CARB-X
Combating Antibiotic Resistant Bacteria

Minimal Entry Criteria and Development Stages in Scope
Diagnostics

Minimal Entry Criteria

CARB-X is seeking diagnostics to support diagnosis of acute infection of Salmonella enterica serovar Typhi, the causative pathogen in typhoid fever. The primary health care level is the preferred use setting, with ease-of-use, high performance and affordability prioritized.

For diagnosis of acute infection caused by *Salmonella enterica* serovar Typhi, the Minimal Entry Criteria for diagnostic programs are as follows:

- Programs must be between the beginning of technical feasibility (TRL 3) and the completion of clinical studies to support product approval (TRL 8).
- **Preliminary data supporting each of the claims below is required.** See below for additional detail:
    - A marker of acute infection to detect *Salmonella enterica* serovar Typhi **is required.** *Note: Approaches that include IgG or IgM as the only target are not in scope for this call. A marker of acute infection such as IgA is sought.*
    - A sample type that is blood, serum, plasma or a less invasive sample type (eg. saliva, urine) **is required.** *Note: Stool samples are excluded*.
    - A time to result ≤ 60 minutes from sample collection to result output **is required**. *Note detection from positive blood culture is out of scope.*
    - Preliminary clinical sensitivity and specificity of ≥ 85% **is required**. A clear proposal to optimize test performance to increase this to ≥ 90% **is required**. The reference test should ideally be a comparison with the gold-standard "blood cultures" or on other methods like composite reference standards with Latent Class Model (LCM) statistical analysis. The reference method and number of independent samples tested **must be reported in the Expression of Interest (EOI).**
      Note: A nucleic acid amplification test is unlikely to be compatible for detection of Salmonella enterica serovar Typhi, given the intended use specificity and sensitivity requirements (considering the very low cfu/ml).
    - Preliminary COGs ≤5 USD **are sought.**

Please note that these are minimum requirements for entry **only**. Final target product performance metrics may vary. Please review the Priority Product Requirements document to view a list of other preferred test characteristics for this funding call.

For this call, CARB-X supports diagnostics proposals within the development stages outlined below (TRL 3-8). Some guidance is provided below as to typical activities that would be considered in or out of scope in these stages.

Feasibility

Benchtop feasibility demonstrated with clinical specimens. Sufficient data to support the feasibility of the approach including data that infection due to the pathogen of interest can be detected. Plan downstream, critical-path activities, evaluate critical requirements and outline a high-level target product profile. For instrument-based systems, develop and evaluate an initial bench-top prototype of the system or of high-risk modules, including software. Demonstrate understanding of relevant

clinical care pathway, testing algorithms, and clinical interpretation of the results. Describe how product would be differentiated from competition. Continue prototype testing, as required, to support assay development. Finalize diagnostic target(s) and methods for detecting or quantitating target(s). Develop detailed product development plans and finalize critical design requirements. Finalize initial instrument and software architecture, incorporating input on manufacturability of proposed product. Identify and execute commercial agreements with key external development partners. Begin implementing a Quality Management System; draft regulatory strategy, intended use statement, analytical and clinical study plans. Complete technology transfer from Research to Development.

Early-stage Development, Alpha-prototype

Develop reagents and buffers. Build and test prototypes of components and subsystems. Code and unit test software. Build first release of instrument software for integration testing. Develop protocols for assay and integration testing. Finalize User Interface specification. Produce initial assay lots with quantities sufficient to initiate real-time stability studies on development lots. Demonstrate key product requirements, including sensitivity and specificity, with fully integrated prototype using clinical samples, preferably in the hands of external users. Continue implementation of a Quality Management System. Prepare for pre-submission with the FDA or relevant Stringent Regulatory Authority (SRA). Integrate and test alpha instruments/devices, software and assays, evaluating performance and updating specifications.

Late-stage Development, Beta-prototype

Implement design improvements to address defects discovered during alpha-testing. Conduct beta-testing. Produce and evaluate pilot lots of reagents and instruments. Increase the maturity of software. Prepare for clinical testing.
Complete short-term stability testing of reagents.

Analytical Verification

Evaluate assay and integrated diagnostic system performance utilizing contrived, retrospective human and animal samples. Make preparations for clinical evaluation. Begin preparation for full scale production of instruments and assays.

Clinical Studies

Complete clinical evaluations. Prepare and submit Stringent Regulatory Authority (SRA) filing, plus receipt of approval. Finalize GMP manufacturing preparations.

Certain aspects of this list of priority product requirements were guided by the following full Target Product Profiles. Please refer to these references for the expanded list of product requirements.

- Mather et al. Redefining typhoid diagnosis: what would an improved test need to look like? BMJ Glob Health. 2019 Oct 31;4(5):e001831. Link here.
- WHO Draft Target Product Profile for Acute Typhoid Fever Surveillance. Link here

CARB-X Diagnostics Priority Product Requirements			
Variable	**Minimal Requirement**	**Preferred Requirement**	**Notes**
1. Product use summary			
Intended Use(s)	Point-of-care test to detect acute infection caused by *Salmonella enterica* serovar Typhi	Minimal requirement plus ability to detect and distinguish among infections caused by *S. enterica* serovars Typhi, Paratyphi and invasive non-typhoidal Salmonella (iNTS)	
Target level of health system	District hospital with basic laboratory facilities	Primary health care facilities	For detailed descriptions of these settings, please see the WHO Draft Target Product Profile for Acute Typhoid Fever Surveillance
Proposed target populations	All patients that meet the WHO surveillance standard case definition of a suspected typhoid case		As described in the World Health Organization, Typhoid and other invasive salmonellosis. Vaccine-Preventable Diseases Surveillance Standards, 2018. "Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area. Or, Fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever"
2. Design			
Specimen	Whole capillary blood, ≤ 25 uL, ≤ 25 uL serum* ≤ 25 uL plasma*	Same as minimal or less invasive sample types (e.g. saliva, urine)	*Included to enable use in laboratories where these specimens are used. Whole capillary blood is the sample type for use in level 1 facilities where phlebotomy is not available.

3. Performance			
Clinical sensitivity in the first week of illness	≥90%	≥95%	These levels should be met at the lower bound of the two-sided 95% confidence interval. Assessment should ideally be a comparison with the gold-standard “blood cultures” or on other methods like composite reference standards with Latent Class Model (LCM) statistical analysis
Clinical specificity in the first week of illness	≥90%	≥95%	
Time to result	≤ 60 mins	≤ 30 mins	
4. Manufacturing/commercial details			
Target avg. sales price per test	< US$5.00	< US$2.00	