EMBARGOED FOR RELEASE UNTIL
THURSDAY, NOVEMBER 14 AT 8:00 AM EST // 2.00 PM CET
(1300 Hours GMT)

MALARIA VACCINE TECHNOLOGY ROADMAP

NOVEMBER **2013**

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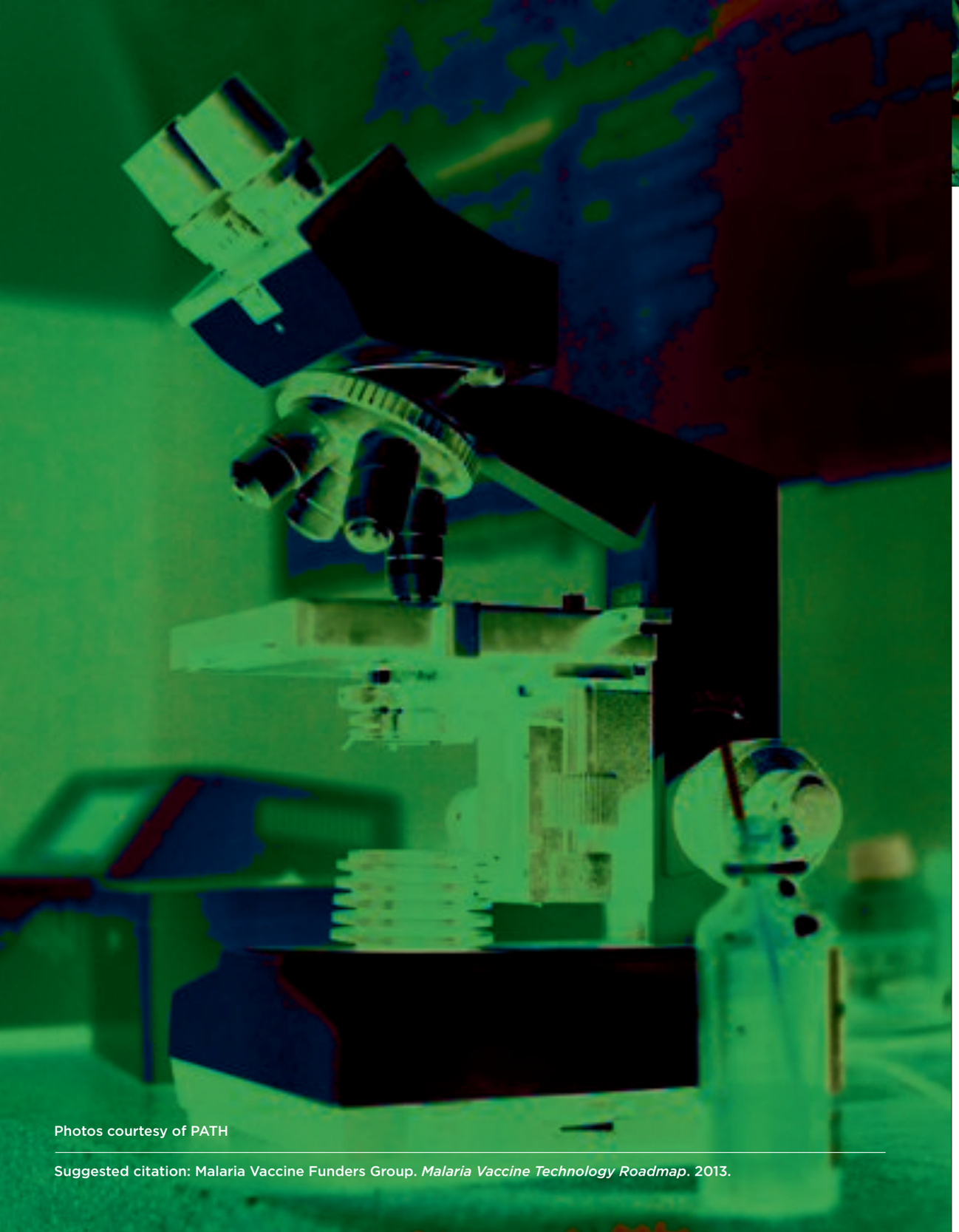


Photos courtesy of PATH

Suggested citation: Malaria Vaccine Funders Group. *Malaria Vaccine Technology Roadmap*. 2013.

Background

This publication represents the result of a review process facilitated by the World Health Organization (WHO), which worked with the Malaria Vaccine Funders Group to update the vision and strategic goals of the Malaria Vaccine Technology Roadmap.[1] Originally launched at the 2006 WHO Global Vaccine Research Forum and supported by the Funders Group, the Roadmap forms a strategic framework that underpins the activities of the global malaria vaccine research and development (R&D) community.

This update responds to the recognition that the malaria epidemiological and control status has changed markedly since 2006 when the Roadmap was originally launched. For instance, substantial changes in malaria epidemiology are now being observed in many settings following a reduction in malaria transmission,[2] which has occurred in association with the scale-up of malaria control measures. The reduction in malaria transmission is associated with a shift in the peak age of clinical malaria to older children,[3] as well as an increase in the median age of malaria-related hospitalization in some settings.[4, 5]

In response to these developments and acknowledging substantial changes in the strategic direction of malaria research, the shared vision and strategic goals of the Roadmap have been expanded. The vision and goals now encompass the current ambitious aims of the global malaria community, which include prevention of malaria disease and deaths, accompanied by the accepted goals of progressive malaria elimination and—ultimately—global eradication. In addition, the revision includes the need to address *Plasmodium vivax* malaria infections (in contrast to *Plasmodium falciparum* alone), all malaria-endemic areas

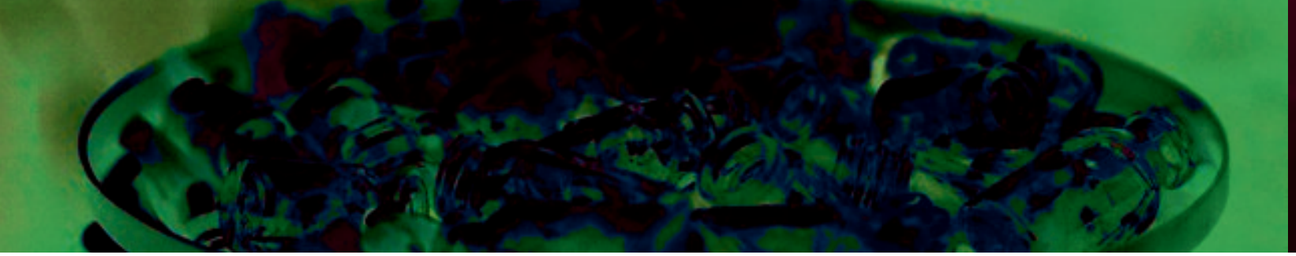
[1] Malaria Vaccine Funders Group. *Malaria Vaccine Technology Roadmap*. 2006. Available from: http://bit.ly/1hdPaS4

[2] World Health Organization (WHO). *World Malaria Report 2012*. Geneva: WHO; 2012. Available from: www.who.int/malaria.

[3] Carneiro I, Roca-Feltrer A, Griffin JT, et al. *Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis*. PLoS ONE. 2010;5(2):e8988.

[4] O'Meara WP, Bejon P, Mwangi TW, et al. *Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya*. Lancet. 2008 Nov 1;372(9649):1555-62.

[5] Ceesay SJ, Casals-Pascual C, Erskine J, et al. *Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis*. Lancet. 2008 Nov 1;372(9649):1545-54.



(in contrast to sub-Saharan Africa alone), and all ages (in contrast to children younger than five only).

The expanded strategic goals also take note of an indicator of progress set by the global health community. The 2012 World Health Assembly for the Global Vaccine Action Plan of the Decade of Vaccines called for "proof of concept for a vaccine that shows greater than or equal to 75 percent efficacy for HIV/AIDS, tuberculosis, or malaria by 2020."

While the strategic goals have been expanded, the priority areas, which include the range of initiatives required to accelerate progress, are updated, as necessary, to reflect the new vision and strategic goals and to take into account the major progress in many of the areas since 2006. On the other hand, the Roadmap's 2015 landmark goal, which focuses on a first-generation malaria vaccine, remains unchanged:

By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50 percent against severe disease and death and lasts longer than one year.

The Malaria Vaccine Funders Group

The Malaria Vaccine Funders Group, an informal group of some of the key funders of malaria vaccine development, includes the Bill & Melinda Gates Foundation, the European & Developing Countries Clinical Trials Partnership, the European Vaccine Initiative, the European Commission, the PATH Malaria Vaccine Initiative, the US Agency for International Development, the US National Institute of Allergy and Infectious Diseases, the Wellcome Trust, and the World Health Organization.

Keeping the Roadmap up to date in the future

IT WILL BE IMPORTANT FOR THE MALARIA VACCINE community to work with the malaria control and elimination communities to ensure that products under development are suitable for use alongside current WHO-recommended malaria prevention, diagnostic, and treatment measures.

Vision

Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent disease and death and prevent transmission to enable malaria eradication.

Strategic goals

By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* that encompass the following two objectives, for use by the international public health community:

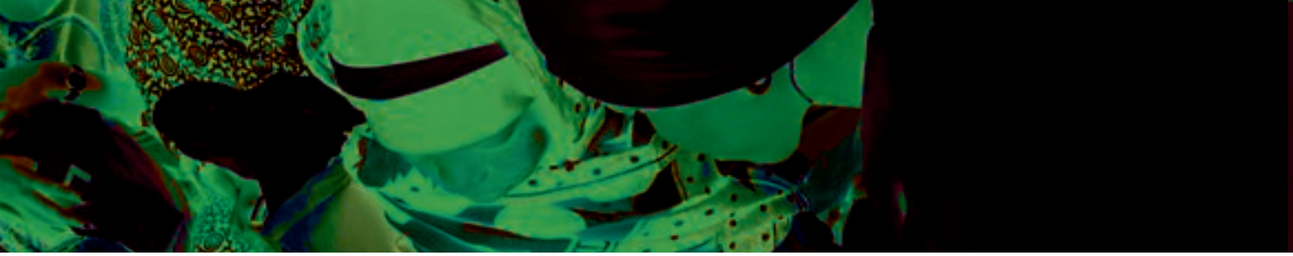
1. Development of malaria vaccines with protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas.[6]

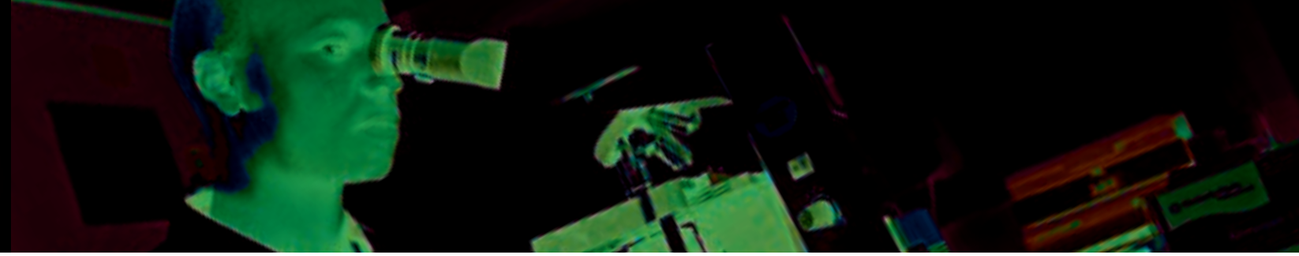
2. Development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns.

Addressing the public health need for malaria vaccines

VACCINE R&D SHOULD ADDRESS AN UNMET PUBLIC HEALTH need. To do this, the unmet need would need to be identified and defined, and product development plans put in place. The Roadmap's strategic goals provide guidance on the two highest priorities in terms of the public health need for malaria vaccines. However, WHO provides further guidance for product development groups on the vaccine characteristics that would address these strategic goals.

[6] Duration of protection will be demonstrated over at least two years. Booster doses will be required no more frequently than annually.





Two sets of WHO preferred product characteristics (PPCs), developed in 2013-2014, identify the malaria vaccine characteristics that would most likely meet the two strategic goals of the Roadmap and that could be suitable for use in malaria-endemic settings. Any malaria vaccine that becomes available for use in malaria-endemic countries will undergo evidence-based policy assessment by WHO through standard policy processes. The PPCs provide information on the desired characteristics of vaccines both in terms of meeting the public health need and in terms of lowering the burden on developing countries' immunization and malaria control programs. However, those vaccines that do not meet the WHO PPCs will not be excluded from WHO consideration for policy recommendation and prequalification.

WHO encourages that each product development group develop its own target product profiles (TPPs) before finalizing Phase 3 plans for vaccine development. TPPs may be submitted as part of pre-Phase 3 discussions. If groups seek WHO recommendation and prequalification, their TPPs should be informed by the WHO PPCs.

Target audience for this update

- **The vision** and strategic goals are intended to inform leadership within international and national donor, financing, research, and public health agencies, as well as governments of malaria-endemic countries.
- **The strategic goals** are also of interest to malaria vaccine developers in academia, government agencies, public-private partnerships, and industry.
- **The WHO** malaria vaccine PPCs are intended to inform a technical audience in R&D in industry, public-private partnerships, academia, and government agencies who have an interest in developing malaria vaccines to meet the public health need in malaria-endemic countries.

Malaria Vaccine Technology Roadmap updated priority areas

Research

1. **DEVELOP** immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.
2. **STANDARDIZE** clinical trial design and assessment to allow comparison of data.
3. **USE** state-of-the-art approaches to identify novel potential candidate vaccine targets.

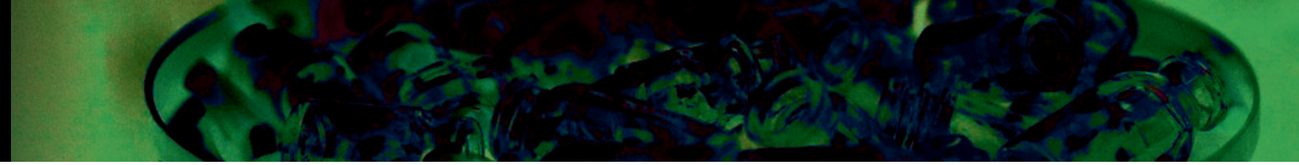
> **NOTE** **Priority areas 1, 2, and 3**: These continue to be major priorities for activity. A great deal of progress has been made in these areas since 2006, and further work is encouraged from 2013 onward.

4. **CONFIRM** candidate vaccine targets and mechanisms of protection, using controlled human malaria infection models as appropriate.

> **NOTE** **New priority area 4**: It is a community priority to transition new candidate vaccine antigens and constructs beyond antigen discovery and validation to clinical proof-of-concept studies. The potential role of controlled human infection studies to accelerate timelines is highlighted.

5. **ENSURE** that results from all funded malaria vaccine clinical trials are publicly available within 12 months of the last visit of the last subject for the primary endpoint, and encourage public sharing of all funded nonhuman primate studies within 12 months of completion of the primary immunological endpoint.

> **NOTE** **New priority area 5**: This timeline stipulates availability of key outcomes of clinical trials within 12 months of the last visit of the last subject for the primary endpoint of the study, regardless of study completion date. It is understood that exploratory analyses will not always be available at this time, but neither lack of study completion nor ongoing exploratory analyses should prevent presentation of key outcomes in a public forum such as a research conference. Where results cannot be published because of difficulties securing journal publication, another option for public disclosure would be website posting (e.g., for trials with negative outcomes).



Vaccine development

6 **ESTABLISH** a systematic approach for prioritizing vaccine candidates (including multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches). Candidates will be prioritized, taking into account PPCs, back-validation from clinical to nonclinical models, immune correlates, and/or head-to-head comparisons.

NOTE **New priority area 6**: This area merges two previous vaccine development priorities.

7 **DEVELOP** immunological correlates of vaccine-induced protection and surrogate efficacy end-points to advance vaccine development and licensure timelines.

NOTE **New priority area 7**: Success with this new priority would dramatically improve the prospects for second-generation malaria vaccine development.

Key capacities

8 **ACCESS** to low-cost vaccine manufacturing under current Good Manufacturing Practices (cGMPs) for late-stage development and commercial production.

NOTE **Priority area 8**: The wording of a previous priority area has been revised to better reflect the intent articulated in the 2006 Roadmap that formulations be developed that can be economically manufactured in a cGMP environment. Low-cost manufacturing, a common term used in industry, is not meant to imply low quality or to specify a particular currency amount.

9 **PROMOTE** sufficient and sustainable Good Clinical Practice (GCP) clinical trial, regulatory, and ethics capacity in malaria-endemic regions to accommodate a variety of clinical trials (including clinical trials with human-to-mosquito transmission endpoints) required for malaria vaccine development.

NOTE **Priority area 9**: This area has been updated to include the need for regulatory and ethics capacity in addition to GCP capacity. The costs of this effort should be integrated into capacity development for all new product evaluation in developing countries, and the malaria vaccine community should not bear the costs alone. In addition, this priority area encompasses clinical trials with mosquito transmission/infection endpoints as well as those with disease endpoints.

10 **DEVELOP** approaches to address the need for appropriate, post-approval pharmacovigilance and effectiveness testing capacity in malaria-endemic regions in order to ensure timely malaria vaccine introduction and implementation.

NOTE **New priority area 10**: This area represents a critical gap in the product development and evaluation landscape for products intended specifically for developing countries. R&D funding agencies cannot bear the costs for this activity alone, and broad support is required from many partners to fill this gap. It should be noted also that the malaria vaccine community does not necessarily need to be alone in carrying the burden of building and sustaining capacity and will work with others outside the community to ensure that capacity is sufficient when needed.

Policy and commercialization

11 **ENSURE** data are available to support timely, evidence-based decision-making by national immunization and malaria control programs.

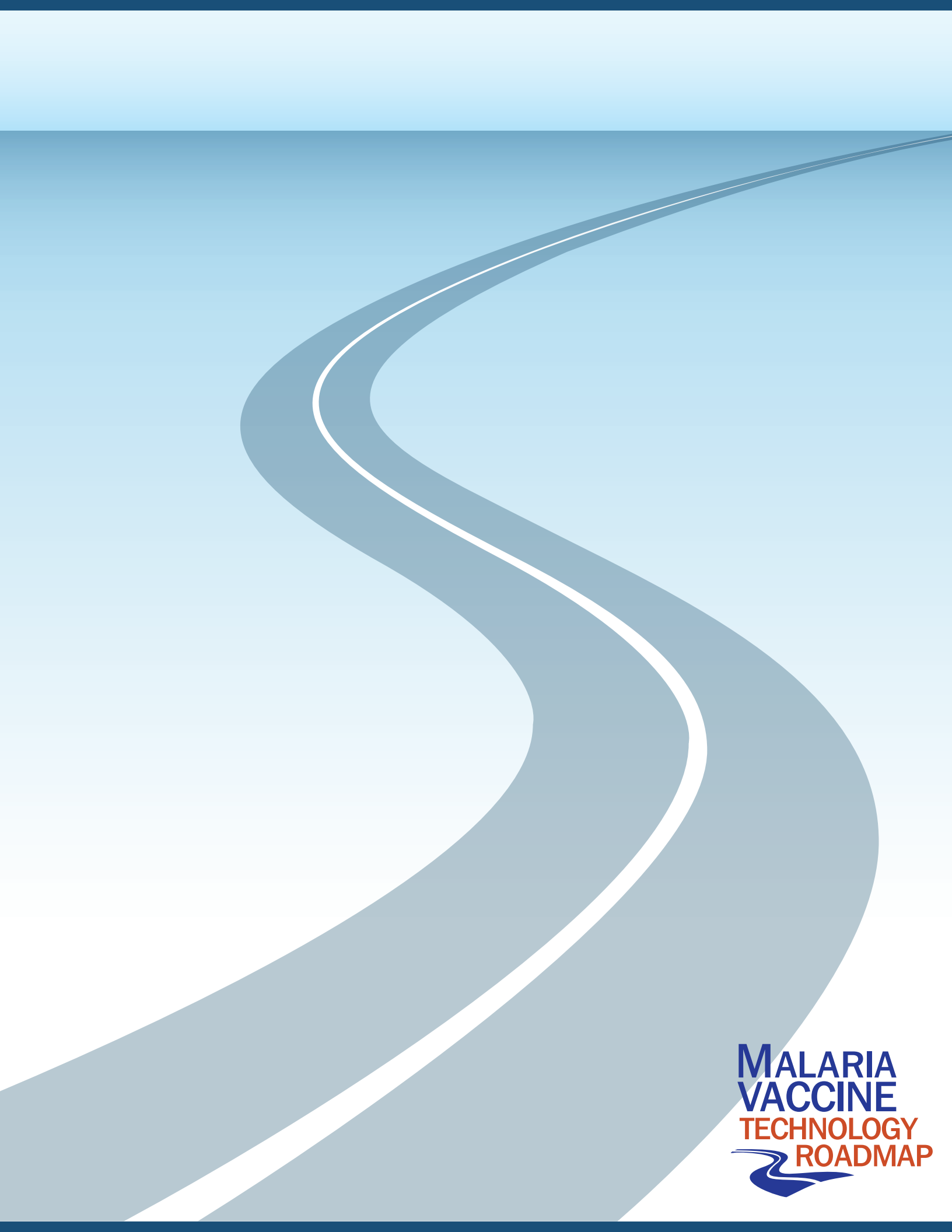
NOTE **Priority area 11**: A substantially revised previous priority area now emphasizes the generation of country-level data to support independent decision-making by national authorities about potential malaria vaccine introduction.

12 **DEVELOP** and encourage responsible stewardship and support for malaria vaccine development and implementation through appropriate project management and investment strategies (e.g., through developing a business case).

NOTE **New priority area 12**: This area highlights the importance of preparing business and investment cases for product development pathways. Rather than focusing on financing alone, it is important to look at the costs to support development and implementation overall. As such, business cases would need to be developed prior to investment in each stage of development. Prior to proof of concept, a business case would include a value proposition, PPCs, estimated development costs, options for financing, and an initial market assessment. Prior to entering into Phase 3, the case would be more comprehensive and would be developed and agreed upon among manufacturers, donors, WHO, global-level financiers, and countries. This process will be especially important for an eradication agenda. The detailed business case prior to Phase 3 would include a value proposition, a TPP, late-stage development costs, a financing plan, a strategic demand forecast, estimated capital costs, and pricing assumptions.

13 **DEVELOP** novel regulatory strategies to expedite approval while ensuring quality and safety.

NOTE **Priority area 13**: This area includes a minor edit to the previous wording, with the addition of the word ‘quality’.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