Measles-Rubella Microarray Patch Vaccines:

A Business Case Analysis

PATH

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Please send any comments or feedback on this document to maps@path.org.

Mailing Address
PO Box 900922
Seattle, WA 98109 USA

Street Address
2201 Westlake Avenue
Suite 200
Seattle, WA 98121 USA

www.path.org

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Abbreviations

BioE	Biological E
CAPEX	capital expenditure
CDMO	contract development and manufacturing organization
COGS	cost of goods sold
DCVM	developing country vaccine manufacturer
DRC	Democratic Republic of the Congo
GNI	gross national income
GVMM	Global Vaccine Market Model
IRR	internal rate of return
LMIC	low- and middle-income countries
M&RI	Measles & Rubella Initiative
MAP	microarray patch
MCV	measles-containing vaccine
MCV1	first dose of measles-containing vaccine
MI4A	WHO Market Information for Access
MMR	measles-mumps-rubella
MMRV	measles-mumps-rubella-varicella
MNC	multinational corporation
MR MAP	measles-rubella microarray patch
N&S	needle and syringe
NPV	net present value
OPEX	operating expenditure
RI	routine immunization
ROI	return on investment
SIA	supplementary immunization activity
SIIPL	Serum Institute of India Private Limited
TPP	target product profile
UNICEF	United Nations Children’s Fund
VIPS	Vaccine Innovation Prioritization Strategy
WHO	World Health Organization

Executive summary

Despite the availability of a safe, effective, and affordable vaccine, the percentage of children globally receiving at least one dose of measles-containing vaccine (MCV) has stalled at around 85%, having increased only by 5% in the past decade. A microarray patch (MAP) for the delivery of measles-rubella (MR) vaccine has emerged as a promising alternative to the lyophilized injection currently in use. MR MAPs have the potential to increase immunization coverage in underserved populations while reducing the waste and safety risks inherent in the lyophilized formulation.

The eventual transfer of MAP technology to an established developing country vaccine manufacturer (DCVM) with the capacity to product MAPs at commercial scale is expected to accelerate market entry and increase the likelihood of affordability and sufficient supply in low- and middle-income countries (LMICs). However, to date the potential financial risks and rewards for investment in MR MAPs from the perspective of a manufacturing partner have not yet been evaluated as part of a publicly available analysis.

The objective of this business case is, therefore, to define the market opportunity of MR MAPs and evaluate incentives for commercialization partners and global health stakeholders (e.g., donors, procurers) to invest in bringing MR MAPs to licensure for LMIC use.

Recognizing that MR MAPs may be deployed in different usage strategies to achieve coverage goals, we analyzed four different usage scenarios and modeled low, base, and high results:

- Targeting hard-to-reach populations in all countries currently using MR or expected to adopt MR by 2030.[1]
- Routine and supplementary immunization activities (SIAs) in six Measles & Rubella Initiative (M&RI) priority countries.
- SIAs and outbreak response immunization in all countries currently using MR or expected to adopt MR by 2030.[1]
- Routine immunization (RI) in 12 selected countries with the largest populations lacking an MCV first dose (unimmunized MCV1 populations) and the largest populations that are forecasted to use MR in 2030.

We estimated the potential return on investment to an Indian manufacturer (as an assumption since both manufacturers of WHO-prequalified MR vaccines are based in India), weighing all the upfront and yearly developmental and production costs against the expected cash inflows from product sales. The analysis found suboptimal returns on the investment. Our base results—with a net present value (NPV) ranging from a $3 million loss to a $3.2 million gain from 2023 to 2040 among the four usage cases—suggest an investment unlikely to attract manufacturers. Nonetheless, this business case may provide a starting point for donors, manufacturers, and other key stakeholders to identify key factors influencing the commercial viability of MR MAPs. Its methodology and conclusions may help stakeholders develop new strategies to address the risks of producing a novel MR MAP vaccine presentation for low- and middle-income markets and strengthen the commercial value proposition.

[1] Excludes supplementary immunization activities in Egypt and Libya due to lack of forecast data.

Background

Measles and rubella disease burden

Measles is a highly infectious disease caused by the measles virus. It is a seasonal disease in endemic areas and also causes outbreaks.[1] Rubella is an acute, usually mild, viral disease, typically affecting susceptible children and occurring in a seasonal pattern, with epidemics every five to nine years. Rubella infection just before conception and during early pregnancy may result in miscarriage, fetal death, or congenital defects known as congenital rubella syndrome (CRS). Vaccination and maintaining high population-level immunity against measles and rubella are key strategies to reduce measles deaths and prevent CRS.[2]

The World Health Organization (WHO) recommends that all children receive two doses of measles-containing vaccine. In countries with ongoing transmission and where measles mortality remains high, WHO advises a first dose at 9 months and a second dose at 15 to 18 months.1

Challenges with the current presentation

Despite the availability of a safe, effective, and affordable vaccine, the percentage of children globally receiving at least one dose of MCV has stalled at around 85%. Ten countries account for 60% of unprotected children (Angola, Brazil, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, Philippines, Vietnam).[3] The lowest rates of coverage remain among children in the poorest communities and most difficult-to-reach populations.

The current vaccine presentation is a lyophilized multidose vial which needs to be reconstituted before administration. Once a vial is opened and reconstituted, the vaccine must be used within six hours and any unused portion discarded. As a result, one of the reasons for the immunization gap is the reluctance to open a multidose vial when only a few children are present for vaccination; the fear of vaccine wastage can contribute to missed vaccination opportunities. A single-dose presentation could reduce these missed opportunities.

There are also potential safety risks for the current lyophilized presentation, including contamination through the reuse of reconstitution syringes and mismatching dry vaccine and diluent. The dry vaccine and diluent are often shipped and stored separately, with the vaccine in the cold chain and the diluent at ambient temperature, which increases logistical complexity and risk of use of the incorrect diluent. For example, in Syria in 2014, 15 children died after a muscle relaxant was accidentally administered instead of the proper diluent. In 2017, another 15 children died in Syria after receiving vaccine that was contaminated during reconstitution. In 2018, two children in Samoa died after receiving vaccine incorrectly reconstituted with expired muscle relaxant. These recent reports demonstrate that vaccine handling and preparation errors pose a significant safety risk. Vaccine product innovations that eliminate these risks could have a major impact on improving the safety of immunization programs in LMICs.[4]

The need for a measles-rubella microarray patch

A microarray patch (MAP) for the delivery of measles-rubella vaccine has emerged as a promising alternative—one with the potential to increase immunization coverage and strengthen safe practices in underserved populations. A novel, investigational drug delivery platform, MAPs are under development

for a variety of health indications, including immunization, sustained-release drug delivery, and contraception.

A MAP is a patch that contains microscopic projections loaded with the active drug. When pressed firmly onto the skin, the microprojections pierce the outermost layer and release the drug into the body. A MAP presentation offers several potential programmatic benefits compared to the current MR vaccine presentation, including eliminating the need for reconstitution, reducing programmatic wastage (due to its single-dose form), increased thermostability (if optimized), and increased ease of use. During outbreak scenarios, the MAP presentation would offer significant advantages—removing barriers to mass outbreak response such as cold chain storage (if optimized), sharps waste disposal, and delivery by skilled health workers. In its recent position paper on measles vaccines, WHO emphasized the potential of MAPs in measles elimination efforts, stating:

> Advances of major importance are in development, of which the most significant are likely to be administration of measles vaccine through microarray patches, and point-of-care diagnostic tests. Microarray patches would allow house-to-house vaccination and allow non-medically trained personnel to administer vaccine, which would be of great benefit for countries with limited human resources. Such innovations would increase the likelihood of success in reaching regional elimination goals.[1]

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on Measles and Rubella highlighted that MR MAPs have the potential to become game-changers for achieving MR elimination. In response, WHO's Immunization, Vaccines and Biologicals (IVB) department established an MCV MAP Working Group and held an MCV MAP Product Development Workshop in April 2018. In 2019, WHO and UNICEF also published an MR MAP target product profile (TPP) after a comprehensive review process including soliciting stakeholder review and holding a public comment period.[5]

Objective

The business case for an MR MAP

A substantial and concerted investment will be required to move an MR MAP candidate through clinical development, regulatory approval, manufacturing scale-up, and eventual program introduction. Two developers (Micron Biomedical and Vaxxas) are currently advancing MR MAPs and are expected to initiate Phase 1 clinical studies in early 2021 with support from the Bill & Melinda Gates Foundation. Transferring technology and know-how to DCVMs has been identified as a key factor in bringing affordable vaccines to market rapidly.[6] Therefore, transferring the MAP development technology to an established DCVM should accelerate market entry and increase the likelihood of an affordable, sufficient supply in LMICs.

Potential DCVMs for a technology transfer include vaccine manufacturers who currently have a lyophilized MR product such as Serum Institute of India (SIIPL), Biological E (BioE), and Brazil's Bio-Manguinhos (BioM). SIIPL has commanded the UNICEF MR vaccine supply for 10 years and currently provides the MR antigen for MR MAP development. BioE's MR vaccine was WHO prequalified in 2019, providing another affordable option for UNICEF procurement beginning in 2021. BioM is another potential partner, with an MR vaccine candidate currently in Phase 3. Some of these manufacturers have entered MR MAP development discussions, but at the time of writing this report none have been willing to invest in advancing a candidate for commercialization.

Coupled with the inherent risks of bringing a new combination product to market, uncertain demand prospects and an unclear path to revenue generation have been key barriers to identifying a commercial partner for an MR MAP.[7] Vaccine manufacturers seem to see insufficient financial incentive (margins) to invest in the new facilities and late-stage clinical trials required to compete for market share in an already well-established market. Moreover, while country governments have commissioned preliminary analyses to study the potential delivery cost savings of using MR MAPs in their immunization programs, the potential risks and rewards for investment in MR MAPs from the perspective of a manufacturing partner have not yet been evaluated.[8]

Therefore, this business case aims to define the market opportunity of MR MAPs and evaluate incentives for commercialization partners and global health stakeholders to invest in bringing MR MAPs to licensure for LMIC use. This analysis quantifies the upfront investment and manufacturing costs (and possible risks) of an MR MAP investment and helps articulate the potential returns for a DCVM—with the aim to inform investment decisions and also act as a starting point for necessary dialogues between global actors and manufacturers.

Approach

Estimating global MR MAP demand

To develop an estimate of the potential market size for an MR MAP, we generated a set of assumptions on adoption, timing, and usage scenarios by consulting with internal and external stakeholders and experts.

The demand model is based on Linksbridge's Global Vaccine Market Model (GVMM)—where annual vaccine demand is forecasted by country based on target population, immunization schedule, an analog for coverage/uptake, and programmatic wastage. We also included future MR adoption assumptions generated by WHO's Market Information for Access (MI4A) initiative.[b] The full demand results, in doses, are presented in the appendix.

As MR MAP development is still in its early stages, we inferred product characteristics based on WHO's MR MAP target product profile to assume a product non-inferior to the lyophilized MR vaccine presentation delivered by needle and syringe (N&S) in efficacy and superior in wastage and thermostability. This was an underlying assumption when making the demand estimates.

MR MAP demand estimate inputs MAP

Usage

Recognizing that MR MAPs would ideally be used in specific, targeted strategies to achieve measles vaccine coverage and elimination goals, we examined demand across four potential usage scenarios with different implications given the country scope (Table 1).

Table 1. MR MAP usage scenarios and country scope.

Usage scenario	Country scope
1. Targeting hard-to-reach populations [c]	All countries that currently use or are forecasted to use the measles-rubella (MR) vaccine
2. Routine immunization (RI) and supplementary immunization activities (SIAs) in six Measles & Rubella Initiative (M&RI) priority countries	Democratic Republic of the Congo (DRC), Ethiopia, India, Indonesia, Nigeria, and Pakistan
3. SIAs and outbreak response immunization	All countries that currently use or are forecasted to use the MR vaccine
4. RI in 12 selected countries with the greatest proportion of children who have not received the first dose of measles-containing vaccine (MCV1) and the largest populations that are forecasted to use MR in 2030	Afghanistan, Bangladesh, Chad, DRC, Ethiopia, Indonesia, Mozambique, Nigeria, Pakistan, South Africa, Tanzania, Uganda

[b] MI4A is funded by the Bill & Melinda Gates Foundation and is a collaboration between WHO, Linksbridge SPC, and MM Global Health Consulting.
[c] Defined as the difference between MCV1 95% coverage target and UNICEF National Immunization Coverage Estimates of MCV1.

Displacement/switching

Assuming that MR MAPs would be considered a preferred product for campaigns, and in light of the complexity of stocking and providing multiple presentations of the same vaccine in a country (i.e., mixed presentations), we assume full displacement of N&S vaccines by MR MAPs for each of the usage scenarios indicated in Table 1.

Adoption

Assuming that private market users in LMICs are more likely to purchase products with additional antigens like measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccines, we excluded private market use of MR MAPs as part of our initial analysis. For more information on the potential opportunity of MMR MAPs, see the 'Opportunities and Challenges' section below. Since Gavi currently supports MR RI and SIA vaccination in all Gavi-eligible countries, whether Gavi would financially support the MR MAP is a key driver to forecasting demand. We modeled two different scenarios in this analysis: one with no Gavi support and one with Gavi support; the first scenario limits its demand forecast to Gavi-graduated and non-Gavi countries.

Gavi's current support policy dictates that when a country's gross national income (GNI) per capita is below the World Bank's low-income-country threshold, the government's contribution is a flat amount of $0.20 per dose for any vaccine it receives from Gavi. After a country's GNI per capita has surpassed the low-income-country threshold, the government's contribution increases by 15% per year until it graduates from Gavi support. To simplify the analysis, we assumed that all countries eligible for Gavi support would switch to the MR MAP presentation for all usage scenarios. However, in practice, the decision to switch from the N&S lyophilized vaccine to the MAP would be initiated by countries.

Although Gavi has expressed interest in MR MAPs, and the Vaccine Innovation Prioritization Strategy (VIPS,[9] an Alliance-wide effort led by Gavi, the Gates Foundation, PATH, UNICEF, and WHO) has prioritized the MAP technology platform, Gavi has not clearly signaled whether it would support the MR MAP or what that support could look like. This analysis assumes the organization's current level of support for the lyophilized MR presentation would be applicable to MAP presentation.

Production launch timeline

Our analysis assumes that the MR MAP technology would complete Phase 2 trials in 2022, and technology transfer to a DCVM would begin in 2023. Based on expert opinion and historical vaccine development timelines, we assume that it would take seven years for the DCVM to develop, test, and eventually launch the product in 2030, although there are potential opportunities to accelerate the product development timeline such as scaling up MAP manufacturing at-risk. For this analysis, we assume the product would be available in the market starting in 2030 and therefore present demand forecasts for the period 2030 to 2040. However, the recent COVID-19 vaccine development has demonstrated that the typical vaccine development timeline can be truncated with an existing manufacturing infrastructure.

Supply and procurement constraints

We modeled low, base, and high demand scenarios with different supply constraints (Table 2). When supply is limited (demand > supply), the prioritization of allocation of the MR MAP is assumed to be based on country MCV coverage, from low to high. Unconstrained demand results are presented in the appendix for reference, which illustrate the demand potential based solely on market demand if no supply constraints existed.

Table 2. Low, base, and high market demand scenario inputs.

	Level of Gavi support	Supply constraints
Low demand scenario	No Gavi support	Start: 5M, increase by 1M each year to reach 15M annual supply production in 2040
Base demand scenario	Gavi support	Start: 10M, increase by 3M each year to reach 40M annual supply production in 2040
High demand scenario	Gavi support	Start: 20M, increase by 5M each year to reach 70M annual supply production in 2040

Estimating the financial returns of an MR MAP

To determine the return on investment for a manufacturer that invests in the MR MAP, we generated assumptions on price, development costs, and other necessary costs for commercialization. For our analysis, we assumed that one India-based DCVM with existing MR production infrastructure would receive the technology transfer and produce the MR MAP. Currently, both manufacturers of WHO-prequalified MR vaccines (SIIPL and BioE) are based in India.

Technology and transfer

Based on industry consultations, we estimated that a manufacturer would begin the adoption of MAP technology in 2023—incurring approximately $15 million in total R&D costs, including technology transfer fees (including both patents and trade secrets), late-stage clinical trials, and licensing and regulatory fees over seven years. Since license fees vary widely depending on the type of deal, we have excluded potential license and milestone fees from the current analysis.

Development and production

We assume that the DCVM would co-locate its MAP and N&S vaccine production by adding MAP-specific equipment to its existing MR vaccine facility, eliminating the need to build a new manufacturing site for the product. To simplify the analysis, however, we have excluded the potential opportunity costs from same-facility production in these results. Capital expenditure (CAPEX) and operating expenditure (OPEX) assumptions were based on internal analyses of the necessary costs for cleanroom construction, machinery, and overhead. We estimated cost of goods sold (COGS) for the MR MAP based on the cost of the antigen and developer input using existing COGS information, arriving at an estimated COGS ranging from ~$0.70 to $1.11 per dose, assuming an annual volume of 20 million doses per year. These estimates were also informed by previous MAP COGS assessments conducted by PATH and McKinsey & Company.

Vaccine price

Because the MR MAP is a novel combination product, its price per dose would likely be more than the price of the current injectable vaccine. This price increase aligns with the WHO/UNICEF MR MAP TPP, which states that a MAP can be more expensive if it offers sufficient additional programmatic benefits.[5]

Based on this assumption, we derived a set of differential pricing within MR-using market tiers (Table 3) from GVMM-forecasted N&S MR vaccine price values.

We assume one vaccine manufacturer will have 100% of the MR MAP market share without competition for the duration of the modeling period. The model assumes fixed pricing in each market segment and has not made any adjustments for inflation or other price increases during the analysis period.

Table 3. MR MAP price assumptions by price tier.

Price tier	Price per dose
India	$0.85
UNICEF	$1.06
Lower-middle income	$1.80
Upper-middle income	$2.56
High income	$4.34[1]

[1]Although an MR MAP price was estimated for high-income markets, MR MAP doses were not allocated to this market in our analysis based on the model assumptions.

Results

The case for MR MAP investment

We estimated the potential return on investment (ROI) to an Indian DCVM by weighing all the upfront and yearly developmental and production costs against the expected cash inflows from product sales. The estimates do not include any assumptions of potential external funding. For our analysis, we use the concept of net present value (NPV)[d] to translate future cash flows into present-day terms. We applied a discount rate[e] of 10% to account for the time value and risk of annual future cash flows in our NPV calculations. Although manufacturers do not share detailed information regarding their internal decision-making process, previous analyses have shown that a typical discount rate for vaccine manufacturers falls in the 10% to 20% range. We assume that DCVMs producing MR MAPs may adopt this typical range of discount rates since they would be entering into a vaccine market already established for the lyophilized MR vaccine. Availability of donor funding could also influence the discount rate selected by a vaccine manufacturer as they assess the risk profile of investment in MR MAPs. We also assessed the internal rate of return (IRR),[f] or hurdle rate, required for a manufacturer to break even on an NPV basis.

NPV is typically used by vaccine manufacturers to make capital budgeting decisions; only projects that meet a certain level of return are considered further. A positive NPV indicates that the projected earnings from an investment exceed the anticipated costs (and hence that an investment would generate value for the company). However, as resources are often limited, with multiple opportunities on the horizon, the threshold for what constitutes sufficient NPV for prioritizing an investment may vary by manufacturer. The decision to go ahead with a project should therefore also involve other criteria such as strategic benefits, which are not captured in the NPV analysis.

As the analysis currently stands, the ROI for an MR MAP is suboptimal. Our base results—with a net present value ranging from a $3 million loss to a $3.2 million gain from 2023 to 2040 among the four usage cases—suggest an investment unlikely to attract DCVMs.

The low commercial viability suggested by the business case analysis was not unexpected based on preliminary MR MAP demand forecasting previously conducted by the US Centers for Disease Control and Prevention (CDC) and UNICEF suggesting uncertain market demand. Moreover, manufacturers in early MAP discussions have raised doubts about returns.

Below we present detailed base case results for four usage scenarios, as well as a summary of the low, base, and high NPV results.

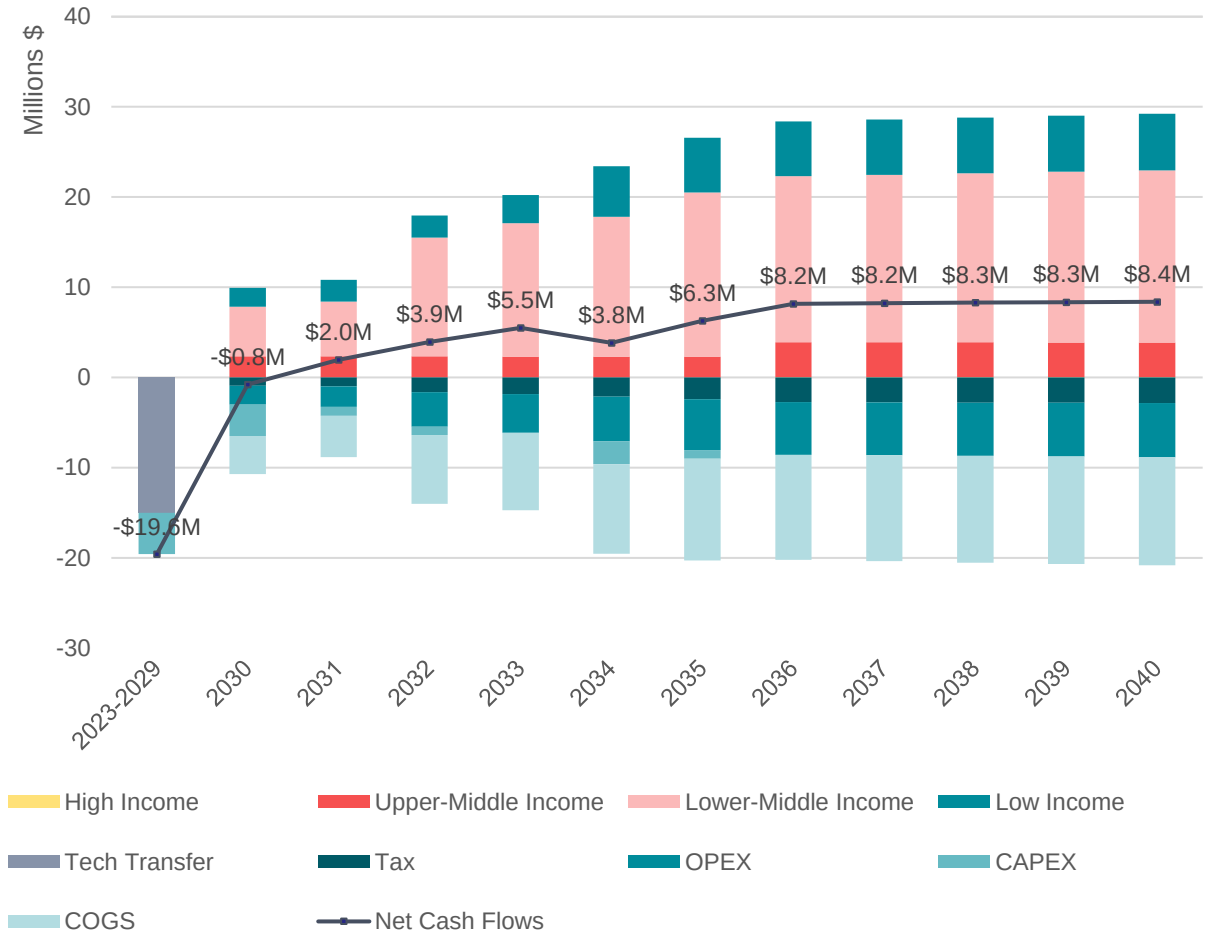
[d] Net present value (NPV) is the current value of a series of future projected cash flows. NPV is often used in capital budgeting and investment planning to analyze the profitability of projected investments or projects.
[e] A discount rate is the rate of return used to discount future cash flows back to their present value, which describes the rate of return needed to see a return on an investment.
[f] Internal rate of return (IRR) is the expected compound annual rate of return that will be earned on a project or investment. When calculating IRR, expected cash flows for a project or investment are given and the NPV equals zero.

Cash flow by year and market for the MR MAP usage scenarios (base case)

Targeting hard-to-reach populations

We estimate that the global annual market for MR MAPs when targeting hard-to-reach populations is $29.2 million at market peak (2040) with 26.7 million doses procured (Figure 1). Assuming Gavi support for procurement, lower-middle-income markets would account for more than half the revenue, followed by low-income and then upper-middle-income markets. There is no demand from high-income markets, since most of those countries use higher valency MCVs instead of MR. At a 10% discount rate, a DCVM could realize an NPV of $3.2 million between 2023 and 2040 and an IRR of 13% in 2023 dollars under the targeting hard-to-reach population scenario.

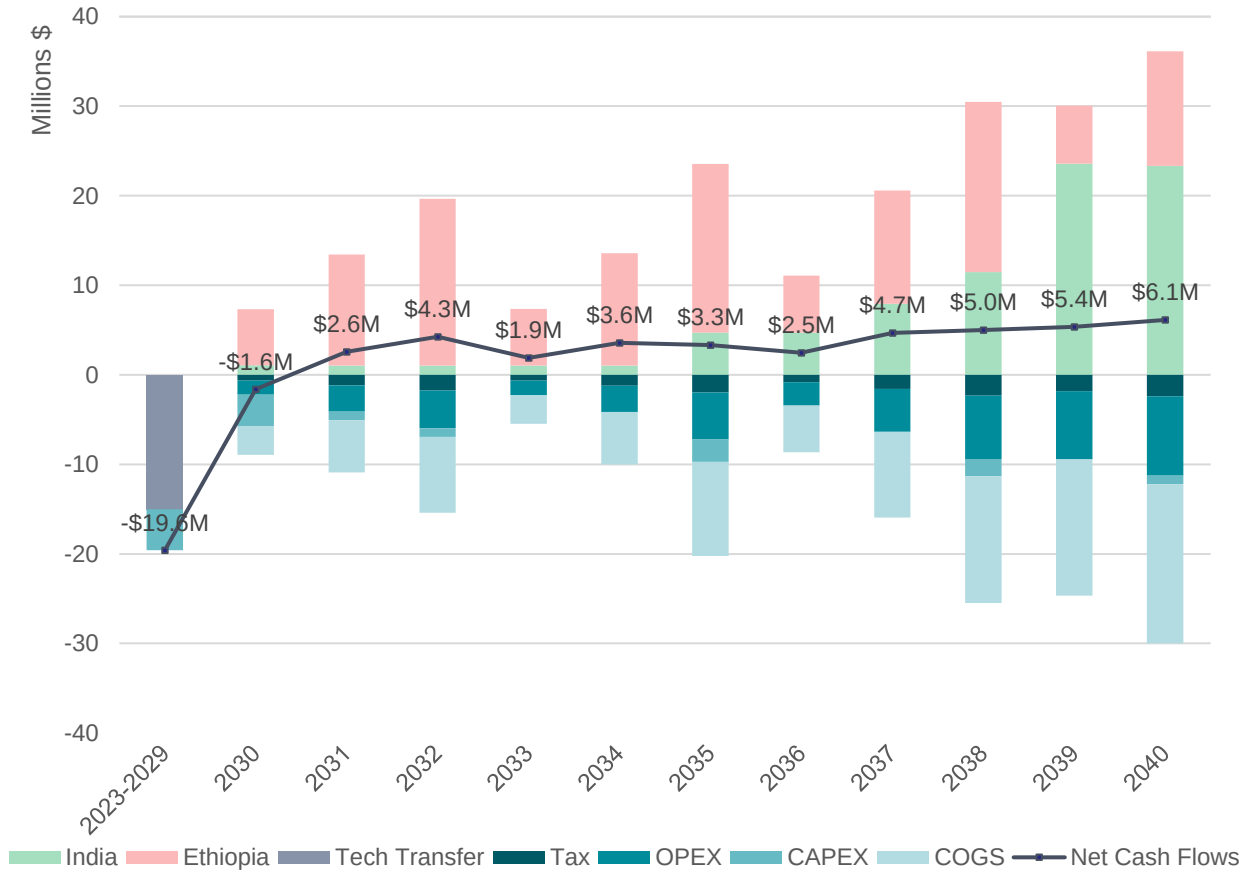
Figure 1. Cash flow by year and market for targeting hard-to-reach populations.



RI and SIA delivery in six M&RI priority countries

We estimate that the global annual market for MR MAPs for both RI and SIAs in the six M&RI priority countries is $36.1 million at market peak (2040) with 39.5 million doses procured. With limited supply, in this scenario only Ethiopia and India are allocated MR MAP supply (Figure 2), based on their lower MCV coverage compared to the other four countries. As seen for current lyophilized MCVs, due to the erratic nature of campaign schedules, demand will ebb and flow, bringing demand uncertainty to the manufacturer. At a 10% discount rate, a DCVM would realize an NPV of a $3 million loss (i.e., a negative NPV) between 2023 and 2040, and an IRR of 7% in 2023 dollars.

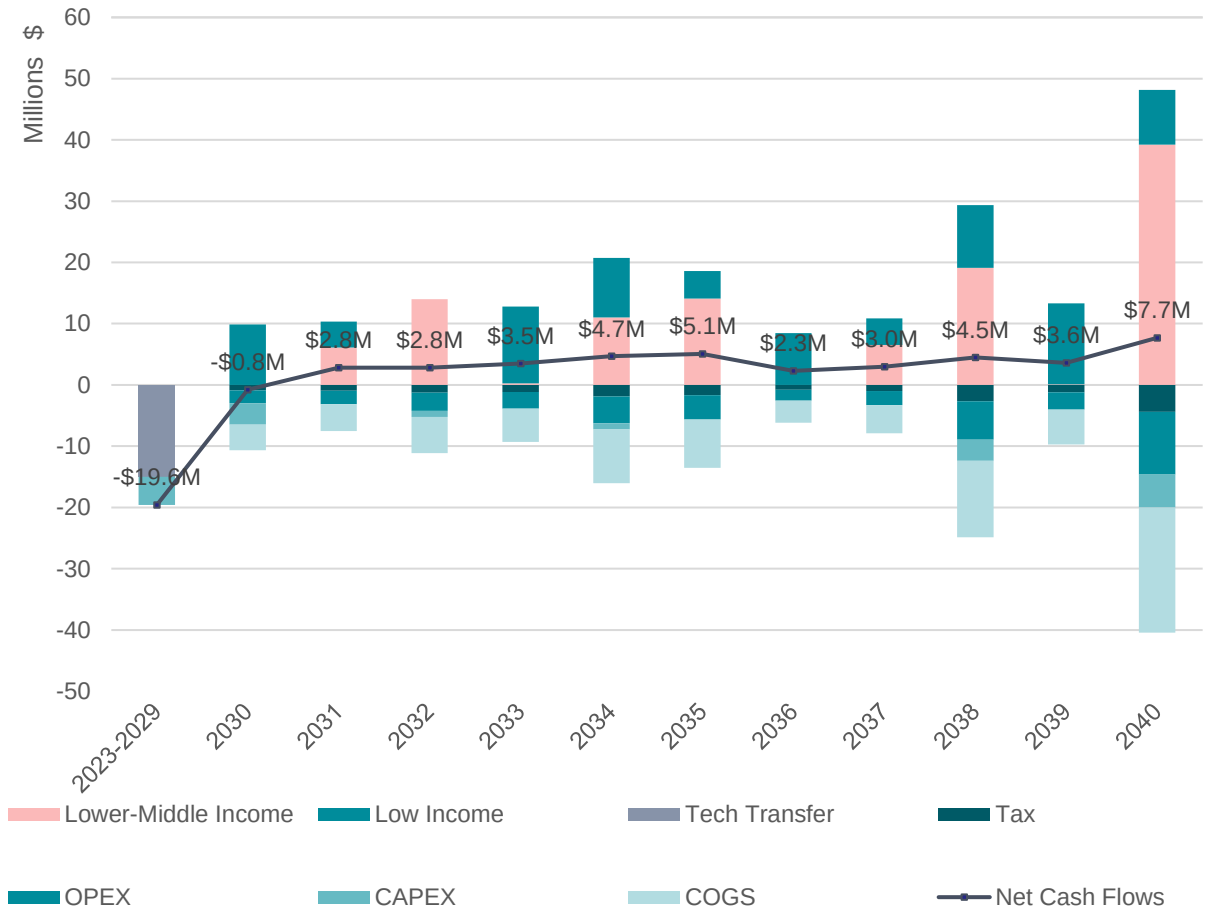
Figure 2. Cash flow by year and market for RI and SIAs in six M&RI priority countries.



SIAs and outbreak response immunization

We estimate that the global annual market for MR MAPs for SIAs and outbreak response campaigns (in all countries that will adopt MR) is $48.1 million at market peak (2040) with 45.4 million doses procured. With limited supply, low- and lower-middle-income markets with lower MCV coverage are prioritized for MR MAP use in this scenario (Figure 3). Demand is significantly impacted by the SIA schedule for MR in these countries and the MR MAP supply constraints. In particular, demand fluctuates based on the years when SIAs are scheduled to be conducted in lower-middle income countries who we estimate would procure MR MAPs at a price per dose of $1.80 compared to $1.06 in low-income countries. As more doses become available, we observe higher revenue in 2040. At a 10% discount rate, a DCVM could realize an NPV of a $2.3 million loss (i.e., a negative NPV) between 2023 and 2040 and an IRR of 8% in 2023 dollars.

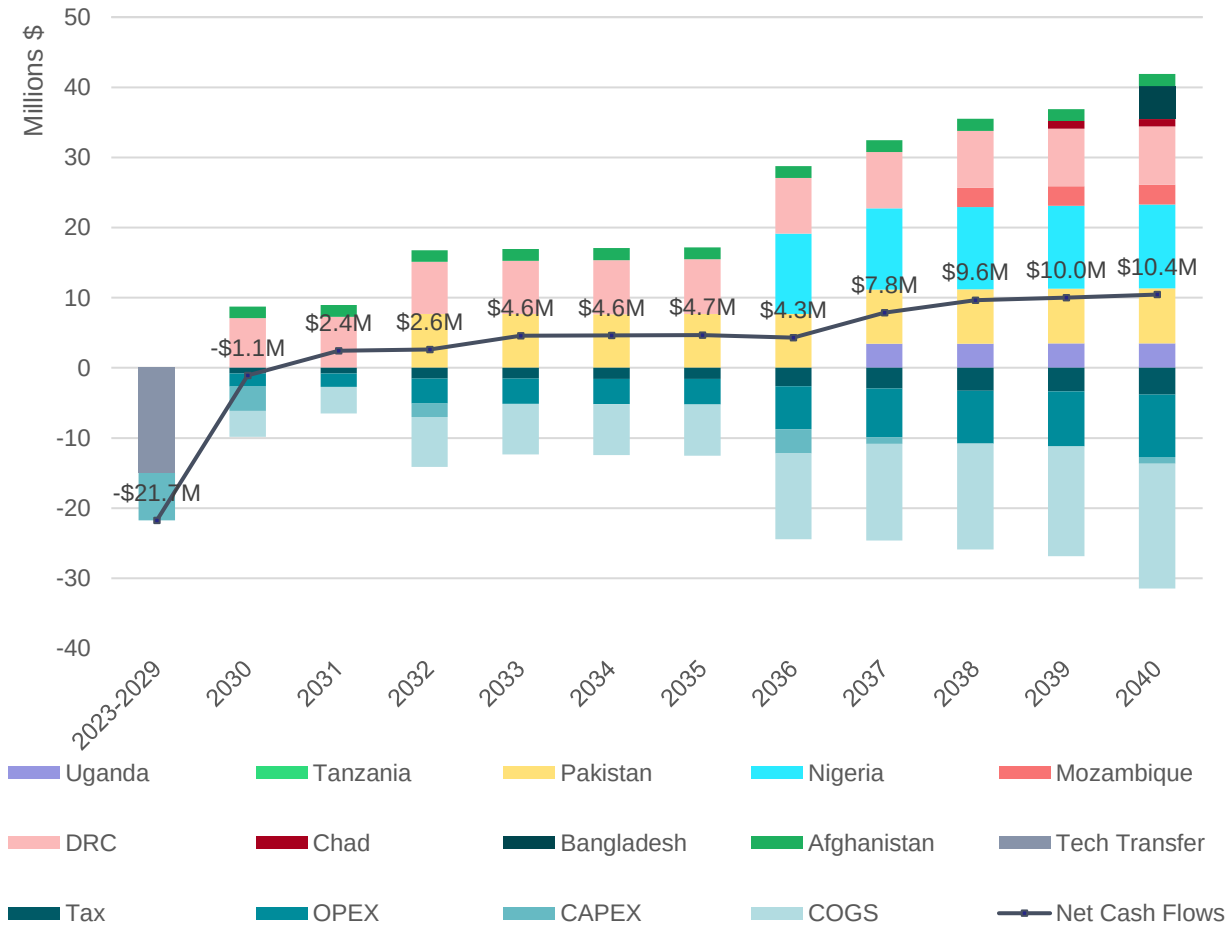
Figure 3. Cash flow by year and market for SIAs and outbreak response immunization.



RI delivery in 12 selected countries with the largest unimmunized MCV1 populations and the largest populations that are forecasted to use MR in 2030

We estimate that the global annual market for MR MAPs for RI in 12 selected countries is $41.9 million at market peak (2040) at 39.5 million doses procured (Figure 4). At a 10% discount rate, a DCVM could realize an NPV of $2.2 million between 2023 and 2040 and an IRR of 12% in 2023 dollars.

Figure 4. Cash flow by year and market for RI in 12 selected countries with the largest unimmunized MCV1 populations and the largest populations that are forecasted to use MR between 2030 and 2040.



Given the supply constraints outlined in the model, doses were allocated using a strategy based on maximizing the number of countries that could meet their entire RI demand within the constraints shown in Table 2. For example, in 2030 with 10 million doses in supply, MR MAP doses were allocated to only DRC and Afghanistan. Although Nigeria has the greatest number of unimmunized children, the expected total required supply for 2030 in Nigeria is approximately 16 million doses which exceeds the assumed number of available MR MAP doses in 2030. To avoid instances of mixed presentations, delivering both the MAP and lyophilized MR vaccines in a country at the same time, doses in a given year were

prioritized to countries where the total RI demand could be met with the MR MAP presentation. As a result of the supply constraints, only 9 of the 12 priority countries were allocated doses of MR MAP between 2030-2040 in this use scenario; Ethiopia, Indonesia, and South Africa were excluded from the base case analysis. See the appendix for unconstrained scenarios without supply constraints.

Sensitivity analysis

Figure 5 illustrates the effect on NPV estimates (at a 10% discount rate) of varying the MR MAP price per dose within the model, comparing the ROI at the base price estimates presented earlier against scenarios of a 20%, 50%, and 100% increase at static COGS. Figure 6 presents the same data but at proportionally increasing COGS. We also present the NPV at base price in the case where all the technology transfer fees are excluded (illustrating a hypothetical scenario where a funder covers those fees).

The results suggest that even if the COGS are higher than assumed in the analysis, an increased price might improve the value proposition of the MR MAP sufficiently to affect DCVM decision-making. Further, removing the technology transfer costs (an assumed $15 million) produced positive NPVs in all usage scenarios even at the base price—suggesting that a funder's subsidization of the fees may be a viable strategy de-risking investment without increasing the product price significantly.

Figure 5. NPV by price scenario for hard-to-reach, 6 priority, SIA, and 12 selected countries.

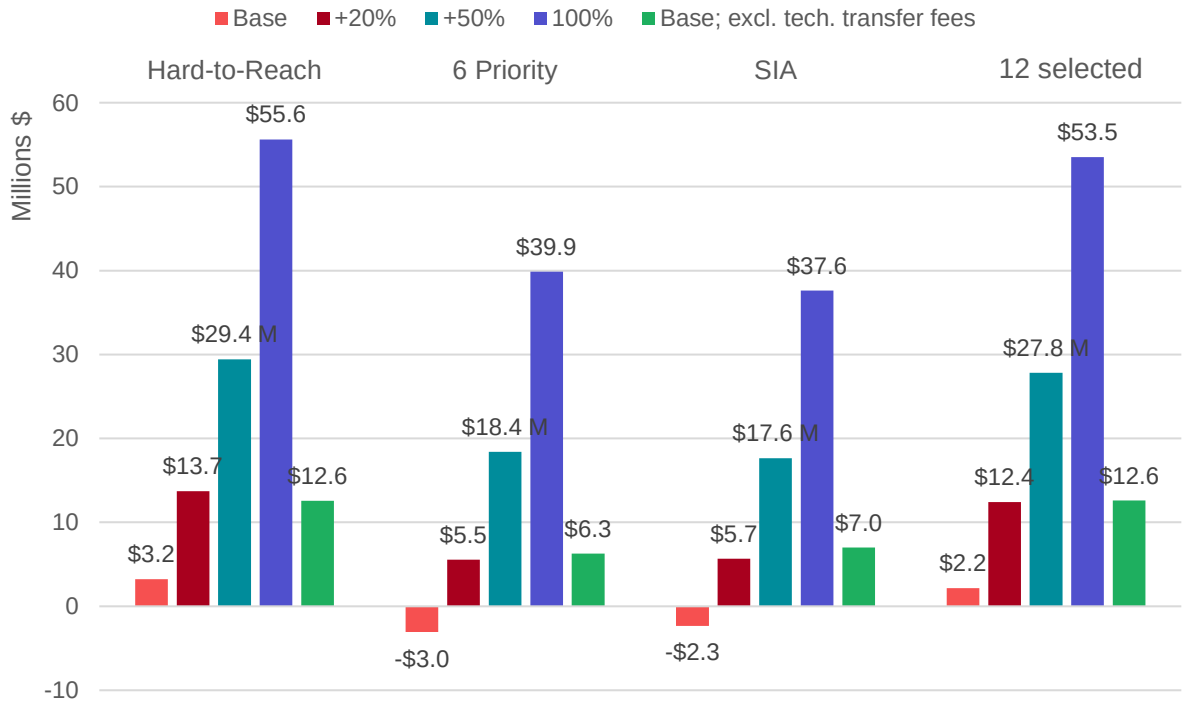
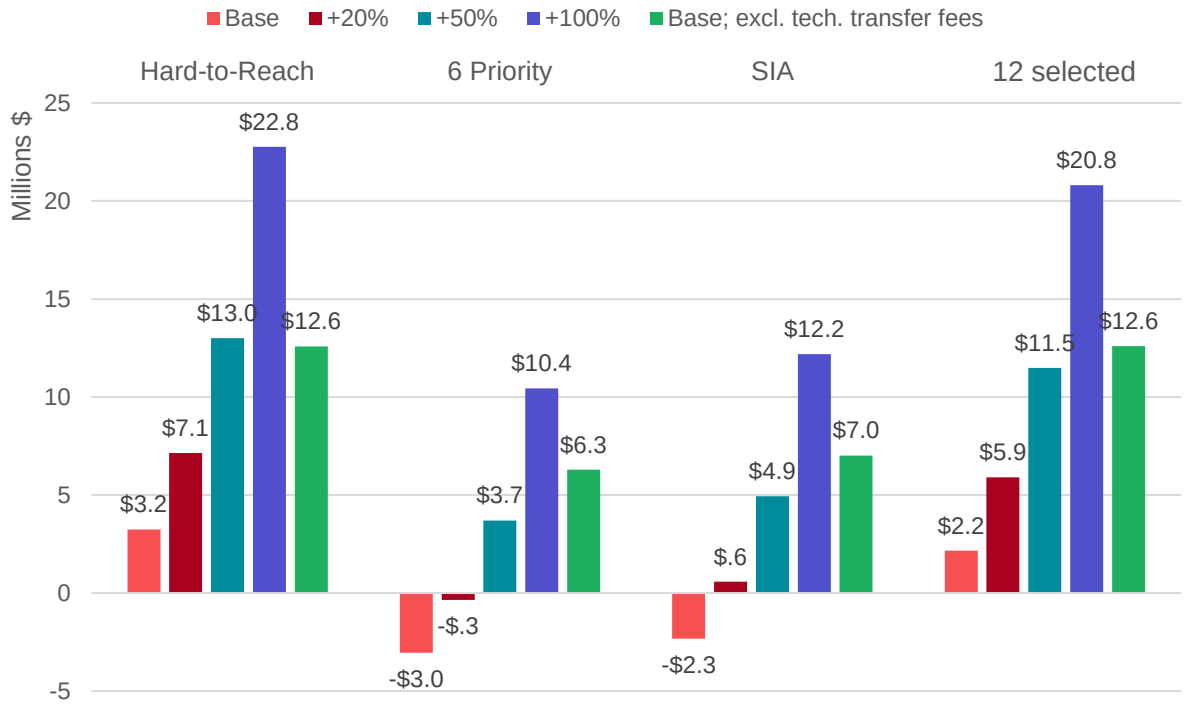


Figure 6. NPV by price and by proportionally increasing COGS scenario for hard-to-reach, 6 priority, SIA, and 12 selected countries.



Challenges and opportunities

Based on the analysis results and interviews with experts, we outline below some factors that may impact the MR MAP value proposition for DCVMs and suggest potential solutions.

Reducing the risk of targeting resource-limited markets

Gavi currently provides financial support to LMICs to use the N&S MR vaccine in routine immunization and campaigns. Without similar assistance for the MR MAP, the countries with the lowest MCV coverage may not be able to adopt the new product. The perceived lack of clarity for vaccine manufacturers on future Gavi assistance (and resulting lack of clarity on potential demand) is a risk for manufacturer investments in MR MAPs. Increased clarity on Gavi's position on MR MAP support is expected as a component of the upcoming VIPS 5-year Action Plan for vaccine MAPs.[9]

The MR MAP has the potential to improve coverage and equity. However, a low-cost MR vaccine already exists—making it unlikely that countries would be willing to pay much more for a new presentation. Based on lessons from the introduction of vaccines using the Uniject™ injection system,[g] the price per dose plays a major role in the adoption of vaccine product innovations for LMIC markets.

De-risking the endeavor through advanced purchase agreements—–which might be warranted given the potential benefits of an MR MAP—could reduce economic uncertainty for manufacturers and improve their confidence for expected returns. A higher price premium than N&S vaccines would also boost potential revenue. As shown in the sensitivity analysis results, increasing the price of the product would improve the NPV of the investment in all usage scenarios.

Mitigating R&D, regulatory, and licensing risks

MR MAP candidates are still in early clinical development and have not yet demonstrated capabilities for mass production. Although we have used plausible assumptions for the cost estimates, our analysis did not account for failure rates and technical challenges that may arise from the process of adopting a complicated new technology at an industrial scale.

The necessary regulatory costs for MR MAPs are also unknown. Because MR vaccines were licensed many years ago, the costs and risks of reopening safety profiles or changing production processes to meet current regulatory requirements may exceed our estimates. Further, supporting data from bridging studies demonstrating immunological non-inferiority may be needed for regulatory approval of MAPs in general for existing vaccines.[7] Additionally, because MAPs represent a new technology in the vaccine world, manufacturers will need guidance to develop good manufacturing practices and quality control methods for production and characterization.[10]

One strategy to mitigate the risk is to subsidize early technology adoption costs. The sensitivity analysis results demonstrate that excluding technology transfer costs resulted in positive NPVs across all usage scenarios. Reducing the overall development and regulatory timeline may also have a significant impact on the valuation metrics (since future cash flows are discounted in the NPV calculation). Options for accelerating the regulatory process include obtaining support and recommendations from Gavi and WHO

[g] Uniject is a trademark of BD.

and initiating dialogue with regulatory authorities on the potential implementation of expedited approval processes for adapting MAPs to existing vaccines.

Innovative solutions

In addition to the opportunities outlined above, we also generated some potential 'creative' solutions—beyond the scope of our analysis—that could improve the investment value proposition.

Adding an additional antigen to enhance the commercialization opportunity

Most upper-middle- and high-income countries employ costlier measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) combination vaccines in their immunization programs. Although currently not in the MAP development pipeline, a MAP-based MMR or MMRV vaccine could open markets in upper-middle- and high-income countries and present a more attractive investment for both DCVM and multinational corporation (MNC) manufacturers. Based on interviews with experts, it is technically feasible for a manufacturer to simultaneously produce MR and MMR/MMRV MAPs in the same facility—enabling a dual-market opportunity where the manufacturer could subsidize MR MAP delivery to LMICs using profits generated from the MMR/MMRV MAP in high-income markets.

To examine the potential financial returns of this opportunity, we conducted a separate exercise to determine the ROI of selling an MMR MAP product for needle-phobic populations in high-income countries. Expecting that the development of the MMR MAP would take longer, we assumed a launch date of 2032. For revenue calculations, we assumed the same price point (Table 4) as what countries are forecasted to pay for N&S MMR vaccines in 2032. For COGS, we assumed the additional mumps antigen would increase the COGS by one-third.

In Figure 7, we estimate that the potential global market of using MMR MAPs for needle-phobic populations (~10%[11]) in high-income countries would reach $65 million at 2.7 million doses in 2040. At a 10% discount rate, a DCVM could realize an NPV of $86 million between 2023 and 2040 and an IRR of 45% in 2023 dollars. Based on these results, the business case for marketing the MMR MAP in high-income markets could appeal to both MNCs and DCVMs as a potential investment and incentivize adoption of the technology for the MR MAP. It is important to note, however, that Indian-produced vaccines are not currently supplied to North American or European high-income countries.

Table 4. MMR MAP price assumptions by price tier.

Price tier	Price per dose
High income	$11.68
Super-high income	$16.15
United States	$72.72

Figure 7. Cash flow by year and price tier for the MMR MAP in needle-phobic populations in high-income countries.

Addressing inconsistent demand and optimizing the manufacturing process through modular techniques

There is considerable pressure to reduce the high capital costs, complex processes, and long development cycles involved in vaccine manufacturing. Flexible, single-use, modular manufacturing techniques have long been used in biologic production and have gained traction as an emerging technology in vaccine development. Several companies are now evaluating the use of modular manufacturing platforms to innovate the vaccine production process, including Belgium's Univercells, which has been working on applying its NevoLine™[h] micro-facility technology to develop a low-cost N&S MR vaccine.

Modular manufacturing platforms offer multiple benefits, including flexibility to scale up or scale down capacity depending on need, multiple product manufacturing in the same space, and lower capital investment and operator expertise—all of which translate to a less risky and costly technology transfer

[h] NevoLine is a trademark of Univercells.

process. The ability to respond to rapid deployment needs and unpredictable demand could address manufacturers' concerns about providing vaccines for campaigns and outbreak response.

Moreover, typical facilities can take years to build and the capital commitment must be made when the product is still in early trial stages—increasing the financial risk. Pursuing a modular facility concept may allow a manufacturer to hold off on committing the capital until the risk profile of the product is substantially lower.

Although the use of modular manufacturing technologies for MAP production has not been explored, coupling both technologies may help address several MR MAP production risks faced in traditional vaccine manufacturing—which is complex, manual, and based on decades-old technology that has not been updated because of regulatory implications for licensed vaccines. Modular manufacturing may also address manufacturer concerns about high upfront costs and inconsistent annual demand due to the nature of campaign schedules and outbreaks and may lower COGS in the long run; it may also streamline the complicated antigen processing steps required to formulate MR MAPs.

Partnering with CDMOs to lower overhead costs

Another potential opportunity is to transfer the MAP technology to a contract development and manufacturing organization (CDMO). CDMOs have emerged in recent years as preferred partners for vaccine development and scale-up, offering potential capability and cost advantages over in-house manufacturing for pharmaceutical and biotechnology companies. CDMOs have greater flexibility around which technological assets they invest in and may see the long-term value of MAP technology, which also has applications outside of vaccines. CDMOs for vaccine MAPs currently do not exist.

Conclusion

Our analysis shows that a strategy of targeting hard-to-reach populations would generate the highest MR MAP return on investment at $3.2 million in net present value (base case): a scarcely adequate return from the perspective of DCVMs. The findings underscore the critical need to bridge public health expectations with production requirements to ensure that the market assumptions related to any new innovation are informed by the technical and timeline realities inherent in the product development process. A combination of strategies (including demand guarantees, price premiums, and direct financial support for the manufacturing and development process) may be necessary to further boost revenues and improve the attractiveness of the investment.

Overall, the financial models demonstrate that MR MAPs do not currently represent a strong and financially compelling investment opportunity for DCVMs, and this business case provides a starting point to reconsider strategies and promote dialogue on ways to address the risks of producing a novel vaccine presentation for low-resource markets. Highlighted below are some recommended next steps that may help to enhance the MR MAP business case and bring the product to markets in need.

- One of the most compelling public health benefits of MR MAPs is their potential ability to increase measles vaccination coverage rates and address stalled progress to meet measles elimination targets. To accelerate the development process and boost partner engagement, Gavi should clarify their position on MR MAP support to vaccine manufacturers and propose activities to further clarify the business case, which is expected as part of the upcoming VIPS 5-year Action Plan for vaccine MAPs.
- Building on the initial assumptions and methods used in this analysis, donors should actively work with potential manufacturers to iterate and clarify the financial return scenarios based on individual manufacturer assumptions—which can vary significantly depending on location, existing facilities, expertise, etc.—to identify the support and incentives that manufacturing partners would require to de-risk the endeavor and pursue MR MAP development for LMICs.
- Further analysis is needed to clarify the regulatory pathway and determine the studies and costs necessary to bring the MR MAP to market and through WHO prequalification. Conversations with MR MAP developers about technology transfer and future licensing costs must be quantified as well.
- Stakeholders should explore the potential solutions highlighted above, including a potential MMR or MMRV MAP, using modular manufacturing platforms, and partnering with CDMOs as additional options for investment.

Finally, it is important to note that the technology is still in its early stages and many technological and market uncertainties remain that this analysis could not capture. As the MAP technology matures, MR MAP clinical data are generated, and the benefits of the MAP platform are demonstrated with other vaccines and essential medicines, the business case and incentives for investment may improve.

Appendix

MR MAP demand heatmap (by usage scenario and demand case)

MR MAP demand is presented in the heatmap below by usage scenario and demand case (results in the main report present the base demand case only). Overall, demand is highest in the high-demand case and unconstrained scenario.

		2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Base	Hard-to-Reach	9.4M	10.2M	16.9M	19.1M	22.1M	25.1M	25.9M	26.1M	26.3M	26.5M	26.7M
	SIA	9.3M	9.8M	13.2M	12.1M	19.6M	17.5M	8.0M	10.2M	27.7M	12.6M	45.4M
	6 Priority	7.1M	12.9M	18.8M	7.2M	13.0M	23.3M	11.6M	21.3M	31.4M	33.8M	39.5M
	12 Selected	8.3M	8.4M	15.8M	16.0M	16.1M	16.2M	27.1M	30.6M	33.5M	34.8M	39.5M
High	Hard-to-Reach	20.6M	24.5M	24.7M	24.9M	25.5M	25.7M	25.9M	26.1M	26.3M	26.5M	26.7M
	SIA	0.0M	26.0M	22.3M	15.1M	15.8M	39.9M	43.6M	55.9M	11.9M	64.2M	70.6M
	6 Priority	11.1M	21.8M	21.7M	11.0M	11.0M	36.1M	50.9M	57.1M	60.9M	65.4M	68.6M
	12 Selected	23.8M	29.7M	35.8M	40.5M	47.4M	47.7M	48.0M	61.3M	61.5M	75.2M	75.6M
Low	Hard-to-Reach	4.4M	4.4M	6.6M	6.5M	6.5M	6.5M	6.5M	6.5M	13.8M	13.9M	14.0M
	SIA	2.7M	0.6M	1.3M	8.6M	8.0M	3.4M	7.3M	0.6M	8.4M	8.9M	11.5M
	6 Priority	0.0M	0.0M	0.0M	0.0M	5.9M	11.7M	0.0M	5.9M	11.9M	0.0M	6.0M
	12 Selected	0.2M	0.4M	0.4M	0.4M	0.4M	0.4M	0.4M	0.4M	11.3M	11.2M	11.2M
Unconstrained	Hard-to-Reach	24.3M	24.5M	24.7M	24.9M	25.5M	25.7M	25.9M	26.1M	26.3M	26.5M	26.7M
	SIA	100.3M	154.1M	85.0M	116.6M	146.0M	84.5M	132.5M	152.9M	66.2M	150.3M	150.6M
	6 Priority	116.9M	168.1M	109.2M	146.7M	131.0M	126.4M	129.9M	170.3M	97.6M	149.6M	130.6M
	12 Selected	71.1M	71.9M	72.3M	73.8M	73.2M	73.6M	74.0M	74.4M	74.8M	75.2M	75.6M

Abbreviations: MR MAP, measles-rubella vaccine microarray patch; SIA, supplemental immunization activity.

MR MAP revenue heatmap (by usage scenario and demand case)

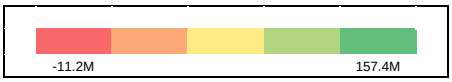
MR MAP revenue is presented in the heatmap below by usage scenario and demand case (results in the main report present the base demand case only). Overall, revenue is highest in the high-demand case and unconstrained scenario.

		2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Base	Hard-to-Reach	$9.9M	$10.8M	$17.9M	$20.2M	$23.4M	$26.6M	$28.4M	$28.6M	$28.8M	$29.0M	$29.2M
	SIA	$9.9M	$10.3M	$14.0M	$12.8M	$20.7M	$18.6M	$8.4M	$10.9M	$29.4M	$13.3M	$48.1M
	6 Priority	$7.3M	$13.5M	$19.7M	$7.4M	$13.6M	$23.5M	$11.1M	$20.6M	$30.5M	$30.0M	$36.1M
	12 Selected	$8.8M	$8.9M	$16.8M	$16.9M	$17.1M	$17.2M	$28.8M	$32.5M	$35.5M	$36.9M	$41.9M
High	Hard-to-Reach	$22.7M	$26.9M	$27.1M	$27.3M	$28.0M	$28.2M	$28.4M	$28.6M	$28.8M	$29.0M	$29.2M
	SIA	$0.0M	$27.5M	$23.6M	$16.1M	$16.8M	$42.3M	$46.2M	$59.3M	$12.6M	$68.0M	$74.9M
	6 Priority	$11.8M	$23.1M	$23.0M	$11.7M	$11.6M	$38.2M	$53.9M	$58.8M	$59.4M	$64.2M	$66.5M
	12 Selected	$25.2M	$31.5M	$37.9M	$43.7M	$51.0M	$51.3M	$51.6M	$65.7M	$66.0M	$80.4M	$80.8M
Low	Hard-to-Reach	$5.5M	$5.6M	$7.9M	$7.9M	$7.9M	$7.9M	$7.9M	$7.9M	$15.6M	$15.7M	$15.8M
	SIA	$6.9M	$1.4M	$3.4M	$21.9M	$26.1M	$8.6M	$18.7M	$1.5M	$27.9M	$22.8M	$29.4M
	6 Priority	$0.0M	$0.0M	$0.0M	$0.0M	$6.2M	$12.5M	$0.0M	$6.3M	$12.6M	$0.0M	$6.3M
	12 Selected	$0.5M	$1.1M	$1.1M	$1.1M	$1.1M	$1.1M	$1.1M	$1.1M	$12.6M	$12.5M	$12.5M
Unconstrained	Hard-to-Reach	$26.7M	$26.9M	$27.1M	$27.3M	$28.0M	$28.2M	$28.4M	$28.6M	$28.8M	$29.0M	$29.2M
	SIA	$139.4M	$175.7M	$124.2M	$156.1M	$188.0M	$109.2M	$189.4M	$175.2M	$105.6M	$193.5M	$200.0M
	6 Priority	$114.3M	$168.6M	$106.2M	$146.0M	$129.4M	$124.7M	$128.5M	$171.5M	$94.5M	$149.7M	$129.6M
	12 Selected	$75.8M	$76.9M	$77.4M	$79.0M	$78.3M	$78.7M	$79.2M	$79.6M	$80.0M	$80.4M	$80.8M

Abbreviations: MR MAP, measles-rubella vaccine microarray patch; SIA, supplemental immunization activity.

MR MAP NPV heatmap by discount rate, usage scenario, and demand case

MR MAP NPV at both 10% and 25% discount rates are presented in the heatmap below by usage scenario (results in the main report present the base demand case only). The NPV is highest in the unconstrained SIA scenario at a discount rate of 10%. The lowest NPV is in the low demand case in both the 6 priority countries (RI and campaigns) and 12 selected countries (RI only).



		Low	Base	High	Unconstrained
NPV (10%)	Hard-to-Reach	-$5.2M	$3.2M	$9.4M	$9.9M
	SIA	$10.8M	-$2.3M	$7.9M	$157.4M
	6 Priority	-$11.2M	-$3.0M	$11.6M	$71.2M
	12 Selected	-$10.7M	$2.2M	$17.8M	$39.8M
NPV (25%)	Hard-to-Reach	-$6.4M	-$4.9M	-$3.2M	-$3.1M
	SIA	-$3.4M	-$5.7M	-$4.3M	$28.2M
	6 Priority	-$7.5M	-$6.0M	-$3.5M	$9.0M
	12 Selected	-$7.6M	-$5.2M	-$2.0M	$3.3M

Abbreviations: MR MAP, measles-rubella vaccine microarray patch; NPV, net present value; SIA, supplemental immunization activity.

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