Annex A: Yellow fever diagnostics and laboratory capacity

At its November 2018 meeting, the Gavi Board approved an effort to strengthen yellow fever laboratory capacity in Africa in order to facilitate the efficient and effective use of yellow fever vaccine as part of the Eliminating Yellow Fever Epidemics (EYE) Strategy, including an amount of up to US$ 8.2 million during 2019-2021 for costs related to the procurement and distribution of laboratory reagents, supplies, and equipment for yellow fever diagnostic capacity strengthening through a diagnostic procurement mechanism based on Gavi's existing application, review and approval processes. The Gavi Board also noted the expected use of Partners' Engagement Framework (PEF) funds, estimated at approximately US$ 5.3 million during 2019-2021, to support yellow fever diagnostic capacity strengthening, including technical assistance, quality assurance/quality control assessments, support for sample transportation, and coordination.

Specific outcomes expected by the end of 2021 were discussed during the October 2018 meeting of the Policy and Programme Committee of the Gavi Board and during the November 2018 Gavi Board meeting. Progress has been made against all of those goals, and many have already been met. Continuing Gavi involvement with yellow fever diagnostics and laboratory capacity beyond 2021 will allow Gavi's planned US$ 488 million investment in yellow fever immunisation during the 2021- 2025 strategic period to be used more effectively, efficiently, and equitably.

Part I: Yellow fever laboratory capacity progress to date

Goal: Introduction and distribution of at least one validated YF diagnostic assay by end of 2021 (October 2018 PPC meeting)

Status: A yellow fever PCR test kit produced by the German manufacturer Altona has been validated by EYE Laboratory Technical Working Group for use in the WHO yellow fever laboratory network. UNICEF Supply Division is in the final steps of concluding the contractual agreement with Altona for distribution of this test kit within the yellow fever laboratory network. In addition, WHO has posted an invitation for manufacturers to submit expressions of interest for participation in evaluation of yellow fever serology tests, and at least one manufacturer has submitted an expression of interest. Gavi involvement with yellow fever diagnostics has also helped trigger progress in the development of assays of a new class that detect yellow fever NS1 protein as a marker for acute infection. Initial testing results are encouraging, and if this type of test proves sufficiently accurate it would be a much simpler and cheaper alternative to PCR testing. Gavi secretariat is working with WHO and other partners to arrange further evaluation of this new test type.

Twenty-one of 24 African countries at high risk for yellow fever outbreaks and eligible for Gavi support have applied for and been approved for Gavi yellow fever diagnostic procurement support. Despite disruptions to international shipping and other logistical challenges from the COVID-19 pandemic, the UNICEF Supply Division organised delivery of initial allocations of YF Dx reagent bundles and ELISA instruments to all countries is expected to be fully completed by early May.

Goal: Increased number of African laboratories able to reliably detect and confirm YF cases by end of 2021 (October 2018 PPC meeting)

Status: Due to work by the Gavi Alliance supported yellow fever laboratory network, particularly by WHO and CDC, the number of African laboratories able to reliably detect and confirm yellow fever cases has increased from one Regional Reference Laboratory (in Senegal) at the start of 2018 to four, with two additional Regional Reference Laboratories at the Centre Pasteur Cameroon and Uganda Virus Research Institute able to confirm yellow fever with the full range of diagnostics and a national laboratory in Nigeria able to confirm yellow fever with molecular diagnostics. Further increases are expected as molecular testing comes online because positive molecular testing results do not require further confirmation if done correctly.

Goal: Decrease in the average time needed to confirm YF cases in high-risk African countries by end of 2021 (October 2018 PPC meeting)

Status: Despite the challenges for laboratory testing caused by the COVID-19 pandemic, surveys of Gavi-eligible countries at high risk for yellow fever in Africa and eligible for Gavi support indicate that the time from positive result at national labs to confirmation has dropped 70% from an average of 106 days in 2017 to 39 days in 2020.[1] This has resulted both from a decline in time needed to ship samples from national laboratories to Regional Reference Laboratories for confirmatory testing thanks to Gavi-funded and WHO-steered international sample transportation and completion of confirmatory testing at an increasing number of laboratories, reducing the need for samples to be sent internationally for confirmatory testing.

Goal: Yellow fever laboratory capacity contributes to efficient and effective use of yellow fever vaccine (December 2018 Board meeting)

Status: The Gavi Alliance supported yellow fever laboratory network plays an integral role in informing decisions on yellow fever routine immunisation, preventive campaigns, and outbreak response campaigns in Africa. For example, in 2019, yellow fever laboratory network assistance combined with epidemiological and clinical insight reduced uncertainty about the causes of suspected yellow fever cases in the context of a Dengue outbreak in Cote d'Ivoire and indicated that an outbreak response campaign under consideration was unnecessary. Laboratory network support was critical in determining that the multiple suspected yellow fever cases in this context were actually due to other causes, particularly since many acute diseases, including other arboviral infections such as Dengue fever, other viral illnesses including viral hepatitis and viral hemorrhagic fevers can resemble yellow fever. Arboviral diseases or yellow fever vaccination can cause false positive results for basic yellow fever antibody tests, which underscores the importance of confirmatory diagnostic testing and in-depth epidemiological and clinical investigations to support interpretation of laboratory diagnostics for

[1] Based on data from both 2017 and 2020 from Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Ethiopia, Ghana, Kenya, Mali, Nigeria, South Sudan, Sudan, and Togo.

suspected outbreaks. 2008 and 2011 yellow fever outbreak response campaigns in Cote d'Ivoire targeted 2,000,000 and 800,000 people respectively. There was subsequently an example in another high-risk country were the network helped differentiate a Hepatitis E outbreak in circumstances where initial serology results had suggested a diagnosis of yellow fever.

In addition, 2019 and 2020 yellow fever testing results from the Uganda Virus Research Institute, one of the African laboratories that can confirm yellow fever cases by itself, and the associated surveillance and risk analysis were critical to the Ugandan Ministry of Health's decision to introduce yellow fever vaccine into routine immunisation, which is now planned later this year with Gavi support followed by a preventive mass campaign. This introduction into Routine Immunisation should eventually help reduce the need for yellow fever outbreak response campaigns in the country.

New in-country confirmation of suspected yellow fever cases in Nigeria in 2019 allowed yellow fever outbreak response campaigns to be initiated substantially earlier than had been the case in the past when further testing at a Regional Reference Laboratory was always required for the initiation of such campaigns. Although testing by the Regional Reference Laboratory is still required for quality purposes, this new development contributed to faster interventions. Confirmation that hemorrhagic fever outbreaks in southern Nigerian states in 2020 were due to yellow fever prompted the acceleration of implementation the of yellow fever preventive campaigns in those states. These actions addressed the outbreaks, and boosted population immunity state-wide. The outbreaks largely came to an end shortly after the completion of the vaccination campaigns.

Goal: Progress on transitioning financial responsibility for yellow fever laboratory capacity to national governments receiving Gavi support. (December 2018 Board meeting)

Status: As part of country applications for Gavi yellow fever procurement support, the national governments of all countries approved for that support agreed that they would eventually assume financial responsibility for procuring yellow fever diagnostic supplies. Engagement with countries through the Gavi application process and subsequent scheduling of supply shipments and with manufacturers through UNICEF SD procurement outreach and negotiations indicates that the per country recurring cost of yellow fever serology reagents and consumables is approximately US$ 12,000 per year (range US$ 7,000 to US$ 39,000). Even with increasing testing volumes and additional types of tests (e.g., molecular tests), average recurring costs should be in the lows tens of thousands per year per country.

Countries at risk for yellow fever outbreaks that have transitioned from Gavi support (in particular, Angola) have indicated that a lack of validated test kits have been a major impediment to their own efforts to procure yellow fever diagnostic assays. Once validated test kits are available to guide country procurement decisions national finances have stabilised from the shocks from the COVID-19 pandemic enough to allow country transitions from all types of Gavi support to

resume, Gavi should be able to start to transition procurement funding responsibility to national governments given the relatively modest recurring cost of yellow fever laboratory procurement.

This progress has been accomplished with approved or forecasted expenditure through the end of 2021 of approximately US$ 3.8 million for procurement of reagents, consumable supplies and equipment and US$ 4.3 million for laboratory network activities, including validation of tests, technical assistance to laboratories, and international transportation of samples. As more tests are validated and deployed, the annual amount allocated for procurement will likely rise somewhat while the amount allocated for laboratory network activities will likely decline somewhat.

Part II: Eliminating yellow fever epidemics strategy programmatic needs for disease diagnostics and surveillance

Despite marked progress in closing gaps in yellow fever population immunity through routine immunisation and preventive campaigns, the EYE Strategy will continue to need yellow fever diagnostic and surveillance data to guide decisions on when and where yellow fever vaccine should be used. Even in a best-case scenario all relevant immunity gaps will not be closed until 2024. Surveillance data to guide interpretation of laboratory diagnostic results and gain understanding of the disease dynamic and risk are needed for decisions about how different immunity gaps should be prioritised for closure through preventive campaigns and strengthened routine immunisation. More detailed, granular mapping of yellow fever risks should facilitate more precise efforts to close immunity gaps. Until all such gaps are closed, and even afterwards, it is important to detect and confirm YF outbreaks as early as possible so they can be rapidly contained through outbreak response campaigns and international spread can be prevented. Rapid outbreak detection, confirmation and response can reduce overall death, disease, and disruption from outbreaks as well as the costs and amount of vaccine needed to contain them.

Given the EYE strategy's progress in improving the population prevalence of yellow fever antibodies, there is increasing potential for individuals suspected of having yellow fever testing positive for yellow fever antibodies even though they do not actually have acute yellow fever. Such results could potentially lead to the triggering of unnecessary yellow fever outbreak responses without efforts to document and understand the epidemiological context and to ensure the quality of yellow fever diagnostic testing and interpretation of test results, particularly since testing for yellow fever antibodies is currently the mainstay of yellow fever diagnostic testing in Africa. Expansion of diagnostic capacity for detecting yellow fever virus, e.g., with molecular or NS1 testing, will also allow for yellow fever diagnostic testing to be less reliant on testing for yellow fever antibodies and therefore reduce the risk of future unnecessary yellow fever outbreak responses.

Part III: No Cost Extension Through the End of 2022

Given the continued relevance of Gavi support for yellow fever diagnostics and laboratory capacity for yellow fever vaccination efforts and the progress to date from that support, Gavi yellow fever diagnostic procurement support should

potentially be extended beyond the end of 2021. A no cost extension through the end of 2022 for yellow diagnostics procurement support will provide the Gavi Board more time to consider the ultimate duration of this support. Given forecasted expenditures, the funding remaining from the US$ 8.3 million approved by the Board in 2018 should be sufficient to cover additional procurement support through the end of 2022. However, an extension through the end of 2022 will not provide sufficient time to develop an adequate healthy market for validated yellow fever diagnostics or leave sustainable laboratory capacity. Therefore, this extension will only be for the purpose of continuing the program while giving the Board adequate time to fully consider its future, potentially as part of a broader Gavi 5.0 effort on disease surveillance in support of efficient, effective, and equitable use of vaccine.