costs of development, provides a view of the financial attractiveness of development, manufacture and commercialization of the vaccine from the perspective of a commercial entity. A financial analysis based on the discounted cash flow (DCF) methodology has been used to assess, from a manufacturer's standpoint, the return on investment of the initiative, the potential need for non-market financial incentives and potential alternative financing avenues that can be used.

3. METHODS

The assessment employed a standard DCF methodology to compare positive and negative flows of cash generated by a project, discounting the flows of cash for the time value of money. If the result of consolidating all yearly flows of cash, called the net present value (NPV), is positive, the initiative can recover the initial costs, rewarding the capital invested at an appropriate rate based on the specific risk of the business and generating a surplus.

The analysis focuses on the period 2020–2040 to cover a sufficient number of years (12) during which the product is commercialized. The analysis therefore provides a balanced view of both negative and positive cash flows.

3.1 Profit and loss statement

A pro-forma profit and loss (P&L) was built to allow for the calculation of the free cash flow – ideally positive – made available by commercialization of the vaccine. The P&L statement included the following components:

Calculation of revenues
Calculation of revenues: For each year, based on the doses required by the programme as calculated in the demand forecast, the total revenues were calculated according to the formula "doses employed × price per dose" (see "Assumptions" section below for dose and price values).

Calculation of cost of goods sold (COGS)
For each year, based on the doses required by the programme as calculated in the demand forecast, the total costs of producing the doses of vaccine sold were calculated on the basis of the formula "doses employed × COGS per dose" (see "Assumptions" section for the value of COGS).

Calculation of costs of clinical trials and regulatory processes
For each year, the total cash disbursement required to finance the clinical development programme – inclusive of costs of clinical trials, clinical trial materials and regulatory processes – is calculated by adding all components (see "Assumptions" section for costs of clinical trials, regulatory processes and manufacturing of clinical materials). Those costs are to be expensed during the year in which they are incurred and therefore represent cash outflow.

Calculation of gross profit
For each year, gross profit was calculated as "Revenues – COGS".

Calculation of the investment in the manufacturing facility
For each year, the cash disbursement is calculated for the construction of the manufacturing plant (see "Assumptions" section for manufacturing facility investment). Those costs are capitalized and depreciated. Their disbursement contributes to the calculation of the free cash flow.

Calculation of depreciation

For each year, starting from the year of registration (assumed also as the year of start of depreciation of the costs incurred in the construction of the manufacturing plant), the depreciation amount was calculated as "total cost of manufacturing facility/depreciation rate" (see "Assumptions" section).

Calculation of sales, general and administrative (SG&A) costs

For each year, the total cost incurred for the sales force, marketing and administrative expenses was calculated as "total revenues $\times$ SG&A rate" (see "Assumptions" section for the SG&A rate).

Calculation of the operating margin

For each year, the operating margin was calculated as gross profit *minus* depreciation *minus* SG&A.

Calculation of income tax

For each year, the income tax due by the company producing and commercializing the vaccine was calculated as "operating margin $\times$ income tax rate" (see "Assumptions" section for the income tax rate).

Calculation of net result

For each year, the net result was calculated as the operating margin *minus* income tax.

3.2 NPV Calculation

The calculation of the NPV starts with the calculation of free cash flow – i.e. the amount of cash available to the company to operate.

For each year, the free cash flow generated by the company is calculated, adding back the non-financial items to the net result in line with the formula "net result + depreciation".

Once all cash flows were calculated, the NPV of the initiative was calculated by applying the appropriate discount rate for the relevant industry (see "Assumptions" below) in accordance with the following formula:

$$\frac{\sum_{t=0}^{n} \text{Cach Flow}^{t}}{(1 + \text{Discount Rate})^{t}}$$

where t is the number of time periods (i.e. years).

No residual value for the cash flow streams generated post-2040 has been included in this analysis.

4. ASSUMPTIONS

4.1 Vaccine demand

Drawing from the GBS vaccine demand forecast completed in late 2019, three scenarios were considered. Those scenarios vary by schedule (i.e. by the number and timing of doses given to an individual). The scenarios that were simulated in the GBS demand forecast and used in this analysis are shown in **Table 1**.

Table 1. Overview of scenario assumptions

	Base case	2 doses in pregnancy	Priming in adolescence
Schedule	1 dose 24–34weeks	2 doses 1st visit (24–34 weeks) + 2nd visit (later)	2 doses 1 with HPV + 1 dose (24–34 weeks)
Countries	First introduction in 2029 178 countries to introduce by 2040 16 countries to introduce after 2040		

The peak demand resulting from these scenarios ranged from 115 to 218 million doses annually in 2040 (**Fig. 1**).

Fig. 1. Demand under different scenarios (million doses)

- Sum of ANC 1 dose Dose Demand
- Sum of ANC 2 doses Dose Demand
- Sum of HPV 1 dose + ANC 1 dose Dose Demand
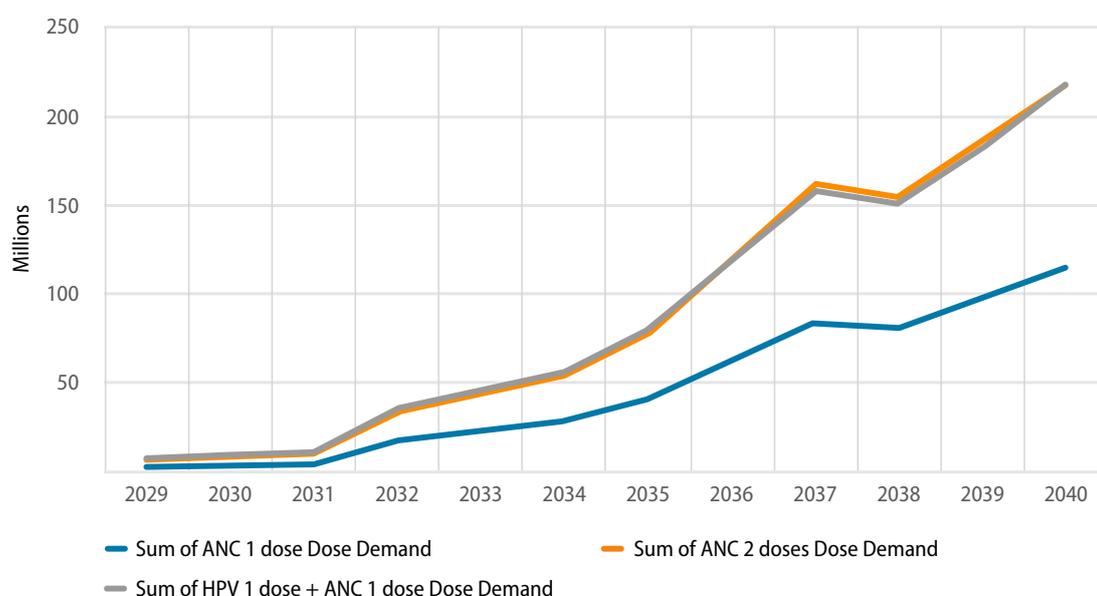
4.2 Vaccine prices

Vaccine price estimates were reached by both benchmarking prices and an analysis of COGS. Price benchmarking of rotavirus, pneumococcal conjugate and human papilloma virus vaccine in a range of country income levels was conducted averaging the country values from the WHO Mi4A vaccine price database.

Table 2. **Human papillomavirus vaccine (HPV), Pneumococcal conjugate vaccine (PCV) and Rotavirus vaccine (RV) average price per dose stratified by income group**

Country income level, 2018 sample size	Average price per dose (US$)					
	2013	2014	2015	2016	2017	2018
HIC, *n*=49	41	45	36	47	45	49
UMIC, *n*=34	51	21	15	16	20	17
LMIC, *n*=41	6	5	5	4	5	4
LIC, *n*=30		2	3	4	3	3

HIC: high-income countries; UMIC: upper middle-income countries; LMIC: lower middle-income countries; LIC: low-income countries.

An analysis of COGS provides a floor price for the lowest income countries and serves as a comparator to the other new vaccines used for benchmarking and is particularly relevant in lower-income countries. Based on the very limited information currently available on the vaccine characteristics and manufacturing processes, COGS was estimated at US$ 2.50 per dose. It is important to note that the volume of production can have a strong effect on COGS so any significant decrease in the anticipated volume of doses sold for an individual manufacturer could result in increased COGS. A higher COGS scenario of US$ 4 has been simulated. A lower COGS scenario is not simulated as it would directly result in an improvement in the baseline NPV.

As result of the above consideration, price assumptions by country income group have been defined as shown in **Table 3**, splitting the market into three segments.

Table 3. **Price assumptions by country income group**

Market segments	Price per dose (US$)
High income countries *n*=51	50.00
Upper middle-income countries *n*=22	15.00
Lower middle-income and low-income countries • Lower middle-income countries (Gavi and non-Gavi eligible) *n*=35 • Low income countries (Gavi eligible) *n*=49	3.50

The analysis assumes the same price per dose regardless of the number of doses required. Consequently, a vaccine with a two-dose schedule will enhance the business case, even if those circumstances will create additional implementation costs. It is possible that a two-dose schedule will result in a lower price per dose.

4.3 Timeframe

The analysis was performed on the basis of a 20-year timeframe from 2020 to 2040 covering the time for development and commercialization. On the assumption of a product launch in 2029, 12 years of sales were included in the base case.

4.4 Clinical development and manufacturing investments

4.1 Clinical trial costs

The costs and cash outflow for all planned clinical trials were estimated as follows:

PHASE 1 | Completed prior to 2020: US$ 6.8 million.

PHASE 2 | Completed between 2020 and 2022: US$ 16.8 million.

PHASE 3 | Completed between 2023 and 2027 with 7000 subjects: US$ 52.3 million based on the assumption that an immunogenicity trial will be acceptable for the primary registration. There is significant uncertainty regarding this assumption and a much larger and longer efficacy trial may be required. Under this more conservative assumption, 40 000 subjects will be required for a Phase 3 trial that will span eight years from 2027 to 2034 at a total cost of US$ 204.5 million. Those estimates are based on a total cost per subject of 4.612 USD[1], actualised to 2020 and include regulatory and manufacturing related costs.

4.2 Manufacturing facility investment

Expenditure (primarily capital expenditure) of US$ 150 million was estimated for the period 2023–2028[2].

The combined disbursement for clinical development and manufacturing is assumed to total US$ 226 million on the assumption of an immunogenicity trial and US$ 378 million in the full efficacy trial scenario.

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[1] https://doi.org/10.1016/j.vaccine.2009.07.077

[2] https://doi.org/10.1016/j.vaccine.2017.06.003

4.5 Other market and financial assumptions

5.1 Competition

The base case scenario was developed on the assumption that only one manufacturer reaches the market and commercializes the vaccine for the entire period, benefitting from the total return on the sales of the GBS vaccine. A more conservative scenario has also been simulated whereby a second manufacturer licenses a product in 2034 and over a period of three years can gain a 40% market share that is equally split across the three market segments, namely: (a) high-income countries; (b) upper middle-income countries; and (c) lower middle-income countries/low-income countries.

5.2 Plant depreciation rate

Using the United States Generally Accepted Accounting Practices (GAPP), a period of 15 years was used to depreciate the facilities.

5.3 SG&A rate as a percentage of revenues

A proportion of 14% of total revenues was used as the SG&A rate. This percentage is based on a proxy represented by the SG&A expenditure reported in 2019 by Sanofi in its annual report for the vaccine business.

5.4 Discount rate

In accordance with a recent analysis by Di Masi et al. *(5)* a discount rate of 10.5% has been used in the calculation. This discount rate is higher than the weighted average cost of capital (WACC) of 8.55% calculated by the New York University Stern Business School for pharmaceutical and biotechnology companies *(6)*. The higher discount rate (also known as the "hurdle rate") used in evaluating projects and deals reflects the additional return – in this case 2% that companies normally require in their investment above the basic reward of debt and equity as represented by the WACC.

5.5 Taxation rate

Using estimates of the Tax Foundation from 2019 *(7)*, the average worldwide taxation rate of 23% was applied.
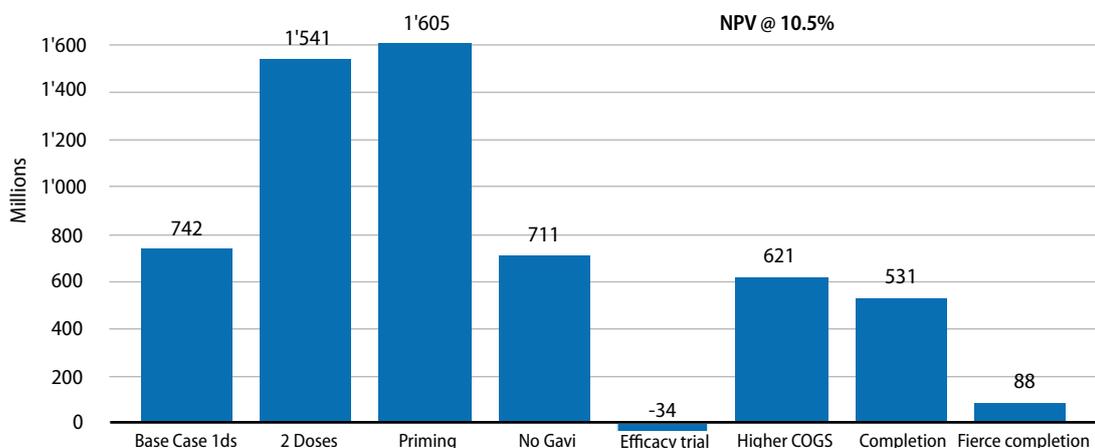
5. RESULTS

The NPV of GBS vaccine development and commercialization was calculated for eigth scenarios – the three scenarios developed in the demand forecast plus five sensitivity analysis scenarios to capture the impact of: (a) the need for an efficacy trial; (b) a higher cost of good; and (c) the presence of a competitor in the market; (d) the presence of two competitors in the market; (e) the absence of the positive impact of Gavi support (**Fig. 2**).

Fig. 2. Assessment of total revenues over 11 years in different scenarios
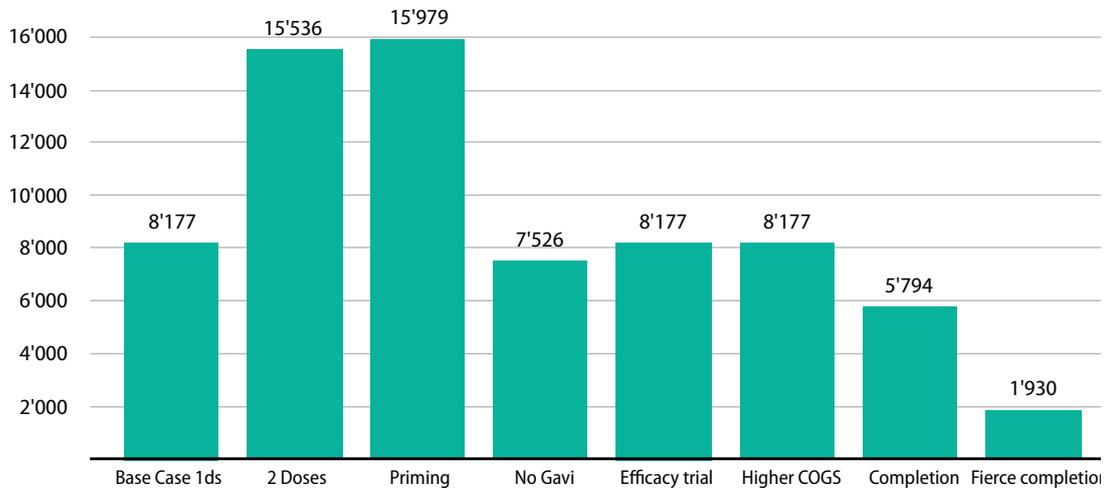
The NPV is positive in all evaluated cases where no efficacy trial is required and ranges from US$ -34 million to US$ 1.6 billion, depending on the scenario (**Fig. 3**). These results are highly dependent on revenue from high-income countries which represents approximately 2/3 of all revenue in the scenarios. The circumstances under which an efficacy trial may be required result in an NPV equal to 0.

Fig. 3. Assessment of the NPV in different scenarios

6. CONCLUSIONS

The financial analysis resulted in a positive NPV for the development of a GBS vaccine across all scenarios, thus indicating full commercial viability for this product for a vaccine manufacturer. No additional financial support appears to be required for manufacturers to pursue the development of the GBS vaccine. There is no apparent need either for reducing the cost of clinical development (by push funding) or by de-risking the prospective demand (by pull funding).

However, this result is dependent on several important conditions that need to be met, including the three mentioned below that represent the highest risks for a vaccine developer:

- Significantly higher **clinical development costs** that would be associated with an efficacy trial represent the largest risk to a profitable business model for the first manufacturer (or others that may be in late-stage development prior to licensure of the first vaccine).

- The assumption of **no or moderate competition** with all global revenue earned by one manufacturer or with the first-to-market retaining a share of 60% or above also has significant impact on the profitability of the vaccine. A second or third manufacturer in the market would gain market share at the expense of the first and would thus lower the overall revenue and financial sustainability for each manufacturer. It is also possible that the second or third manufacturer would incur lower development costs – while the first manufacturer's development costs would be likely to remain constant regardless of the number of manufacturers that follow. This could allow for more aggressive pricing strategies to gain a relevant share of the market; for instance, three competitors in the market from the second year, reducing the market share of the first-to-market to 20% by the fifth year, would cut the revenues and NPV of the first-to-market by three quarters.

- The revenues are highly dependent on **registration and use in high-income countries** which would provide two thirds of revenue during the first decade after licensure. Inability to achieve registration or a significantly lower demand in this market segment will greatly affect the profitability of the vaccine.

A full understanding of potential future demand in countries of all income levels will be important in order to support awareness and advocacy efforts with potential manufacturers. It is equally important to understand the most likely regulatory pathway to approval and the type of pivotal study required since this choice is the one that is most likely to affect the GBS vaccine business case.

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