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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

Cholera Diagnostics Capacity

PUBLIC SUMMARY
FINAL

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 cholera diagnostics for Gavi supported countries, while including global market considerations to highlight interdependencies and their impact on overall market health.

Current epidemiological context of cholera and Gavi engagement in cholera diagnostics

Cholera is an acute diarrhoeal infection caused by a toxigenic O1 or O139 bacterial strain of *Vibrio cholerae* (VC). While control measures including early detection and response, treatment of cases with rehydration therapy and antibiotics for severe cases, and use of oral cholera vaccines (OCVs) reduce cholera morbidity and mortality, improving water, sanitation and hygiene (WASH) conditions is essential for a sustained reduction in risk of outbreaks.

In 2018, the Gavi Board authorised funding to support implementation of OCV preventive vaccination and cholera outbreak response campaigns, and since 2023 the Gavi secretariat opened an application window for countries to submit requests for such funding support on a routine basis. The Gavi Board's approval was premised on the OCV preventive vaccination campaigns focusing on cholera "hotspots," i.e., areas where outbreaks are predictable and recur on a regular basis,[1] and such campaigns being part of long-term, multi-sectorial strategies integrating additional risk reduction measures (such as improved sanitation infrastructure and surveillance). Given the relatively short duration of protection from OCV, i.e., three to five years, individual hotspots may require repeated preventive campaigns over time for the populations in those hotspots, particularly if cholera continues to circulate in those hotspots.

Although accurate identification of hotspots is critical if preventive OCV campaigns are to be effectively targeted, currently available data have major shortcomings. Limitations in the availability and use of cholera diagnostic tests have resulted in many areas not having cholera data incorporating laboratory or diagnostic confirmation, especially over long periods of time. For example, of 223,370 cholera cases reported to WHO in 2021, almost all of which were from countries eligible for Gavi new vaccine support, only 23,656 samples (11%) reportedly underwent some level of diagnostic testing, including use of Rapid Diagnostic Tests (RDTs).[2] In addition, the lack of available and reliable diagnostic tools has led to extensive variation in applied sampling and testing strategies and inconsistency of test methods in use, further complicating data analysis. As a result, only data on suspected cholera or acute watery diarrhoea cases are consistently available across all countries for targeting of preventive OCV campaigns. Since cholera resembles many other diseases, (e.g., acute diarrhoea can be caused by a range of bacteria, viruses, and parasites), the lack of reliable diagnostic data may lead to some areas reporting high numbers of suspected cholera cases being inadvertently and inaccurately identified as high priority for OCV campaigns. Conversely, actual high priority areas may not be targeted for OCV preventive campaigns in a timely manner. Given the finite supplies of OCV, this approach to targeting may in these instances, result in an ineffective and unnecessary increased use of OCV in lower priority areas and/or late or worse, non-targeting of high priority areas in greater need

[1] Report of Annual Meeting of International Coordination Group on Vaccine Provision for Cholera, 11 September 2019

[2] World Health Organization. Cholera, 2021. Weekly Epidemiological Record. 2022; 97: 453-64.

for OCV. However, the alternative of only conducting preventive OCV campaigns in areas showing persistent transmission of laboratory-confirmed cholera could currently result in even more areas that have persistent cholera not being targeted for OCV preventive campaigns because such targeting would largely be driven by the presence or lack of cholera testing capacity in a context in which many areas do not routinely have the capacity to diagnostically confirm cholera cases.

Gavi funding for cholera preventive and outbreak response vaccination campaigns during 2021-2025 is currently estimated at US$ 380 million[3]. Given the scale of Gavi's planned funding for preventive OCV campaigns, even relatively small improvements in their effectiveness, efficiency, and equity could make a substantial difference to the current constrained OCV supply environment. Gavi Alliance support for the availability and use of cholera diagnostic tests can address major gaps that have limited their availability and use so that use of such tests can aid immunisation programme decision making on where and when to vaccinate against cholera in a sustainable and effective manner.

Three main types of cholera testing exist: culture, molecular diagnostics methods, and Rapid Diagnostic Tests (RDTs), each with their own advantages and limitations.

- Culture testing is the simplest and cheapest confirmation technique. It requires specialized training, which has uneven availability and reliability. The reliability of the results is too often challenged by logistical constraints and inadequate transport systems for the timely and reliable carriage of samples of suspected cholera cases to well-equipped laboratories. The current number of capable laboratories is grossly insufficient, and the time, training and high costs required to increase laboratory capacity globally create further complexities.
- Cholera molecular tests, e.g., polymerase chain reaction (PCR), have broadly similar drawbacks as culture-based tests related to sample transportation, test complexity, and logistical challenges and costs. Although they offer the potential for greater standardization and scale-up among reference laboratories than culture, (particularly with the expansion of PCR testing in many countries during the Covid-19 pandemic) they are more costly and would require more skilled staff that is lacking in low-income countries, and laboratory culture will remain critical at least for microbial testing. However, country access to PCR testing is essential, particularly at central level for toxigenicity testing.
- RDTs are at present, non-confirmatory test and not a replacement for culture and/or PCR. However, they can effectively address the current limitations of culture and molecular testing and optimise the use of limited culture and molecular testing resources since they are cheap, easy to use and typically intended for field condition (investigation/surveillance) and point-of-care use. RDTs also require less training and would need a less complicated and expensive supply chain.

In 2021, only 23,656 (approximately 10.6%) of the 223,370 cholera cases reported globally were tested by PCR, culture or RDTs. Of the 23,656 samples tested; 3.6% (8,038) were tested by PCR or culture and 7.0% (15, 618) were tested by RDTs. This low proportion of cases reported to WHO as having had diagnostic testing results illustrates that clinical diagnoses remains the basis of identification for most cholera cases and the variability of the countries testing strategy considerably limit the interpretation despite the existence of these three types of tests. Routine, systematic use of RDTs would increase the overall cholera

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

capacity by optimising use of culture and molecular as confirmatory techniques, reduce costs and potentially result in increases in the overall reliability of test results.

Based on WHO's estimates and expectations that annual cholera testing volumes will steadily increase if reliable, validated[4] and cost-effective test kits were fully available, the 'unconstrained' annual demand (i.e. no funding, policy, resource or other constraints) is currently projected to range between 460,000 and 760,000 test kits per year in Gavi-eligible countries: and 260,000 and 540,000 test kits per year in non-Gavi eligible countries.

Addressing these gaps in global cholera diagnostic testing capacity should ultimately result in faster, more accurate testing, which in turn should allow substantially more efficient, effective, and equitable prevention of cholera morbidity and mortality over time.

Overview of cholera diagnostic tests market health

No RDTs or molecular tests have received WHO prequalification, or otherwise been fully validated by a WHO expert review group. There are however, two cholera RDTs from Arkray Healthcare Pvt Ltd and Abbott Diagnostics/SD Bioline that have been procured for years by WHO and UNICEF for use in outbreaks following reviews of those products characteristics by WHO and UNICEF staff. A recent meta-analysis indicates such tests have sensitivity of 91% and specificity of 80%, with the specificity increasing to 98% if samples are first enriched using alkaline peptone water.[5] For the two RDTs that are procured by WHO and UNICEF, funded demand from international organizations and national governments is generally episodic, driven by outbreaks, with little use of RDTs in between outbreaks.

Since 2017, the GTFCC has focused on encouraging availability and use of RDTs, developing Target Product Profiles (TPPs) published in 2017 and related WHO prequalification standards[6], although the lack of steady, predictable funded demand has limited manufacturers' interest in developing and validating reliable, accurate cholera RDTs. No TPPs currently exist for cholera molecular test kits, although the GTFCC has recently begun to develop such TPPs based on use cases for such tests as adjuncts to RDTs to provide confirmation of positive RDT results, improve quality assurance, and assess the toxigenicity of cholera strains at the early stages of an outbreak.

Healthy market dynamics and current challenges

The greatest challenges currently facing the Cholera diagnostics market are: (1) ability to predict the global demand for cholera diagnostic tests and (2) ensuring supply availability from viable suppliers whose diagnostic products meet the Alliance's standards for procurement of their products and can sufficiently meet the global demand.

Although efforts by the GTFCC and others to date provide a basis for further progress, overall, the current cholera test kit 'market health' is categorised as unacceptable and requires further intervention over the next 12 months. Our assessment indicates that high and medium impact 'healthy market attributes' are either unmet or only partially met: the supply of quality assured, reliable, and cost-effective test kits has major limitations, and demand is uncertain, difficult to predict and highly episodic. Six market health attributes are

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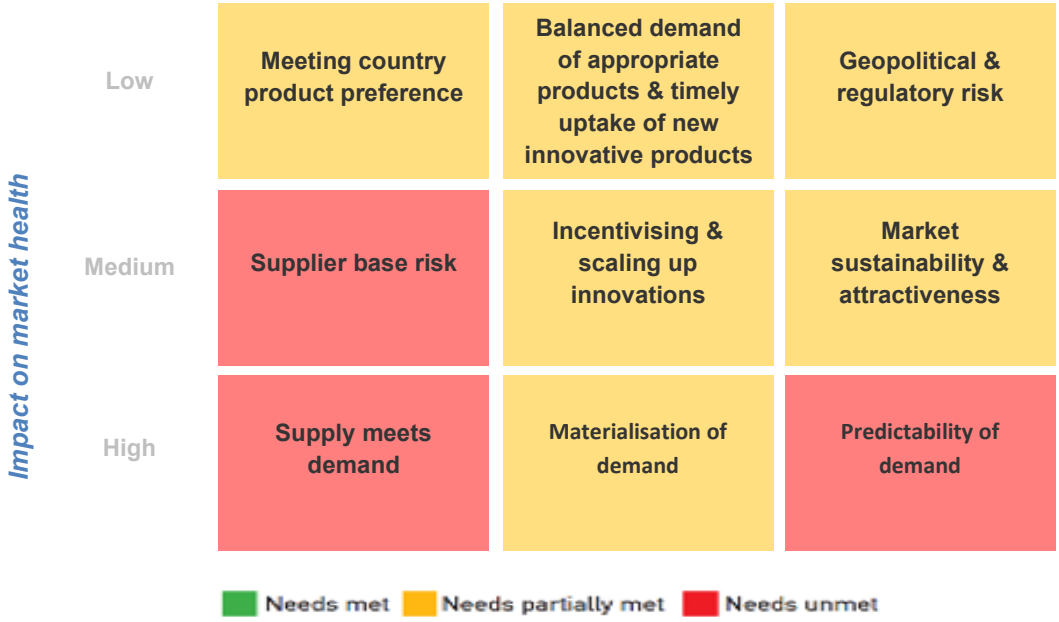
[4] 'Validated' refers to products that have received WHO pre-qualification or endorsement by a WHO expert review committee such as a Expert Review Panel for Diagnostics

[5] Muzembo BA, Kitahara K, Debnath A, Okamoto K, Miyoshi S. Accuracy of cholera rapid diagnostic tests: A systematic review and meta-analysis. Clin Microbiol Infect. Published online September 7, 2021. DOI: https://doi.org/10.1016/j.cmi.2021.08.027.

[6] World Health Organization. Global Task Force on Cholera Control Target Product Profile (TPP) for the Development of Improved Cholera Rapid Diagnostic Tests. Available at: https://www.who.int/cholera/task_force/cholera-rapid-diagnostic-test.p

partially met: materialisation of demand, balanced demand of appropriate products & timely update of new products, country preferences for specific diagnostic products, geopolitical & regulatory risks, market sustainability & attractiveness and product innovation. Three attributes are however unmet: highlighting difficulties in predicting demand and concerns on supplier base risk and supply meeting demand.

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



Materialisation of demand: **Partially Met**. Whilst demand during outbreak is established, demand for routine testing is unknown. Feedback from manufacturers notes significant demand for tens of thousands of rapid diagnostic test kits during outbreaks and very few, if any purchases outside of outbreaks.

Predictabily of demand: **Unmet**. Demand is uncertain, volumes may increase more than expected depending on availability of test kits & countries' adoption, particularly as cholera test kit demand is primarily driven by outbreaks. For purposes of cholera vaccine support programme decision making, it would be very helpful if cholera test kit use shifted to more regular, steady testing outside of outbreaks, which would create more predictable demand, and test supply kept up with this shift.

Balanced demand of appropriate products & timely uptake of new innovative products: **Partially met**. Test kits used to date for Cholera outbreak responses indicate a positive and widespread demand and uptake of the existing rapid diagnostic tests (RDTs) due to affordability, ease of distribution and use at point of care.

Supply meets demand: **Unmet.** Although two cholera RDTs that have been procured for years by WHO and UNICEF for use in outbreaks following reviews of those products characteristics by WHO and UNICEF staff, there are currently no cost-effective cholera test kits that have been approved by a stringent regulatory authority, received WHO prequalification, or otherwise been validated. Our market review indicates that there is one validated (FDA-approved) and commercially available diagnostic kit, but it is so expensive that it is not cost-effective enough for use on a routine basis for cholera surveillance or even cholera surveillance quality assurance. Additionally our review indicates that a shift to more regular, steady testing outside of outbreaks, is likely to secure the interest of multiple

manufacturers to provide test kits to meet this expanded demand and improve security for supply.

Meeting country product preferences: **Partially met.** Test kits need to be usable in settings relevant to countries eligible for Gavi new vaccine support, and many commercially available cholera test kits already are, particularly rapid diagnostic tests which can be used in low resource point of care settings without extensive consumable supplies or additional laboratory equipment. However, these test kits still need to be fully quality assured.

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**. Target Product Profiles and related WHO prequalification standards for assessment & qualification of cholera rapid diagnostic tests were published in 2017, and the WHO diagnostics prequalification team has actively been reviewing submissions from manufacturers. However, the Global Task Force for Cholera Control has recently identifed a role for cholera molecular tests in confirming postiive RDT results, improving testing quality assurance, and assessing the toxigenicity of cholera strains as an adjunct to RDT testing. The GTFCC is working on developing Target Product Profiles for such tests, and further quality assurance /validation standards may need to be defined, test kits assessed and any quality related risks with in-field use assessed and addressed. Based on test kits purchased and distributed to date for cholera outbreak responses, there are no known risks of release or exports of these and/or future test kits from the countries of production.

Market sustainability & attractiveness: **Partially met**. There are a number of manufacturers with available test kits with a high potential for improved competition in the future with a larger stable diagnostic market, assuming these manufacturers' tests meet quality assurance standards. Larger market could incentivize additional manufacturers to fully validate tests, e.g., seek WHO prequalification.

Incentivising & scaling up innovations: **Partially met**. A number of innovative approaches are currently available or in advanced development; e.g. RDTs used during cholera outbreaks in recent years as well as multiple types of molecular tests. At least one manufacturer has been actively working to develop RDTs to better meet Target Product Profiles issued by the Global Task Force for Cholera Control. A good understanding of market incentivies to generate higher level of interest from other manufacturers is needed.

With Gavi Alliance interventions, the health of the cholera diagnostics market can potentially shift acceptable levels in the next 3-5 years. This shift depends on multiple factors, including a change to more routine cholera testing from the current practice of testing in predominantly outbreak situations, improvements in predicting global demand for cholera diagnostics; whether the commercially available kits and those in pipeline successfully pass the Alliance's quality assurance tests and standards for procurement as well as meet country preferences in adopting new diagnostic products; sustained market attraction to existing and new players; and the impact of the next generation diagnostics technologies on long-term competition in the global cholera diagnostics market.

Strategy to sustainably improve market health

Gavi Partners have defined a long-term strategy for the Cholera diagnostics market to address these challenges, by reviewing different scenarios in terms of demand predictability, available

suppliers, product suitability and affordability and long-term business sustainability. It translates into the following strategic market objectives:

***Objective 1** - Secure certainty of demand for cholera diagnostics and generate signals of a more attractive market to suppliers with viable cholera diagnostic products*

Establishing and maintaining a healthy demand for cholera diagnostics is critical to long-term market sustainability and attractiveness to cholera diagnostics suppliers.

- Target Outcome 1: Demand for cholera diagnostics is increased and more predictable
- Target Outcome 2: Diagnostic test(s) are effectively distributed and generates useful data to inform country applications for Gavi vaccine support

***Objective 2** – Ensure supply availability and timely delivery of validated cholera diagnostic tests from viable suppliers resulting in more effective and targeted OCV campaigns*

The number of suppliers has the biggest impact on cholera diagnostics market health as it defines supply availability, supply security, meeting country preferences and product adoption, regulatory and supplier risks and long- term competition.

- Target Outcome 3: At least two commercial test kits of a novel type, (e.g., RDTs), for surveillance of cholera meet the quality standards for procurement

***Objective 3** – Scale up new and/or emerging diagnostic technologies to enable programmatically improved diagnostics and strengthen market health*

The number of new and innovative cholera diagnostics platforms and products is an opportunity to further shape the market and improve its health.

- Target Outcome 4: Gavi Secretariat and Alliance partners update understanding of the actual and/or projected technical breakthroughs in other cholera diagnostic technologies (e.g., molecular testing such as Polymerase Chain Reaction (PCR), Loop-mediated isothermal amplification (LAMP)) to supplement commercially available and validated RDT test kits

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

Demand side interventions:

- Conducting pilot projects to better understand and define country demand for Cholera diagnostic tests.
- Using pilot project results, work to encourage countries to better integrate regular testing for cholera, e.g., between outbreaks, into their disease surveillance platforms.

Supply side interventions:

- Engaging current manufacturers through an in-depth dialogue that will seek to better understand supply barriers and to explore creatively what interventions or investments may improve supply, develop flexibility to meet sudden increases in demand, and ensure sustainable pricing
- Accelerating work with manufacturers that currently supply test kits to WHO and UNICEF 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 cholera test kits that are appropriate for the Gavi market
- Encouraging development of new innovative technologies in cholera sample testing and laboratory platforms
- Facilitating timely supply, delivery and use of validated cholera test kits to target countries.