4

The Market Shaping Goal

Shape vaccine markets to ensure adequate supply of appropriate, quality vaccines at low and sustainable prices for developing countries.

Supply and Procurement Roadmap

Measles IgM Rapid Diagnostics Capacity

PUBLIC SUMMARY
FINAL DRAFT

Purpose and scope

The roadmap is a foundational tool of Gavi's market shaping strategy with the purpose to articulate a mid- and long-term market strategy designed to align market-shaping objectives and target outcomes across the Alliance partners, define a set of interventions to reach these objectives and target outcomes, and inform procurement strategies and decisions. The objectives, target outcomes and interventions articulated in this roadmap focus on provision of measles immunoglobulin M (IgM) rapid diagnostic tests (RDTs) for Gavi supported countries, while including global market considerations to highlight interdependencies and their impact on overall market health.

Current epidemiological context of measles and Gavi engagement in measles IgM rapid diagnostic tests

Measles remains a leading cause of death among young children in low and middle-income countries (LMICs), despite considerable progress over the last decade[1]. The major measles control activities in addition to routine vaccination are supplemental immunisation activities (SIAs), i.e., periodic national or regional campaigns aimed at providing vaccine to everyone in a defined age range.[2] Ultimately, the core solution to measles control lies in routine vaccination with at least two doses of measles-containing vaccine (MCV) but, in much of the world, SIAs are relied upon to achieve adequate coverage. However, even countries thought to have highly successful control sometimes experience large outbreaks because of unnoticed build-ups of susceptible individuals, as occurred in countries such as Zambia, Malawi, and Burkina Faso.[3]

For both preventive SIAs and outbreak response SIAs, timely and reliable information on whom to target for vaccination can potentially help make the SIAs more efficient by reducing the number of unnecessary vaccinations and more effective by identifying at-risk and unreached groups that need to be vaccinated, potentially contributing to a reduced frequency and scope of such SIAs over time. The clinical similarities between measles and other diseases (such as rubella or parvovirus B19) that can cause fever and rash make it important to have validated diagnostic tests to confirm that suspected measles cases are in fact measles.

Without such testing, measles can easily be confused with other diseases that cause fever and rash. Lack of laboratory confirmation may lead to assessments that measles is not a problem in an area when they are in fact causing deaths and disability, or to assessments that measles is a significant burden requiring larger campaigns extending to areas where that is not the case. For example, measles infection data can help indicate whether a few vs. many districts need to be covered by a campaign and whether a narrow vs. wide age range needs to be targeted. Such data can determine how SIAs can be tailored to the local epidemiology in order to make them more effective.

Gavi-supported vaccination against measles and rubella is projected to prevent approximately 1.4 million deaths during 2021-2025 through a mix of routine Immunisation and preventive and outbreak response, with an estimated cost of US$ 239 million for procurement of vaccine for preventive campaigns and routine immunisation use alone.[4] Most

---

[1] World Health Organization. Progress towards regional measles elimination, worldwide, 2000±2014. Wkly Epidemiol Rec. 2015; 90: 623±31. PMID: 26567399

[2] World Health Organization. Global measles and rubella strategic plan: 2012±2020. Geneva: World Health Organization; 2012

[3] Cutts FT, Lessler J, Metcalf CJ. Measles elimination: progress, challenges and implications for rubella control. Expert Rev Vaccines. 2013; 12: 917±32. doi: 10.1586/14760584.2013.814847 PMID:23984961

[4] Gavi Board Paper; Diagnostics to Support Targeted Vaccination In Gavi 5.0; 30 November – 02 December, 2021

of these benefits and costs are specific to measles vaccination. Although measles vaccination is already amongst the most cost-effective Gavi investment, new diagnostic technology is creating opportunities to improve the effectiveness and efficiency of their use. Gavi Alliance support for the introduction and routine use of these diagnostic innovations will help ensure that they can aid immunisation programme decision making by helping make available more reliable and timely information on where and when strengthening of measles vaccination is needed to close immunity gaps.

Improved measles diagnostic tests can aid immunisation programme decision making in several ways beyond contributing to the fundamental role of surveillance underpinning all immunisation programmes. For example, expanded measles diagnostic testing help better identify areas with immunity gaps resulting from under- or lack of vaccination, allowing immunization programmes to focus efforts to improve routine immunization on those areas to reach zero dose children and other groups. Similarly, more detailed and timely measles data incorporating diagnostic confirmation could facilitate more effective and efficient targeting of preventive SIAs to close population immunity gaps, including subnational preventive measles SIAs in countries with relatively high population immunity and strong immunization programmes. When measles outbreaks do happen, improved measles data incorporating accurate, decentralized diagnostic confirmation can allow them to be detected, responded to, and mitigated more quickly and effectively.

Based on WHO's estimates and expectations that annual measles testing will steadily increase as reliable, validated,[5] and cost-effective measles IgM RDT kits become available, the 'addressable' (i.e. taking into account funding, policy and other constraints) annual demand is currently projected as:

- 140,000 RDTs from Gavi-eligible countries with at least 80% coverage for 1st dose of measles containing vaccine. These are the Gavi-eligible countries where measles RDTs will likely have the most demand in the near term
- 130,000 RDTs from Gavi-eligible countries with less than 80% coverage for 1st dose of measles containing vaccine. Near term use of RDTs are expected to be lower priority in these countries
- 100,000 RDTs from non-Gavi-eligible countries

Overview of measles IgM rapid diagnostic tests market health

To date, no measles IgM RDTs have received WHO prequalification, or otherwise been fully validated by a WHO expert review group. However, at least one measles RDT is under development and is expected to become commercially available by 2024. Earlier work by Public Health England indicates that developing an accurate, reliable measles RDT is feasible.[6] The GMRLN has been encouraging development of measles IgM RDTs for years and has developed a preliminary Target Product Profile (TPP) for such tests. The TPP is expected to be finalized by early 2024. The GMRLN is also prepared to evaluate commercially available measles IgM RDTs as it has measles IgM ELISA test kits.

Laboratory-based ELISA testing for sera is currently the mainstay of testing for measles infection. ELISA testing at national reference laboratories is very accurate if performed correctly but has reduced positive predictive value in low incidence settings. The Global Measles Rubella Laboratory Network (GMRLN) organised by WHO and funded by the United States Centres for Disease Control and Prevention (CDC), has played a key role in supporting laboratory testing in Gavi-eligible countries, including evaluating commercially

[5] 'Validated' refers to products that have received WHO pre-qualification or endorsement by a WHO expert review committee such as a Expert Review Panel for Diagnostics

[6] Brown DW, Warrener L, Scobie HM, et al. Rapid diagnostic tests to address challenges for global measles surveillance. Curr Opin Virol. 2020 Apr;41:77-84. doi: 10.1016/j.coviro.2020.05.007.

available measles ELISA test kits. These GMRLN evaluations have resulted in several kits being validated for use in network laboratories, which typically receive more than 270,000 samples per year for measles diagnostic serology from all countries regardless of eligibility for Gavi new vaccine support. GMRLN laboratories also perform genetic characterisation of measles viruses, to track the spread of these viruses within and across countries. GMRLN has established strong quality control systems for serologic and molecular testing.

Many national and regional laboratories also perform Real Time Polymerase Chain Reaction (RT-PCR) to detect viral Ribo-Nucleic Acid (RNA). RT-PCR testing can help confirm measles in very low incidence settings.

Although very valuable for guiding immunisation program decision making, laboratory-based ELISA and RT-PCR testing have several limitations. Most importantly, blood and other specimens from suspected measles cases must be transported from where they are collected to the relevant reference laboratory. At a minimum, this adds substantially to the time needed to complete testing, and at worst can lead to samples not arriving or being in poor condition if they are not stored properly. If accurate measles Rapid Diagnostic Tests (RDTs) were available, they would potentially allow more decentralised testing, which in turn could increase the timeliness and utility of measles diagnostic testing results. Such RDTs can be used with less training and equipment than ELISA tests, so a wide range of front-line health care workers can utilize such tests.

Healthy market dynamics and current challenges

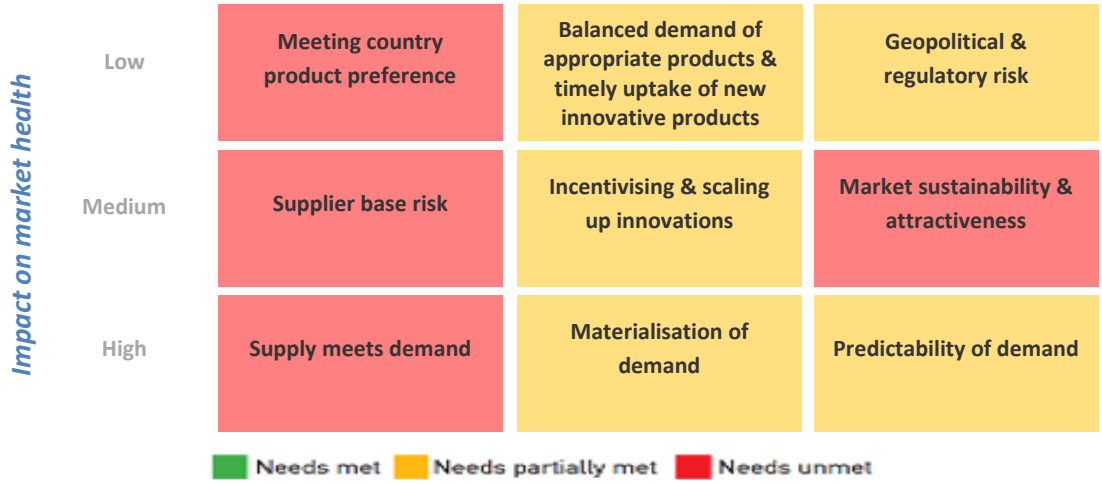
The greatest challenges currently facing the measles IgM RDT market are: (1) ensuring Gavi-countries' specific demand for IgM RDTs versus the current ELISA and PCR tests is well understood and met (2) ensuring supply availability from viable suppliers whose diagnostics products meet the Alliance's standards for procurement of their products and can sufficiently meet the global demand (3) ensuring the measles RDT market remains attractive to current and future suppliers in the long-term.

Although there is scope for improvement, the current measles IgM RDT 'market health' is categorised as unacceptable and requires further intervention given that all high and medium impact 'healthy market attributes' are either unmet or only partially met. Five market health attributes are partially met: predictability of demand, materialisation of demand, balanced demand of appropriate products & timely update of new products, incentivising and scaling up innovations, and geopolitical & regulatory risks. Four attributes are however unmet: highlighting concerns with supplier base risk, supply meeting demand, meeting country preferences and achieving market sustainability & attractiveness.

Once a measles IgM RDT receives basic regulatory approval, funding will be needed for the procurement and distribution of such tests. Gavi Alliance involvement with encouraging the availability and use of measles RDTs in subnational laboratories and clinics or other settings would benefit Gavi-supported measles immunisation efforts, particularly efforts to make measles preventive vaccination SIAs more efficient and effective. Gavi can fund pooled procurement to encourage diagnostic manufacturers' involvement in this market, as indicated by the experience with yellow fever diagnostics.[7, 8]

[7] Johnson BW, Demanou M, Fall G, et al. Laboratory capacity assessments in 25 African countries at high risk of yellow fever, August–December 2018. Pan Afr Med J 2021; 38: 402.
[8] Hampton LM. Improving yellow fever diagnostic testing for more efficient, effective, and equitable vaccination. Sept 7, 2021 https://www.gavi.org/vaccineswork/improving-yellow-fever-diagnostic-testing-more-efficient-effective-and-equitable (accessed 06 Dec 2022)

Figure 1: Market Health Assessment 2022, based on Gavi Alliance Healthy Market Framework Market



Materialisation of demand: **Partially met**. The WHO Global Measles and Rubella Laboratory Network (GMRLN) alone annually receives several hundred thousand samples from suspected measles cases for further testing. All of these samples must be transported from the site of collection to reference laboratories for testing, and many could be tested by RDTs as part of a more decentralised testing approach. Although there are many samples from suspected measles cases that need to be tested, the proportion that countries will want to test with measles RDTs is not yet clear.

Predictabily of demand: **Partially met**. Annual country reporting to WHO indicates that at least several hundred thousand samples from suspected measles cases consistently need to be tested each year, however, the numbers can significantly vary year to year, particularly during measles outbreaks. Also, the proportion of suspected measles cases that countries will want to test with measles RDTs year on year is not yet clear.

Balanced demand of appropriate products & timely uptake of new innovative products: **Partially met**. Currently there are no validated, commercially available measles RDTs. However, a 2020 study conducted in India, Brazil and Malaysia by the WHO-organized, CDC-funded Global Measles Rubella Laboratory Network (GMRLN) using protoptype RDTs indicates a positive and widespread demand and uptake for rapid diagnostic tests (RDTs) due to affordability, ease of distribution and use at point of care.

Supply meets demand: **Unmet.** There are no reliable and cost-effective test kits available in the market that have WHO prequalification, or otherwise been validated by WHO-designated expert committee.

Meeting country product preferences: **Unmet.** Test kits need to be usable in settings relevant to countries. Laboratory-based ELISA testing for measles IgM antibodies and real-time reverse transcriptase polymerase chain reaction (RT-(q)PCR) to detect viral RNA are currently in use by many national laboratories. Despite the significant drawbacks (such as need for extensive consumable supplies or additional laboratory equipment) associated with the current testing methods; preference for use of RDTs in place of or in addition to the current ELISA and PCR tests, is yet to be established.

Supplier base risks: **Unmet**. Due diligence on manufacturers' technical production capacity, reliability, buffer capacity, sustainability, technical risks, diversity, portfolio viability and market interest is needed.

Geopolitical & Regulatory risks: **Partially met**. Draft Target Product Profiles and related WHO prequalification standards for assessment & qualification of measles rapid diagnostic tests are available and expected to be published in early 2024.There is a relatively well established WHO expert committee process led by GMRLN which can evaluate RDTs and

provide interim recommendations on their use. Geopolitical risks which may impact release or exports of diagnostic test kits from the countries of production are unknown and are to be determined.

Market sustainability & attractiveness: **Unmet**. Whilst there are a number of manufacturers with promising RDTs, when compared to other diseases that are considered to be a global threat (such as malaria), demand for measles (potentially millions vs 100s of millions) is relatively small and may not be high enough to sustain the interstets of manufacturers in the long term. Between Gavi and the US Center for Disease Control (CDC) there are multiple interested international funders for cheaper, reliable tests given the global focus on measles.

Incentivising & scaling up innovations: **Partially met**. A number of innovative approaches are currently available or in advanced development. Funding has been made available by some Alliance partners, in particular, the Bill and Melinda Gates Foundation (BMGF) to support and accelerate development through to regulatory approval of a measles RDT initially developed by Public Health England. A good understanding of market incentives to generate higher level of interest from other manufacturers is needed.

With Gavi Alliance interventions, the measles RDT supply market health is expected to shift to acceptable levels in the next 3-5 years. This shift depends on multiple factors, including whether kits in the pipeline become commercially available and successfully pass the Alliance's quality assurance tests and standards for procurement and meet country preferences; sustained market attraction to existing and new players; and the impact of the next generation diagnostics technologies in driving long-term competition in the global measles diagnostics market.

Strategy to sustainably improve market health

Gavi partners have defined a long-term strategy for the measles IgM RDT market to address these challenges, by reviewing different scenarios in terms of annual demand forecast for Measles IgM RDTs, available suppliers, product suitability & affordability and long-term business sustainability. It translates into the following strategic market objectives:

Objective 1 – *Establish and maintain long-term demand for measles IgM RDT and generate signals of a more attractive market to suppliers with viable products*

Establishing and maintaining a healthy demand for measles IgM RDTs is critical to long-term market sustainability and attractiveness to measles diagnostics suppliers

- Target Outcome 1: Understanding demand for measles IgM RDTs, in comparison to existing laboratory-based tests, improves sufficiently to facilitate more steady and predictable demand by 2025
- Target Outcome 2: By 2025, measles IgM rapid diagnostic test(s) are effectively distributed to meet country demand and generate useful data to inform country immunisation program decisions, including applications for Gavi vaccine support and requests for international outbreak response support

Objective 2 *– Ensure supply availability of validated IgM measles rapid diagnostic tests from viable suppliers to enable procurement and delivery to Gavi eligible countries*

The number of suppliers is a key driver of measles diagnostics market health along the dimensions of supply availability, supply security, meeting country preferences and product adoption, regulatory and supplier risks and long- term competition. A 2022 market review indicates that at least one RDT under development may be advanced enough to potentially pass Gavi Alliance quality assurance assessments by 2024. The market review also indicates that that there are at least four manufacturers with early stage but promising innovative RDTs for effectively detecting suspected cases of measles, which may be

available for Gavi Alliance purchase and distribution to Gavi-supported countries from 2025 onwards.

- Target Outcome 3: At least one commercial IgM Rapid Diagnostic Test (RDT) for measles surveillance meets the Alliance quality standards for procurement, by 2025

***Objective 3** – Drive innovation and long-term competition, and encourage competitive pricing*

The number of new and innovative measles RDT products is an opportunity to further shape the market and improve its health by ensuring that:

- Target Outcome 4: Gavi and Alliance partners updates understanding of technical breakthroughs and improvements in the next generation of commercially available and validated measles rapid diagnostic tests
- Target Outcome 5: Long-term market health and competitive pricing for commercially available and validated measles test kits is established

A concerted action plan ensures the coordination between Gavi and Partners and facilitates the achievement of the above strategic market objectives by:

Demand side interventions:

- Rolling out pilot projects, once WHO validated measles IgM RDTs are available, to better understand and define country demand for measles diagnostics, barriers and enablers to implementation
- Using results from the pilot projects to encourage countries to adopt decentralised testing, including use of guidance on how best to use the RDTs to support immunisation programme decision making

Supply side interventions:

- Finalising and disseminating WHO measles IgM RDT TPPs
- Evaluation of commercially available measles IgM RDTs by GMLRN to determine if they warrant use
- Engaging current manufacturers through in-depth exploratory discussions that will seek to better understand barriers to supply and to explore creatively what interventions or investments may improve supply, develop flexibility to meet sudden increases of demand, and ensure sustainable pricing
- Accelerating work with manufacturers that currently supply non-WHO pre-qualified and non-validated measles RDTs to confirm and maintain Good Manufacturing Practices (GMP) status, validate their test kits, and potentially assure volume and reliability of supply
- Working with other pipeline manufacturers to develop and validate additional measles RDTs that are appropriate for the Gavi market
- Encouraging development of new innovative technologies in measles sample testing and laboratory platforms
- Facilitating timely supply and delivery of validated measles RDTs to target countries