CENTER FOR GLOBAL DEVELOPMENT

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MARKET SHAPING ACCELERATOR

APPENDICES
NEOTEST: ACCELERATING NEONATAL SEPSIS DIAGNOSTICS

Proposal for a $60 Million Market-Shaping Facility to Accelerate Rapid Triage Diagnostics for Neonatal Sepsis and Save Newborn Lives

Report of the NeoTest Working Group

Full report available at www.cgdev.org/publication/neotest-accelerating-neonatal-sepsis-diagnostics

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Appendix A. NeoTest Target Product Profile

The NeoTest target product profile (TPP) describes a rapid, low-complexity triage diagnostic for ruling in or ruling out potentially serious bacterial infection. It informs initial management decisions for neonates with suspected serious bacterial infection or neonatal sepsis.

Time to result and price per patient tested are key criteria; small sample volumes are also critical for this patient population. The diagnostic should be feasible for use in low-resource settings, in both primary care and hospital settings (secondary and tertiary facilities), with instrument size and operational requirements suited to the constraints of such settings.

The NeoTest TPP described in Table A.1 aligns closely with the World Health Organization (WHO) Target Product Profile (TPP) for a neonatal sepsis diagnostic. The NeoTest TPP has also been adopted by other funders supporting neonatal sepsis diagnostics, including the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).

TABLE A.1 NeoTest target product profile

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
General			
Aim	To aid in diagnosing serious bacterial infection, including bacterial sepsis, among newborns and young infants		As per WHO, test should reduce diagnostic uncertainty of serious bacterial infection by providing additional objective information to health care professionals who make treatment decisions. Test is not intended to aid in diagnosis of viral or fungal infections; identify bacterial pathogens; detect antimicrobial resistance; or de-escalate, cease, or choose antibiotics.
Target use settings	• Primary care • Level 1 Hospitals (subdistrict and district hospitals) • Level 2 Hospitals (provincial hospitals) • Level 3 Hospitals (tertiary hospitals)		Test that can be used in both primary care and Level 1 hospitals and above is prioritized, as a significant number of suspected sepsis cases are first evaluated in primary care.

TABLE A.1 Continued

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
Target population	Young infants (0–59 days old), including newborns (0–28 days old), who are being assessed for potentially serious bacterial infection (PSBI) or sepsis		Target population likely includes infants being investigated for PSBI/sepsis in facility of birth and infants presenting to a healthcare facility from home. Test is not intended as a universal screening tool.
Target user	Health professionals (medical doctors and nursing and midwifery professionals) and associate health professionals (medical and pathology laboratory technicians, nursing and midwifery associate professionals, and medical assistants). Some users may have requirements for accessibility that product must meet.		As per WHO TPP
Purposes supported by instrument	Single purpose	Multipurpose (may test for additional clinical conditions)	Developers may be interested in developing or using an existing instrument that has other applications; doing so is welcome but not essential.
Test procedure			
Specimen	Capillary whole blood sample <100 uL or other less invasive analyte	Capillary whole blood sample <25 uL or other less invasive analyte	
Hands on time	≤10 minutes per test	≤3 minutes per test; after user prepares test, system requires no further involvement until test is complete (walk-away operation)	As per WHO TPP
Turnaround time	≤30 minutes	≤15 minutes	Given clinical urgency, batching tests from multiple patients is not expected to be appropriate, because of resulting delays. If instrument does use batching, turnaround time must be met for all specimens in the batch.
Performance			
Results format	Qualitative (positive or negative)	Semiquantitative or fully quantitative; for a fully quantitative test, instructions for use must describe how to interpret the result qualitatively or semi-quantitatively to support decision making relevant to target use setting, target population, and target user	As per WHO TPP

TABLE A.1 Continued

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
Clinical sensitivity	≥90%	≥95%	As per WHO TPP
Clinical specificity	≥80%	≥90%	Aligned with specificity range in the WHO hospital-based diagnostic test
Inconclusive results	≤5%	≤2%	As per WHO, Inconclusive results are any results that cannot be used to inform a clinical decision. They include invalid tests (instrument detects an error, such as failure of a process control) and indeterminate (borderline, equivocal) results (instrument detects no error but does not release a positive or negative result). Typically, the test should be repeated.
Operational			
Throughput per site per day	≥6	≥11	Aligned with specifications of the WHO non-hospital diagnostic test
Size of instrument	Portable table-top device, no larger than 25 × 25 × 25 cm and 2 kg		Aligned with specifications of the WHO non-hospital diagnostic test
Electrical power supply	• Operates on worldwide main electrical power (100–240 volts alternating current at 50–60 hertz) • Supports local direct current supplies, including Universal Serial Bus (USB) and solar power • Equipped with user-replaceable, rechargeable battery providing sufficient power for an eight-hour shift • Instructions for use specify the uninterruptible power supply capacity necessary to complete in-progress tests		Aligned with specifications of the WHO non-hospital diagnostic test
Operating environment	• 10°–40°C and ≤90% noncondensing humidity at ≤2,500 meter elevation • Low light to direct sunlight • Dusty conditions	• 5°–45°C and ≤95% noncondensing humidity at ≤4,000 meter elevation • Low light to direct sunlight • Dusty conditions and water splashes	As per WHO TPP

TABLE A.1 Continued

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
Storage environment	18 months at 2°–35°C (including 3 months at 40°C) and ≤90% noncondensing humidity	24 months at 2°–40°C and ≤95% noncondensing humidity	As per WHO TPP
Shipping environment	5 days at 2°–50°C		As per WHO TPP
Training for operation	No more than four hours, with options for remote or self-training	• No more than one hour, with options for remote and self-training • Support for training trainers	As per WHO TPP
Language support	For each country in which product is deployed, documentation provided in at least one widely used language and any additional language (such as the official language or de facto national language) and any language mandated by local regulatory or trade compliance requirements		As per WHO TPP
Biosafety	• Closed, self-contained system operable without a biosafety cabinet under relevant core requirements of laboratory biosafety[16] • Easy decontamination of surfaces with 70% isopropyl alcohol, 70% ethyl alcohol or a bleach solution with 0.5% chlorine		As per WHO TPP
Service and maintenance	• Weekly basic maintenance, including cleaning, of less than five minutes by a user • Mean time to failure of ≥24 months • Automatic self-checks that alert user to instrument errors, warnings, or pending software updates • User-involved calibration checks at set intervals • Technical support available from manufacturer or its representative	• No maintenance required • Mean time to failure of ≥48 months • Automatic self-checks that alert user to instrument errors, warnings, or pending software updates • No user-involved calibration checks required • Technical support available from manufacturer or its representative	As per WHO TPP

TABLE A.1 Continued

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
Internal process control	Product releases result only if the internal process control(s) for assay performs as expected		As per WHO TPP
External controls	Required positive and negative controls are included in test's price and delivered with the tests		As per WHO TPP
Waste disposal	Standard biohazard waste disposal or incineration of consumables	All components of kit are designed to minimize environmental impact during standard biohazard waste disposal	As per WHO TPP
Data fields	Test results, patient identification, user identification, date and time of tests, quality control results, and other information for administration and maintenance		As per WHO TPP
Methods for data entry	Typing with or without protective gloves	• Typing with or without protective gloves • Scanning one- and two-dimensional barcodes	As per WHO TPP
Nonvolatile memory and storage	≥500 patient results, ≥50 quality control results	≥2,000 patient results, ≥200 quality control results	As per WHO TPP
Role-based access control	Provides configurable access to specific data and product features for users with different roles		As per WHO TPP
Data connectivity			
Data connectivity methods	Wired connection (Ethernet or USB) and a wireless connection (Wi-Fi or Bluetooth)	Ethernet, USB, Wi-Fi, Bluetooth	As per WHO TPP
Intermittent connections	User can perform tests and receive results offline; product transmits data automatically, without user action, once connection established		As per WHO TPP
Data exchange standards	Product supports either Fast Healthcare Interoperability Resources (FHIR®) or JavaScript Object Notation		As per WHO TPP
Data destination	Health programmer must be able to choose destination(s) of product's data		As per WHO TPP

TABLE A.1 Continued

CHARACTERISTIC	ESSENTIAL	DESIRABLE	NOTES
Data ownership	Health programmer must be able to manage the product in compliance with local regulations on data ownership		As per WHO TPP
Security and privacy	To facilitate use by health programmer in accordance with the laws, regulations, and policies in their settings and with best practices, product must provide configurable features so that personal data can be: • gathered in a manner that is transparent to users and patients • collected and processed only for purposes compatible with the health programmer's purposes • limited to what is relevant and necessary • stored with personal identifiers no longer than necessary		As per WHO TPP
Pricing and manufacturing requirements			
Price per patient tested, including individual cartridge cost and amortized instrument cost (how the instrument cost will be included and amortized has not been specified at this stage)	≤$5 at scale	≤$3 at scale	As per WHO TPP
Quality management system of manufacturer	Complies with ISO 13485:2016	Certified to ISO 13485:2016 or equivalent	As per WHO TPP

Appendix B. Findings on Possible Use of a Neonatal Sepsis Diagnostic Test

SUMMARY

This report details the findings of a literature review and expert consultation with 32 physicians and healthcare professionals. It was conducted to better understand and estimate the use case for a rapid triage neonatal sepsis diagnostic. Results of the consultations can be summarized as follows:

1. **Where are neonates first assessed for sepsis?** Neonates are first assessed either while still in the facility of birth (during routine observation or if symptoms develop) or after presenting from home, often via primary health centers or district hospitals after caregiver or community health workers raise concern.
2. **What is the current assessment and management pathway?** In facilities, critically unwell neonates receive immediate antibiotics, well neonates are discharged, and "grey zone" neonates are observed and evaluated. All infants presenting from home are screened on arrival, with treatment started if sepsis is suspected.
3. **Are cases of neonatal sepsis missed? Why are all neonates not just treated with antibiotics?** Many cases of neonatal sepsis are missed, because early symptoms are subtle and assessments are brief and subjective (especially in lower-level facilities). Antibiotics are not given to all infants with any sign of illness because of diagnostic uncertainty, treatment risks, and practical constraints.
4. **How might a rapid diagnostic test change these pathways?** A rapid test would be used for all grey-zone neonates in facilities and all 0- to 59-day-old infants presenting from home. It would reliably rule in and variably rule out sepsis, depending on monitoring capacity and clinician risk tolerance.
5. **If a diagnostic test is negative, would clinicians withhold antibiotics?** Clinicians would often, but not always, adhere to a negative result; adherence is likely to be higher where there are well-defined clinical protocols and guidelines, capacity for reassessment, and greater confidence in the test's reliability.
6. **In which settings should a diagnostic be used?** With moderate confidence, experts suggested that a diagnostic should be prioritized for primary care and lower levels of hospitals (subdistrict, district, and provincial hospitals). If a test works there, it will also work at tertiary hospitals. They did not think a test used in the community and by community health workers was feasible. Epidemiological data on where neonates are currently being assessed for sepsis, combined with situations in which diagnostic uncertainty is greatest, would be helpful and drive decision making in the setting of use.
7. **What operational characteristics should a test have?** The test must be used near patients, be simple to operate, require minimal training, be capable of working off a battery, and be integrated with clear rule-in/rule-out pathways and referral triggers.
8. **What other factors influence uptake?** Healthcare worker confidence, ease of use, cost, and the acuity of presenting neonates will shape uptake, with simpler, cheaper, and more intuitive tests more likely to be adopted.

Where are neonates first assessed for sepsis?

Two distinct populations are relevant:

- **Neonates still in the facility of birth:** neonates born in a facility who become suspected of sepsis while

still admitted; this is assessed and identified either if new symptoms develop before discharge or if identified during routine postnatal observation. The facility of birth includes primary health centers and sub-centers, district and sub-district hospitals, as well as tertiary hospitals.

- **Neonates presenting from home:** born at home or recently discharged, who re-present because a caregiver or community health worker (CHW) notices concerning signs. In most programs, CHWs assess and refer rather than initiate antibiotics; formal assessment/treatment occurs at the primary health care (PHC) level or above (with referral upwards for critical illness or non-response). This pattern is embedded in WHO PSBI guidance.[2]

High-quality, nationally representative data that analyze suspected sepsis evaluations by location of diagnosis (still in facility of birth versus presenting from home) are limited. Drawing on the available evidence, several broad patterns emerge:

- Institutional delivery is increasing in most low- and middle-income countries (LMICs). In India, the figure rose from 39% to 79% over a decade;[3] similar trends are seen elsewhere[4] (especially in urban centers). However, home births remain common in rural areas.[5]
- Postnatal observation is generally at least 24 hours for vaginal births and up to a week for caesarean deliveries.[6] Many early-onset sepsis cases are therefore detected in the facility of birth.
- Because many cases present after 48–72 hours,[7] and community births are common, a substantial proportion of sepsis is first suspected in the community. In such cases, suspicion arises at the level of caregivers or community health workers, but formal assessment typically occurs at a primary health care facility or subdistrict hospital. Antibiotics are usually initiated there, with referral to higher-level facilities reserved for critically unwell neonates or those who fail to respond after 48–72 hours. For neonates recently discharged, families often return directly to the delivery institution if accessible.

What is the current assessment and management pathway?

The sepsis assessment/treatment divides neonates into three broad groups:

- **Well and thriving:** No sepsis assessment needed.
- **Critically unwell:** Severe illness obvious "from the end of the bed;" immediate antibiotics and escalation indicated.[8]
- **Diagnostic "grey zone":** Infants with uncertain likelihood of bacterial infection, who undergo formal assessment.[9]

The grey zone typically includes neonates with the following conditions:

- Any concerning signs (poor feeding, lethargy, temperature instability, respiratory distress, cyanosis, abnormal perfusion) or failure to thrive as expected.[10,11]
- Maternal risk factors (e.g., premature rupturing of membranes (PROM) or preterm PROM, intrapartum fever); neonatal risk factors (prematurity); or abnormal labs (e.g., elevated white blood cell (WBC) counts or C-reactive protein (CRP) that are nonspecific but trigger evaluation.[12,13]
- Non-response to therapy for other diagnoses (e.g., persistent respiratory distress despite surfactant).

Healthcare workers are prompted to assess an infant based on any of the above. They also assess infants every 6–12 hours after birth.[14] Assessment typically involves their overall sense of the likelihood of sepsis given the available information,[8] based on signs, symptoms, or subjective assessment by the healthcare worker.[15]

According to the experts interviewed, the distribution of neonates across these three categories is roughly as follows (Figure B.1)

Of those who are critically unwell and screened, an estimated 7%–14% are likely to have sepsis.

Further work could aim to refine these figures based on current studies being undertaken or pooled estimates

FIGURE B.1 Clinical zones of treatment

based on considering the prevalence of different grey zone characteristics.

Neonates born outside of hospitals are assessed if a caregiver or community healthcare worker raises concern because of a nonspecific sign, such as poor feeding, fever, cough, or skin discoloration.[10,11,16] They are then taken to a facility.[2,8] Formal assessment and treatment occurs at least at the primary health care level.[17–19] Community health workers very rarely initiate management of neonatal sepsis.

Given the lack of follow-up capability and lower training levels in these settings, this decision point is critical; missing cases could cause significant harm.[20]

Given that these visits are nonroutine (there is some concern), all infants who present to a healthcare facility from home are screened upon presentation. This protocol is reflected in WHO guidelines[8] and academic studies[21] assessing possible serious bacterial infection diagnosis in neonates presenting outside a hospital.

Are cases of neonatal sepsis missed? Why are all neonates not just treated with antibiotics?

All clinicians interviewed agreed that many cases of neonatal sepsis are missed and that failure to identify them is a significant contributor to the high mortality from neonatal sepsis in LMICs. Cases are missed for several reasons:

- **Even among neonates admitted to special newborn care units (SNCUs) or neonatal intensive care units (NICUs), less than half—often around 20%—receive antibiotics.** Because many presenting conditions (such as normal physiological fluctuations, transient poor feeding, and other noninfectious medical issues) do not warrant antibiotic use, clinicians avoid routinely prescribing antibiotics, in order to avoid associated risks, reduce workload, shorten hospital stays, and control costs of treatment.
- **The symptoms of neonatal sepsis are often ambiguous, difficult to quantify, and subtle at onset.** They may be transient to begin with; fluctuate between vital-sign assessments; or are attributed to benign causes, such as feeding difficulties or thermoregulation problems, leading to delayed escalation. Consequently, particularly at lower levels of care, healthcare workers may assess infants with these mild or fluctuating symptoms, conclude that they are well, and discharge them.
- **Time pressures and limited training are common, especially at lower-level healthcare facilities, such as district and subdistrict hospitals.** Clinical assessments are often performed rapidly and without comprehensive evaluation, resulting in missed cases that would otherwise meet clinical criteria for neonatal sepsis. The availability of a highly accurate, objective, and easy-to-use diagnostic tool could help reduce the subjectivity and human factors that frequently contribute to missed or delayed diagnosis.

How might a rapid diagnostic test change these pathways?

As previously noted, there are two distinct populations—infants still in the facility of birth, and neonates presenting from home. Figure B.2 summarizes which infants would be assessed using the rapid diagnostic test.

- **Still in the facility of birth:** test all grey-zone neonates. Experts agreed that critically unwell infants should get immediate antibiotics even if they had a negative

test result; most experts still felt that testing may still be used to confirm diagnosis and inform escalation. Availability of a rapid test is likely to expand the assessed pool modestly, which is appropriate given the high stakes and time-sensitivity of sepsis.[22]

- **Presenting from home:** test all young infants (0–59 days) who come to a facility for a non-routine visit. This is the same as what is currently done—except that in lieu of screening with a checklist of signs or symptoms, a diagnostic would be used.

FIGURE B.2 Neonates that would be tested using the rapid diagnostic test

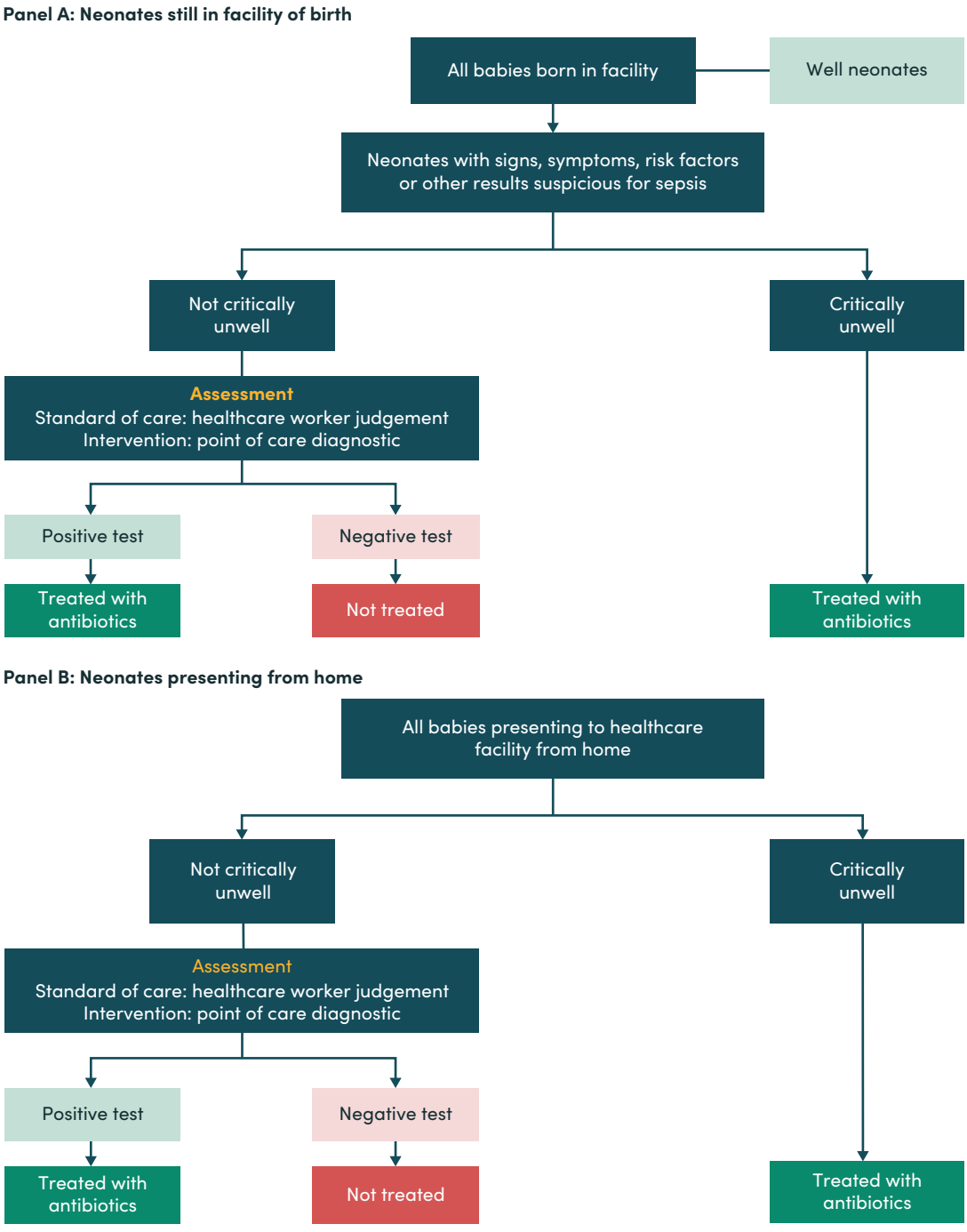
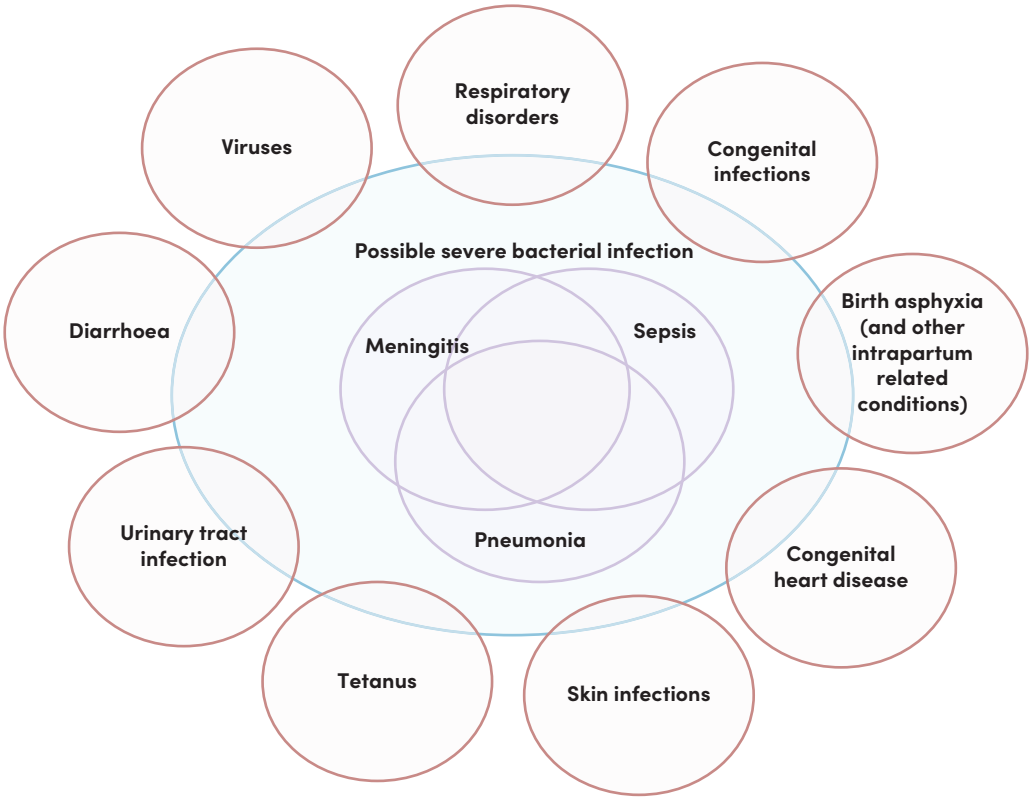


FIGURE B.3 Possible causes of illness in neonates



If a diagnostic test is negative, would clinicians still give antibiotics?

According to experts, a negative diagnostic test in an infant that was not critically unwell would provide reassurance in some cases that the infant did not have a serious bacterial infection or sepsis. Clinicians noted that there are many other reasons that neonates might be unwell other than sepsis (Figure B.3, adapted from WHO guidelines). In this case, clinicians would not administer antibiotics.

Depending on the clinical context, the negative result might prompt clinicians to reassure the caregiver that the infant does not need antibiotics, investigate alternative diagnoses if relevant,[23] or discharge the infant if appropriate.

In some cases, clinicians would administer antibiotics even after an infant tested negative, for several reasons:

- **Clinician factors:** Some clinicians are more risk tolerant than others.[24,25] Clinicians with less training and lower confidence in their skills and judgment (especially at lower levels of care) might be more inclined to follow test results stringently.
- **Caregiver expectations:** Patient preference and expectations for treatment affect clinicians' decision to administer antibiotics given negative test results.[26,27] Pressure to administer antibiotics may be greater in the private sector.
- **Test factors:** Test trustworthiness (its sensitivity and negative predictive value at local disease prevalence levels), and the clarity of guidance on what actions a result should trigger would affect whether or not clinicians would administer antibiotics in the case of a negative test result.

Evidence from the literature from analogous point-of-care programs in LMICs shows high (albeit imperfect) adherence to negative results:

- **Neonatal-specific stewardship signals:** For early-onset neonatal sepsis in high-income hospital settings, procalcitonin-guided algorithms reduced antibiotic duration safely, suggesting that clinicians do follow

biomarker-guided protocols to stop or avoid antibiotics when the probability of bacterial infection is low.[28]

- **Rapid diagnostic tests for malaria:** A systematic review shows average compliance with negative results of 83% (40%–100% across studies/settings).[29] These results suggest that with training and supportive supervision, clinicians frequently withhold antibiotics/antimalarials after negatives, although heterogeneity exists across contexts and risk tolerance.
- **Rapid diagnostic tests for syphilis in antenatal care:** Multifaceted interventions introducing point-of-care syphilis testing achieved increases of more than 80% in appropriate testing and treatment.[30]

Based on these findings, we would expect substantial but incomplete adherence to negative tests (compliance of about 70%–80%) if the following conditions are met:

- The test has high rule-out performance.
- Clinicians are trained to use the test properly.
- Documentation/feedback is in place.
- There is a pathway for reassessment if symptoms evolve.

In which settings should a diagnostic be used?

Expert consultations and the literature reveal broad agreement that a rapid neonatal sepsis diagnostic test should be deployed at points at which many neonates are first assessed for illness (including infants who "bounce back" shortly after discharge) and diagnostic uncertainty is greatest. Lower-tier facilities, which have fewer ancillary tests and less specialized staff, were identified as matching this setting.

Experts agreed that the decision on the setting in which a diagnostic should be used should be driven by large-scale epidemiological modeling and based on the criteria mentioned above. But most agreed that the most likely setting was primary health care facilities and district/subdistrict hospitals.

A common argument raised was that if a test was optimized for lower-level settings, such a test would remain usable in higher-level (tertiary) hospitals. However, the reverse would not necessarily be feasible. Even if a test was validated at higher-level hospitals, it should remain optimized for lower-level settings; the barrier of where a test can be validated and regulated should not determine what setting it is optimized for.

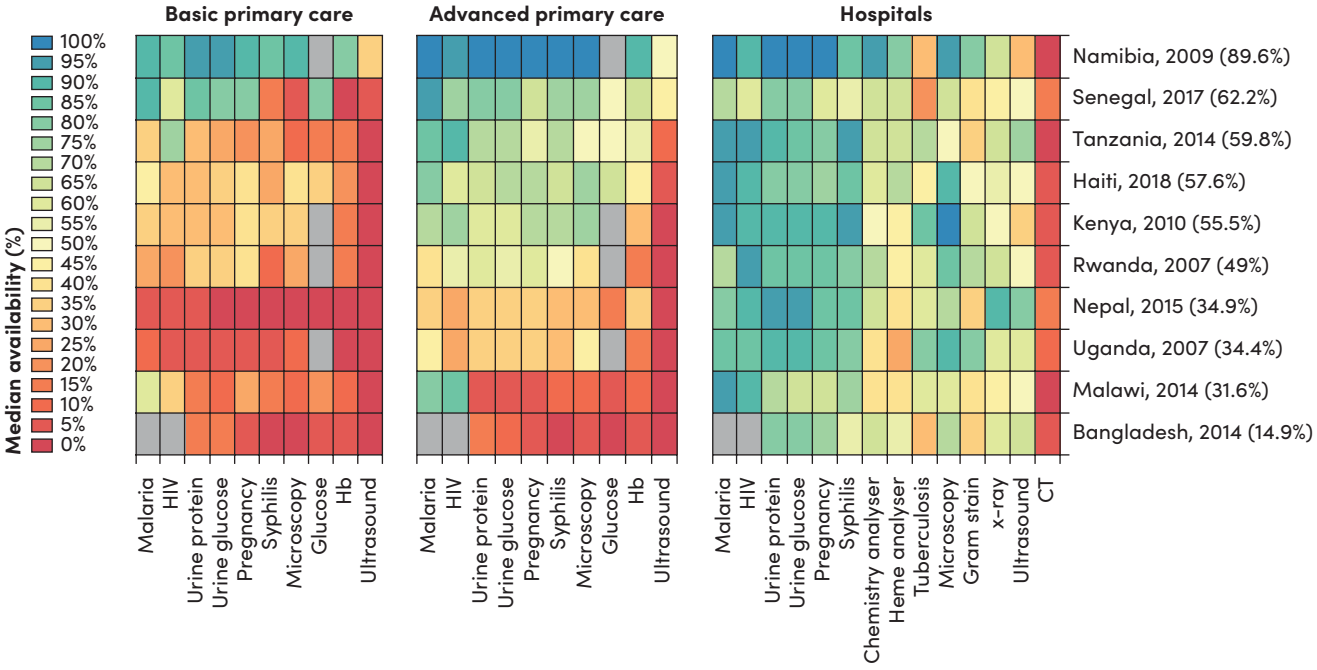
Experts also indicated that a test should be implemented only at a site at which treatment can be offered, because of the high chance that treatment would not be delivered if the patient had to be moved. Use of a diagnostic by community health workers was not considered feasible, at least initially. Pilot programs have tested community health worker administration of antibiotics, but the practice is rare. Until robust workflows, supervision, and supply chains are established for such workers, deployment should prioritize primary health care facilities and first-referral hospitals.

What operational characteristics should a test have?

Experts agreed that neonatal sepsis diagnostics should be designed for easy and true near-patient use, such as within special newborn care units (SNCU) or neonatal intensive care units (NICU) bays, not as laboratory-only instruments or instruments located far from patient care. There was fairly strong consensus that the test should be a table-top device that can operate with a battery and by someone with very little training.

This consensus was motivated by operational feasibility and uptake. Primary health care facilities do not have laboratory infrastructure, and they often have little space, variable electricity, and high turnover of staff. Although subdistrict and district hospitals are, in principle, equipped with laboratories and stable electricity, diagnostics that depend on laboratory infrastructure are often not used reliably, because of power interruptions, equipment downtime, reagent stock-outs, maintenance gaps, and staffing shortage (as highlighted in Figure B.4).[31–33] Experts highlighted parallels with tuberculosis and microbiology programs, which have struggled in peripheral facilities for these reasons. They repeatedly cited the experience of the GeneXpert scale-up, where devices were available but underused.[7,34,35] That negative experience was seen as a strong argument for diagnostics with low operational demands.

FIGURE B.4 Availability of diagnostics by facility tier and country



Source: Yadav et al. 2021.[34]

From Yadav et al. 2021,[34] mortality from neonatal sepsis rises sharply with delays to antibiotic initiation.[22] Test instruments that require a significant amount of space or reliable electricity or lab infrastructure would significantly limit how much they are used.

Experts noted the global trend toward decentralized diagnostics that adhere to the ASSURED (Affordable, Sensitive, Specific, User-friendly)/REASSURED (Rapid/Robust, Equipment-free [or minimal], and Deliverable) principles, with recent extensions adding real-time connectivity and ease of specimen collection.[36]

There was some convergence around a simple, small footprint, near-patient device as the most realistic and sustainable solution for neonatal sepsis diagnostics in LMICs. This consensus is consistent with the WHO target product profile for non-hospital settings,[1] which emphasizes the following:

- operational simplicity,
- rapid time-to-result,
- weight of less than 2 kg,
- ability to run on local direct current (DC) power,
- inclusion of rechargeable battery providing sufficient power for an eight-hour shift.

What other factors influence uptake?

Other commonly cited factors included the following:

- **Healthcare worker confidence.** The higher the diagnostic uncertainty, the more likely clinicians are to use a diagnostic test (especially in lower-tier health services, where healthcare workers have less training and skills[37]). For instance, subdistrict hospitals are more likely to rely on the test than tertiary hospitals.
- **Ease of use.** An easy-to-use test that easily fits into workflow will shape uptake, particularly in lower-level healthcare facilities, where staff have less training and higher turnover.[38,39]
- **Cost.** Price strongly influences uptake.[40] A randomized control trial in Zimbabwe showed steep price elasticity for HIV self-testing.[40] Experts mentioned that cost affects the assessment of budget feasibility, impact, and initial decision of whether to procure a diagnostic.

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Appendix C. Microsimulation of Movement of Neonates through India's Healthcare System

We created a structural microsimulation model to simulate how neonatal sepsis cases move through India's healthcare system. We then used the results to estimate detection, treatment, and survival outcomes. The simulation tracks individual infants who would die from sepsis if left untreated, following them from birth through either successful diagnosis and treatment or death (Figure C.1).

When sepsis symptoms appear, the infant's location at the time of symptom onset primarily determines his or her pathway. Infants still in facilities enter a monitoring system in which detection depends on the facility's check schedule, staff capabilities, and disease progression. Large hospitals check frequently; small clinics have limited monitoring. If sepsis is detected, infants either receive treatment at the facility where they were diagnosed or get referred to higher-level care, with referral success varying by geography and family compliance. If symptoms are missed, they move into the cohort described below.

Infants at home (born there, discharged before symptoms developed, or missed in the facility of birth) rely on community health visits, postnatal checks, and family-initiated care-seeking. The model schedules routine postnatal and home-based newborn care visits, with the distribution of these visits informed by nationally representative survey data.[i] It then calculates the ability of these visits to detect sepsis symptoms based on the timing of the visit relative to symptom onset and worker capabilities. When routine visits fail or happen too late, families begin seeking care through up to three sequential healthcare visits, with timing influenced by disease progression, urban versus rural location, and previous healthcare exposure.

For all detected cases, the model applies treatment outcomes based on facility capabilities and delays between symptom onset and treatment start. It uses survival modeling that accounts for disease progression and treatment quality, with mortality risk increasing as treatment delays lengthen. The simulation tracks each infant through these interconnected pathways to generate final survival outcomes.

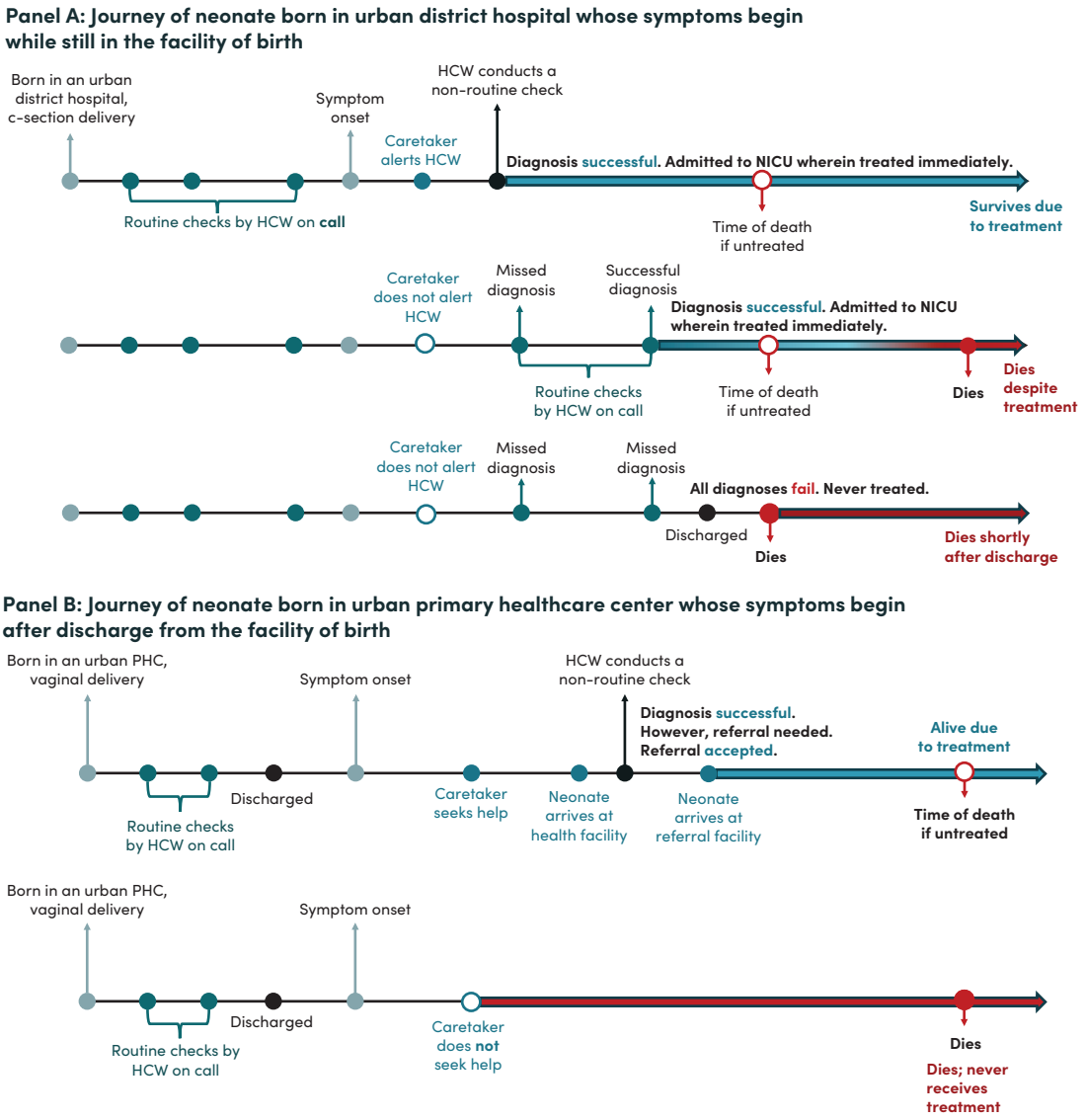
The results of the model suggest a diagnostic test would save the most lives in two settings. Detecting early onset sepsis for facility births at the facility of birth before discharge would reduce deaths by about 37%. Detecting late-onset sepsis when neonates present to healthcare workers from home, either after discharge or following home birth, would reduce deaths by about 15%.

These estimates come from mapping where neonates die based on where they are first assessed. We compare two scenarios: the current standard of care using clinical judgment alone and a diagnostic test with 90% sensitivity (Figure C.2). We focus on the location of first assessment as the relevant use case, as we assume earlier intervention in the disease course provides the greatest opportunity to change treatment outcomes and reduce mortality.

Most neonates with suspected sepsis are first assessed at higher-level facilities. Medical colleges and district hospitals account for the largest share of first assessments (34.9%), followed by subdistrict hospitals or community health clinics

i Health Management Information System: Facility-based service statistics providing absolute numbers on services and events by public/private and urban/rural splits; Demographic and Health Survey, India, 2019–2021 and National Family Health Survey (NFHS-5), a nationally representative survey sample conducted between June 2019 and April 2021. NFHS-5 interviewed 636,669 households and 724,115 women.

FIGURE C.1 Possible simulation pathways of neonate with symptoms of sepsis



Note: HCW = Healthcare worker.

(28.6%) and primary health centers, clinics, or NGOs (24.9%); scheduled home checks (7.9%) and subcenters (3.6%) account for the remainder. The majority of assessments (57.9%) occur in rural settings.

The location of assessment differs substantially by sepsis type. Early-onset cases are concentrated in inpatient settings: of infants who acquire early-onset sepsis, 70.3% of them are first assessed while still in the facility of birth. Late-onset cases are concentrated in outpatient settings: of infants who acquire late-onset sepsis, 79.5% are first assessed when presenting to a health facility or health care worker after discharge or from home.

Across every cohort, the diagnostic roughly halves the share of infants who are never diagnosed with sepsis (Table C.2).

The diagnostic also shifts the composition of where diagnoses are made, pulling cases toward earlier inpatient detection. Inpatient diagnoses rise across the board, and outpatient shares fall correspondingly (Table C.3). Detection at scheduled home checks also rises substantially.

FIGURE C.2 Change in mortality by location of first assessment in India for early- and late-onset sepsis

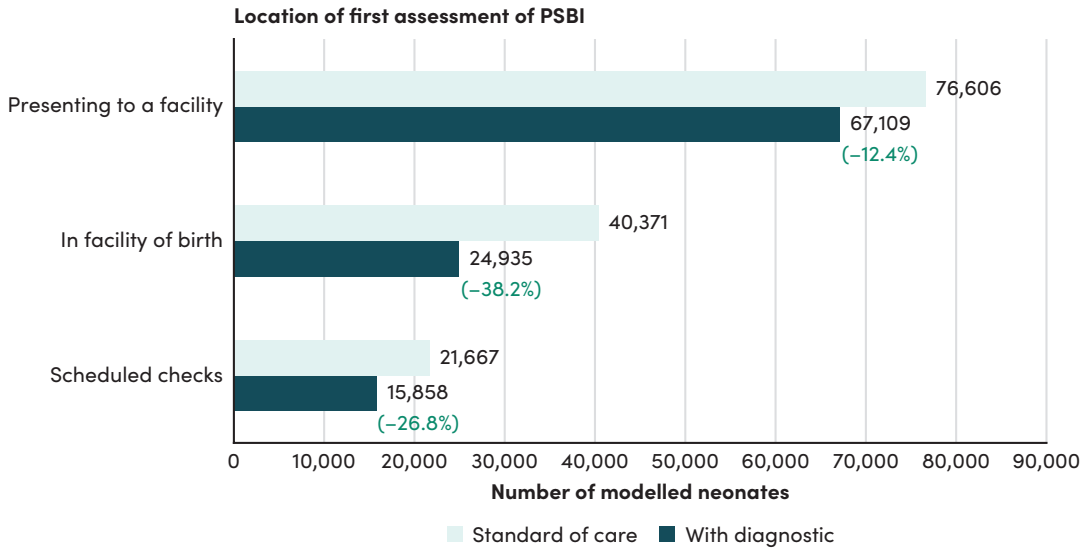


TABLE C.1 Where neonates in India with suspected sepsis are first assessed (percent of cases)

ASSESSMENT LOCATION	FIRST LOCATION OF ASSESSMENT						SHARE OF ASSESSED NEONATES
	EARLY-ONSET SEPSIS			LATE-ONSET SEPSIS			
	URBAN	RURAL	TOTAL	URBAN	RURAL	TOTAL	
Medical college or district hospital			23.0			11.8	34.9
Inpatient	9.3	8.7	18.0	0.3	0.3	0.6	18.6
Post-discharge check	0.2	0.4	0.6	0.3	0.2	0.5	1.1
Outpatient	2.1	2.3	4.4	4.9	6.0	10.9	15.2
Subdistrict hospital or community health clinic			19.7			8.9	28.6
Inpatient	1.9	12.4	14.3	0.3	0.1	0.4	14.6
Post-discharge check	0.0	0.5	0.5	0.3	0.0	0.3	0.9
Outpatient	0.8	4.1	4.9	6.8	1.4	8.2	13.1
Primary health center, clinic, or NGO			17.2			7.8	24.9
Inpatient	2.7	9.2	11.9	0.2	0.1	0.3	12.2
Post-discharge check	0.1	0.4	0.5	0.2	0.1	0.3	0.7
Outpatient	1.1	3.7	4.8	5.4	1.8	7.2	12.0
Subcenter			2.5			0.9	3.6
Inpatient	0.0	2.0	2.0	0.0	0.0	0.0	2.1
Post-discharge check	0.0	0.1	0.1	0.0	0.0	0.0	0.1
Outpatient	0.0	0.4	0.4	0.9	0.0	0.9	1.4
Scheduled home check	0.4	2.9	3.3	3.8	0.8	4.6	7.9
Total	18.6	47.1	65.7	23.4	10.8	34.2	100

The largest absolute reductions come from early-onset cases assessed in the facility of birth, where the test averts roughly 11,900 rural and 2,900 urban deaths (–38% and –36%). In relative terms, the steepest drops are among late-onset cases caught in the facility of birth and at scheduled checks (up to –68%), though these involve far smaller numbers. Across all

TABLE C.2 Projected share of infants never diagnosed with sepsis, with and without diagnostic test (percent of total)

ONSET/LOCATION	STANDARD OF CARE	WITH DIAGNOSTIC TEST	DIFFERENCE
Early-onset			
Rural	13.5	8.1	**5.4**
Urban	6.4	3.2	**3.2**
Late-onset			
Rural	9.8	3.4	**6.4**
Urban	17.1	8.4	**8.7**

TABLE C.3 Modelled location of first diagnosis in India (percent of cases)

FIRST POSITIVE ASSESSMENT LOCATION	EARLY-ONSET SEPSIS				LATE-ONSET SEPSIS			
	URBAN		RURAL		URBAN		RURAL	
	SOC	DX	SOC	DX	SOC	DX	SOC	DX
Diagnosed								
Medical college or district hospital								
Inpatient	45.2	49.8	16.6	18.5	0.7	1.1	2.0	3.0
Postdischarge check	0.4	0.6	0.2	0.3	0.2	0.7	0.5	1.4
Outpatient	13.9	10.8	5.7	4.6	20.8	21.3	55.6	56.2
Subdistrict hospital or community health center								
Inpatient	8.7	9.7	22.0	25.3	0.8	1.2	0.3	0.5
Postdischarge check	0.1	0.2	0.3	0.5	0.3	0.8	0.1	0.3
Outpatient	5.2	4.4	10.7	8.8	28.9	29.6	12.7	12.7
Primary health care, clinic, or NGO								
Inpatient	11.6	13.6	15.1	17.9	0.5	0.8	0.3	0.6
Postdischarge check	0.2	0.2	0.2	0.4	0.2	0.6	0.1	0.4
Outpatient	7.7	6.4	10.0	8.5	22.9	23.4	16.7	17.1
Subcenter								
Inpatient	0.1	0.2	2.6	3.3	0.1	0.1	0.0	0.0
Postdischarge check	0.0	0.0	0.1	0.1	0.0	0.1	0.0	0.0
Outpatient	0.1	0.1	1.8	1.5	4.0	4.0	0.2	0.2
Scheduled home check	0.5	1.0	1.1	2.2	3.5	7.8	1.7	4.4
Never diagnosed	6.4	3.2	13.5	8.1	17.1	8.4	9.8	3.4

Note: SOC = Standard of care; Dx = Diagnostic.

assessment locations and sepsis-onset types, deaths from neonatal sepsis are reduced by 22.2%.

The diagnostic test also shifts the distribution of case-fatality risk at the point of first positive diagnostic. Case-fatality risk (CFR) is the probability of dying from sepsis given treatment with antibiotics at the time of identification. We find that a diagnostic shifts CFRs towards lower-risk strata, consistent with earlier and more frequent detection: the share of cases identified at a CFR below 5% rises by 5.7 percentage points, while the share of cases identified at a CFR of 50% or more falls by 4.8 percentage points (Table C.5). This means neonates are identified with sepsis earlier in the disease course, enabling prompter treatment.

TABLE C.4 Projected change in neonate deaths from sepsis in India as a result of use of diagnostic test by location of first assessment

ONSET/FIRST ASSESSMENT LOCATION	URBAN				RURAL			
	SOC	DX	DEATHS AVERTED	PERCENTAGE CHANGE	SOC	DX	DEATHS AVERTED	PERCENTAGE CHANGE
Early-onset								
In facility of birth	7,927	5,072	**–2,855**	**–36.0**	31,432	19,493	**–11,939**	**–38.0**
Presenting to a facility	7,253	7,151	**–102**	**–1.4**	24,126	22,360	**–1,766**	**–7.3**
Scheduled checks	1,441	1,109	**–332**	**–23.0**	11,096	9,002	**–2,094**	**–18.9**
Subtotal	16,621	13,332	**–3,289**	**–19.8**	66,654	50,855	**–15,799**	**–23.7**
Late-onset								
In facility of birth	234	74	**–160**	**–68.4**	778	296	**–482**	**–62.0**
Presenting to a facility	11,884	10,341	**–1,543**	**–13.0**	33,343	27,257	**–6,086**	**–18.3**
Scheduled checks	1,194	730	**–464**	**–38.9**	7,936	5,017	**–2,919**	**–36.8**
Subtotal	13,312	11,145	**–2,167**	**–16.3**	42,057	32,570	**–9,487**	**–22.6**
Total across early- and late- onset	29,933	24,477	**–5,456**	**–18.2**	108,711	83,425	**–25,286**	**–23.3**

Note: SOC = Standard of care; Dx = Diagnostic. Total population is calibrated to 25 million live births.

TABLE C.5 Modeled case-fatality rates at time of positive diagnosis (percent)

CASE-FATALITY RATE (PERCENT)	EARLY-ONSET SEPSIS			LATE-ONSET SEPSIS			TOTAL		
	SOC	DX	CHANGE	SOC	DX	CHANGE	SOC	DX	CHANGE
Very low (<5)	1.3	5.2	**+3.9**	0.7	2.4	+1.7	1.9	7.6	**+5.7**
Low (5–15)	31.4	32.6	**+1.2**	16.3	16.3	0	47.8	48.9	**+1.1**
Moderate (15–30)	18.9	12.1	**–6.8**	3.2	4.9	+1.7	22.1	17.0	**–5.1**
High (30–50)	3.3	7.5	**+4.2**	4.4	3.3	-1.1	7.7	10.8	**+3.1**
Very high (≥50)	11.7	8.3	**–3.4**	8.8	7.4	-1.4	20.5	15.7	**–4.8**

Note: SOC = Standard of care; Dx = Diagnostic.

Appendix D. Health Technology Assessment

The following working paper is reproduced here in its entirety as originally published:

Fedorov, Maxim Sharakin, et al., 2026. "Cost-Effectiveness of a Target Point-of-Care Triage Test for Neonatal Sepsis in Low- and Middle-Income Countries." CGD Working Paper 744. Washington, DC: Center for Global Development.

Original pagination of Fedorov et al. has been retained. Pagination of the appendices resumes with Appendix E.

CENTER FOR GLOBAL DEVELOPMENT

Cost-Effectiveness of a Target Point-of-Care Triage Test for Neonatal Sepsis in Low- and Middle-Income Countries

Maxim Sharakin Fedorov, Akhil Bansal, Georgia Bradley, Daniel Chong, Yasir Bin Nisar, Edwine Barasa, Yah Ru Juang, Teerawat Wiwatpanit, Siriyada Kitbamrung, Nga Man Juliana Lui, Xue Li, and Yi Wang

Abstract

Neonatal sepsis is a leading cause of mortality in low- and middle-income countries (LMICs). The current diagnostic standard, blood culture, has long turnaround times and high infrastructure requirements, limiting its utility. Consequently, clinicians rely on non-specific clinical signs for initial management. To address this unmet need, the WHO published a 2025 Target Product Profile (TPP) for rapid point-of-care tests (POCTs). We developed a global expert-validated model to estimate the cost-effectiveness of a TPP-compliant POCT in LMICs.

A decision tree compared a TPP-compliant POCT integrated into standard of care (SOC) against SOC alone from a healthcare system perspective over a lifetime horizon. The model evaluated infants (0–59 days) with possible serious bacterial infection across facility-of-birth and community-presenting cohorts. Outcomes included incremental cost per disability-adjusted life-year (DALY) averted. Probabilistic and threshold sensitivity analyses assessed parameter uncertainty.

At a US$ 5·00 unit price, the POCT reduced costs by US$ 37 342 and averted 206 DALYs per 1 000 facility-of-birth patients compared to SOC. In community-presenting patients, it reduced costs by US$ 5 715 and averted 127 DALYs per 1 000. The POCT was dominant in 93·2% (facility) and 84·8% (community) of probabilistic iterations. Results remained robust across wide-ranging epidemiological and cost inputs.

These findings provide an evidence base supporting prioritised investment in developing a TPP-compliant POCT to improve neonatal sepsis management in LMICs.

WORKING PAPER 744 • APRIL 2026

Cost-Effectiveness of a Target Point-of-Care Triage Test for Neonatal Sepsis in Low- and Middle-Income Countries

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All data generated or analysed during this study, including the data dictionary, all extracted parameter values, and step-by-step calculation logic, are deposited in the Mendeley Data repository (DOI: 10.17632/j6kx34b9xm.1). The complete decision-analytic models, available in both R and Microsoft Excel formats, are shared to facilitate transparency and adaptation by other researchers and policymakers. All materials are currently under embargo and will be made fully available to the public without restriction upon publication at: https://doi.org/10.17632/j6kx34b9xm.1

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Research in context

Evidence before this study

Neonatal sepsis (NS) is a leading cause of mortality in LMICs, but diagnosis remains reliant on blood cultures, which are slow and often inaccessible, or clinical judgment, which is limited in accuracy. A POCT could potentially fill these gaps by providing rapid, high-accuracy results, thereby reducing inappropriate antibiotic use, which causes antimicrobial resistance, and treatment delays, responsible for high case fatality rates (CFRs). To date, only one study has modelled the impact of a potential POCT introduction. The objective of that study was to support the development of the TPP, and it estimated that at a unit price of US$21 for hospitals and US$3 for community, the POCT could be cost-neutral through reductions in mortality of 19 to 76% and healthcare expenditure of 17 to 43%. The authors acknowledged several limitations in their analysis, including the high reliance of model parameters on the settings of India and Uganda, limiting the representativeness of the results, the assumption of zero blood culture contamination, perfect referral, and binary antibiotic treatment regimens. Another limitation was the consideration of short-term but not long-term antimicrobial resistance (AMR).

Added value of this study

In 2025, informed by the available evidence, the WHO established the TPP for a POCT for use in infants suspected of NS. Our study is the first to assess the potential cost-effectiveness of this WHO TPP-compliant POCT. To account for the differences in clinical management practices across LMIC settings, a de novo global decision model was developed in consultation with experts to represent the average situation across LMICs. Differences in parameter values were accounted for through prioritization of evidence derived from multi-country studies, expert-validation, and probabilistic sensitivity analysis. Additionally, the model considered blood culture contamination, potential deviations from prescribed referral pathways, and non-binary antibiotic treatment regimens. Another novelty of this model was the inclusion of short-term and long-term complications such as necrotising enterocolitis (NEC) and inflammatory bowel disease (IBD), respectively. These health effects were then translated into DALYs for the first time. An extra feature of the model is the convenient Excel user interface, accessible to all stakeholders.

Implications of all the available evidence

The 2025 WHO TPP is the first globally recognized document intended to guide the development of a POCT by defining the essential characteristics such test must possess to support early, accurate diagnosis of serious bacterial infections among infants. This study demonstrated that introducing a POCT with these characteristics into LMICs has the potential to improve health outcomes and reduce costs when compared to the current SOC, across diverse epidemiological and economic settings of LMICs. These results could support the decision of countries and donors to invest in the development of a TPP-compliant POCT. For settings where funding or policy requirements necessitate local evidence, a flexible decision model that can be populated with country-specific parameters to build a compelling, data-driven case for this POCT, is provided.

Introduction

Neonatal sepsis (NS) is a systemic bloodstream infection that occurs within the first 90 days of life. Globally, it estimated that there are between 1·3 to 3·9 million new cases of NS annually, causing 400 000 to 700 000 deaths, the majority of which occur in LMICs.[1] Whereas it is estimated that 84% of these deaths could be avoided through earlier diagnosis and appropriate treatment, diagnostic capabilities in resource-limited settings are currently constrained.[1,2]

The current diagnostic standard of care (SOC) relies on a combination of clinician judgment based on non-specific clinical signs and symptoms and blood culture (BC), the definitive method for confirming NS where available. However, BC takes up to 48 to 72 hours to yield results and cannot guide life-saving initial treatment decisions.[3] BC poses operational constrains as well. Venipuncture in unwell infants is often difficult or not possible, requiring high blood volumes, and expensive laboratory infrastructure.[4] These turnaround times and operational constrains are partially responsible for the lower BC uptake in LMICs when compared to higher income countries.[5,6] In LMICs, BC often yields false-negative results[4] Consequently, clinicians rely on non-specific clinical signs and symptoms to diagnose NS.[7,8] While this enables immediate decision-making, these signs have limited sensitivity and specificity, particularly in infants with ambiguous presentations.[7,8] This leads to preventable mortality from missed diagnoses, and inappropriate antibiotic use that drives AMR[7,9] and long-term complications.[10]

Currently, no POCT exists to accurately diagnose NS.[3,7] There is an urgent need for rapid triage diagnostics. Thus, the Indian Council for Medical Research[11] and the World Health Organization (WHO)[12] published a Target Product Profile (TPP) intended to guide the development of a POCT by defining the essential characteristics such test must possess to support early, accurate diagnosis of serious bacterial infections (SBI), including NS, in newborns and young infants. One study has assessed the potential cost-effectiveness of a POCT for NS using diverse accuracy scenarios.[13] The study found that across the different scenarios that were investigated, the POCT could decrease total healthcare costs by 17 to 43%, and deaths by 19% in hospitals and 76% in community settings.[13] This work was undertaken to inform the TPP and was used to define the performance characteristics specified within it. There is an opportunity to extend the available evidence by incorporating in the analysis the TPP details and factors such as missed cases, AMR, and long-term complications within an expert-validated framework, combined with a probabilistic sensitivity analysis (PSA) to provide a more comprehensive and representative picture of the cost-effectiveness of the prospective technology.

Our early health technology assessment (eHTA) bridges existing evidence gaps by modeling POCT parameters against benchmarks defined in the 2025 WHO TPP. The model structure was developed in consultation with experts to account for the diversity in clinical management and resource availability across LMICs. This approach was combined with a PSA to explore setting-specific variability, to arrive at a robust POCT cost-effectiveness estimate in the existing heterogenous

LMIC landscape. The objective was to quantify the value proposition of a TPP-compliant POCT across facility-of-birth and community-presenting infant populations.

Methods

Study design and data sources

A decision tree model was developed to estimate the cost-effectiveness of POCT in addition to SOC in a theoretical cohort of 1 000 infants (Figure 1). The current SOC for the management of suspected NS in LMICs comprises clinician judgement (CJ) which relies on the WHO possible serious bacterial infection (PSBI) risk classification system.[8] A suspected case was defined as an infant aged zero to 59 days presenting with any of the WHO-defined pSBI clinical signs.[8] Cases were categorized into two cohorts. Cohort (c_1) is restricted to infants managed in the facility of birth. Cohort 2 (c_2) is restricted to infants managed in the community. The study was conducted from a healthcare system perspective with a lifetime time horizon. A willingness-to-pay (WTP) of US$1 500 per DALY averted was used in the base-case analysis, representing the median of published LMIC estimates, rounded to avoid false precision.[14] Future costs and health outcomes were discounted at a 3·0% annual rate, following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and WHO guidelines.[15,16]

Model development used an iterative expert elicitation process, and the parameterisation followed the ISPOR Good Research Practices.[15] The iterative process began with a non-exhaustive literature review, review of clinical guidelines, and unstructured interviews with experts; this was subsequently targeted via targeted literature searches. Then, the preliminary model was reviewed by experts through semi-structured questionnaires and manuscript comments to validate structural logic and parameter values. In the next iteration, the model was updated based on stakeholder feedback, and an additional targeted literature search was performed. Where evidence was lacking, parameters were populated through expert consultation. The comments from the experts are listed in the Supplementary appendix. This study follows the CHEERS 2022 reporting guidelines.[17] The model and all the analysis were implemented in R (version 4·3·1). For validation purposes and to promote stakeholder use, the model was also built in Microsoft Excel 365. All data and code are available under the data availability statement.

Model structure

Both cohorts were stratified into low (L), moderate (M), and high (H) risk groups upon presentation (Supplementary appendix). In the SOC arm, management decisions were based on CJ alone or in combination with BC. In the intervention arm, L-risk and M-risk groups were managed based on the POCT result, which overrides the initial clinical assessment, alone or in combination with BC. To maintain clinical safety and reflect clinical realities, H-risk infants in both arms followed a

safety-override logic where treatment was initiated and maintained regardless of diagnostic results. For infants in c_2, the initiation of empiric antibiotics and hospital referral success were contingent upon the diagnostic strategy as only the proportion of patients believed to have NS based on CJ or with a positive POCT result were eligible for antibiotic treatment and/or referral. The probability of successful referral was defined based on adherence rates observed in the literature. Infants in c_2 judged not to have sepsis (true negatives [TN] and false negatives [FN]) were assigned a referral probability of 0·0 to capture community-level outcomes. Conversely, for infants in c_1, a structural value of 1·0 was assigned to ensure all infants proceeded to the shared inpatient sub-tree where secondary diagnostic revision based on BC results remains possible. Given that the impact of POCT implementation on referral is difficult to predict, the model structure does not allow for a different referral probability between the two arms. Only patients entering the inpatient decision tree branches are eligible to receive a BC test, and thus for their diagnosis and treatment to be revised. If patients belong to the H risk group, there is no revision to ensure safety. For patients undergoing BC testing, the length of stay (LOS) includes a two-day observation period, reflecting the time required for BC results to become available. During this period patients are treated with antibiotics if initially suspected of NS. On day three a decision is made whether to continue, discontinue, or start antibiotic treatment. If results stay negative, one additional day is added to the LOS to represent the transition to discharge. When results change to negative, three days are added to the LOS for safety reasons. Whenever they stay positive, patients continue their inpatient stay and antibiotic treatment for eight more days to complete the ten-day regimen. If patients' results change to positive, they follow the ten-day antibiotic regimen until completion in the inpatient setting. Further detail on the model structure is provided in Supplementary appendix.

Epidemiology

The risk distribution and prevalence data specific to each cohort were derived from academic literature. For risk strata distribution, two studies in the setting of India were identified (Table 1).[18,19] Where multiple studies were identified, the midpoint of reported estimates was used. Cohort-specific prevalence of true NS among infants with pSBI was informed by multi-country data from South Asia and Africa.[20,21] Prevalence estimates were adjusted for imperfect BC performance using the Rogan-Gladen formula. As prevalence data by specific risk group were unavailable, an expert elicitation process derived multipliers to distribute corrected cohort-level prevalence: 1·0× for the M-risk group (baseline), 0·5× for L-risk, and 2·0× for H-risk.

Diagnostic accuracy

The sensitivity and specificity of CJ represented the accuracy of classifying NS versus no NS based on clinical symptoms. Expert consensus suggested that while literature values focused on community settings, they are representative of the facility-of-birth environment.[22] Consequently, c_2 sensitivity for L-risk and M-risk groups was adjusted 5% lower than c_1 values to reflect the clinical

assessment environment. For H-risk infants, sensitivity was set to 1·0 across cohorts to reflect high clinician risk aversion. POCT accuracy was parameterised directly from the 2025 TPP for NS diagnostics.[12] Whereas WHO recommends 100% referral, observed successful referral rates were used to reflect real-world adherence.[19] BC sensitivity and specificity were retrieved from published literature.[23] These values were also used in the Rogan-Gladen adjustment to ensure internal consistency. Barriers such as low infant blood volume and laboratory downtime, were reflected via an effective BC uptake parameter of 6·0%, a value in the lower end reported by the literature of 5·0 to 15·0%.[6] All sensitivities and specificities directly translated into antibiotic treatment vs. no antibiotic treatment and continuation of inpatient stay or discharge.

Costs

Healthcare resource use and unit prices were derived from the literature. To accurately reflect the economic realities of diverse LMIC settings while maintaining relevance for international donors, costs were adjusted using a mixed approach that stratified inputs into tradable and nontradable resources.[24] The TPP-compliant POCT was classified as a tradable good and valued at a uniform international price of US$ 5·00. Nontradable local resources, such as hospital bed-days and antibiotics, were estimated by extracting historical cost data from representative LMICs. These local costs were first back-converted to their original local currencies (where necessary), inflated to the 2024 base year using country-specific Gross Domestic Product (GDP) deflators from the World Bank, and subsequently converted to 2024 US Dollars (US$) using official market exchange rates. The estimated cost per NS inpatient day ranged from US$ 10[25] to US$ 198[26–28] depending on the setting (community hospital vs. secondary/tertiary neonatal intensive care). The daily costs for inpatient antibiotics ranged from US$ 0·86 to US$ 1·54.[29] Blood culture (BC) costs ranged from US$ 4·78 to US$ 12·22.[25,27,28,30] The cost of the POCT was set as per the WHO TPP.[12] The total costs for an outpatient antibiotic course ranged between US$ 1·55 and US$ 11·68.[31] Outpatient visit costs, excluding antibiotics, were derived from studies in Africa and India, ranging from US$ 1·46 to US$ 10·51 per case.[32,33] The average of each range was taken to represent the representative cost within the LMIC setting. The costs for base-case analysis are presented in Table 1. Details regarding the resources considered in the cost estimation and the specific conversion calculations are available in the files under the data availability statement.

The total cost per inpatient episode was calculated as the sum of the product of LOS, which included 11·2 additional bed-days added when HAI occurred,[34] and the cost per NS inpatient day excluding antibiotics, and the product of antibiotic duration and the cost per day of inpatient antibiotic treatment. The total cost per outpatient episode was calculated as the sum of the outpatient visit cost excluding antibiotics and the cost of outpatient antibiotic course. The costs for long-term complications and AMR were excluded due to high uncertainty in per-episode attribution and the risk of double-counting resources captured as part of HAI.

Disability-adjusted life-years

In the absence of publicly available utility values, disability-adjusted life-years (DALYs) were used as the primary health outcome of the analysis, calculated as the sum of the years of life lost (YLL) and the years lived with disability (YLD) attributed to distinct components to isolate the incremental impact of changes in antibiotic duration and LOS. Morbidity was operationalized as the sum of YLDs due to the inflammatory bowel disease (IBD) complication and AMR. There was no evidence on the relationship between antibiotic use and any other complication. For IBD, a disability weight derived from the literature was extended over ten years and applied to the incidence of IBD in patients exposed to antibiotic treatment early in life, which was estimated by applying a corresponding odds ratio (OR) to GBD cumulative incidence rates.[35]

Mortality included necrotising enterocolitis (NEC), AMR, HAI and the case fatality rates (CFRs) of patients suspected of NS or patients without PSBI symptoms for patients with true NS or non-NS status as proxies, respectively. The estimates were derived from the literature. The NS CFR was adjusted based on expert feedback to reflect differences across risk categories (Table 1). These CFRs were applied to true NS patients receiving a full antibiotic course. To estimate the CFR for untreated NS patients, the NS CFR for treated patients was divided by the antibiotic treatment effect, expressed as relative risk (RR).[36] YLL was calculated using the WHO frontier life table without age-weighting.[37] For NEC, a mortality rate derived from the literature was applied to the incidence of NEC in patients exposed to antibiotic treatment early in life, which was estimated by applying a corresponding OR to the incidence rate of NEC.[38] For HAI, whenever a HAI occurred, an attributable CFR was applied.[34]

The AMR morbidity and mortality was calculated as an expected DALY benefit per prescription avoided, adjusted by a correlation coefficient (0·462) reflecting the association between consumption and resistance.[39–46] An expert-recommended 60% discount was applied to the community-level (c_2) AMR benefit to reflect lower resistance selection pressure (Table 1).

Sensitivity analysis

The sensitivity of results to parameter uncertainty was explored by means of a PSA which employed a Monte Carlo simulation with 10 000 iterations. The values of all parameters were varied simultaneously in each iteration through sampling from the selected probability distributions (Table 1). To determine the key drivers for the ICER, a one-way sensitivity analysis (OWSA), where each parameter value was varied separately, was performed. The base case parameter values were derived from literature that was limited to one or a few LMIC settings. To account for a potentially wider range of clinical, operational and epidemiological heterogeneity across LMIC settings, the lower and upper bounds for the sensitivity analyses were calculated as the mean parameter values ±25% (Table 1).

A performance frontier analysis was conducted to identify acceptable WTP-POCT price-accuracy combinations. Clinical harm was defined as a combination of POCT sensitivity-specificity that

resulted in non-zero DALY loss upon POCT introduction into the SOC. WTP thresholds representing the 25th, 50th, 75th, and 95th percentiles of published LMIC estimates (US$250, US$1 500, US$4 000, and US$8 000 per DALY averted, respectively) were used to capture setting variability.[14] POCT test prices were bound between the aspirational TPP target (US$ 5·00) and an upper exploratory threshold of US$ 15·00. Scenario boundaries were purposefully selected to evaluate a 100% price premium (US$ 10·00, closely approximating the mean blood culture cost of US$ 9·09) and a 200% premium (US$ 15·00). This upper bound accounts for the added clinical value of rapid turnaround times compared to traditional laboratory diagnostics, and allows us to determine the maximum price threshold that remains meaningful for the healthcare system.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

Base-case analysis

Integrating POCT into the current SOC resulted in 48 fewer missed NS cases per 1 000 infants in c_1, and 26 per 1 000 in c_2 (Table 2). It also resulted in a 58·6% and 51·4% reduction in unnecessary treatment, respectively (Table 2).

Table 3 summarises the estimated costs and health outcomes under the SOC and SOC + POCT. In the base-case analysis, the SOC + POCT strategy was dominant across both cohorts, resulting in both lower costs and DALYs. In the facility-of-birth (c_1) and community (c_2) cohorts, POCT usage in 1 000 infants was estimated to reduce costs by US$37 342 and US$5 715, and avert 206·0 DALYs and 127·0 DALYs, respectively.

In c_1, the introduction of POCT into the current inpatient SOC resulted in patients receiving appropriate treatment early and reducing unnecessary treatment in the model, reducing the number of NS and HAI deaths, by six deaths and one death per 1000 infants respectively. The POCT acquisition cost (US$5 000 per 1 000 infants) was negligible compared with the US$37 342 saved by avoiding 985 unnecessary inpatient bed-days.

In c_2, the introduction of POCT into the current community SOC was estimated to reduce false positives by 51·4% (from 461 to 224 per 1 000) and false negatives by 70·3% (from 37 to 11 per 1 000). This diagnostic improvement resulted in an estimated four total deaths being avoided per 1 000 infants (Table 3). In patients who were not referred, the introduction of POCT led to a cost increase; however, this increase was offset by the reductions in hospital expenditures for referred infants, resulting in US$5 715 being saved per 1 000 infants. Overall, the mechanism behind the reduction in

costs, LOS, deaths, and DALYs across all dimensions was the improvement in antibiotic prescription, inpatient management, and referral practices, which resulted from earlier access to more accurate diagnosis.

Sensitivity analyses

The PSA confirmed the robustness of base-case results. Adopting POCT as part of SOC was found to be the dominant strategy in 93·2% and 84·8% of c_1 and c_2 iterations, respectively, demonstrating cost-effectiveness across a wide range of values (Supplementary appendix). The maximum VBP was estimated at US$ 351·30 for c_1 and US$ 200·61 for c_2. For c_1, OWSA identified CJ sensitivity for moderate-risk infants as the main driver, followed by POCT sensitivity and POCT specificity (Supplementary appendix). For c_2, the key drivers were POCT sensitivity, CJ sensitivity for moderate-risk patients, and the CFR for untreated moderate-risk NS (Supplementary appendix).

In the performance frontier analysis, when the specificity of POCT was held constant at the same value as CJ, the minimum sensitivity required to avoid clinical harm and remain cost-effective was 72% for c_1 and 66% for c_2, at the price of US$ 5.00 and WTP of US$ 1 500. Similarly, when sensitivity of POCT was fixed at that of CJ, the minimum specificity required was 52% for c_1 and 58% for c_2. At a sensitivity of 95%, the POCT remained cost-effective even if specificity dropped to 0% (c_1) or 0% (c_2). At a sensitivity and specificity of 90%, the VBP was around US$ 396.17 for c_1 and US$ 218.49 for c_2, due to the cost-savings from avoided or shortened inpatient admissions for patients without NS.

Discussion

This study fills the gaps in the current evidence by providing the first comprehensive, LMIC-level and expert-validated assessment of a WHO TPP-compliant POCT. We found that the implementation of this POCT is the dominant strategy in both facility-of-birth and community-presenting PSBI infants when compared to the SOC alone. The improvements in health outcomes came from better identification and timely treatment of infants with NS who are missed under the current SOC. This reduction in FN diagnoses directly translates in lower neonatal mortality, particularly in community settings where diagnostic gaps are most pronounced.

Beyond mortality reduction, the diagnostic provides a gatekeeping effect that is clinically and economically relevant. In the facility-based model, the reduction in FP diagnoses led to a net saving of 985 inpatient bed-days per 1 000 infants. This decongestion of neonatal wards is an important secondary benefit, as it prevented 5·71 cases of HAI per 1 000 infants. By reducing unnecessary facility-based exposure, the POCT addresses a major driver of iatrogenic morbidity in resource-limited settings. Furthermore, the inclusion of externalities such as AMR and antibiotic-related complications, including NEC and IBD, suggests that the benefits of rapid diagnostics extend beyond the acute episode to long-term health and stewardship goals.

The identification of a performance frontier defining clinical safety is a central insight of this analysis. We established a minimum sensitivity floor of 72% for c_1 and 66% for c_2, considering equal performance of the POCT to the CJ in terms of specificity; below these cutoffs, the diagnostic enters a zone of net clinical harm where the DALY burden resulting from missed NS cases outweighs the benefits of reduced hospital exposure. These frontiers provide a benchmark for future TPPs, indicating that a diagnostic failing to meet these sensitivity floors may not be economically or ethically viable. However, provided these safety floors are maintained, the POCT remains cost-effective at unit prices well above US$5·00. This is driven by the cost asymmetry between a rapid diagnostic and the US$420 cost of a 10-day inpatient neonatal admission.

Our findings build upon the foundational work by Chevalier et al. (2025), which first highlighted the significant mortality reductions achievable through rapid neonatal diagnostics.[10] While that study reported potential mortality reductions of up to 76%, our analysis suggests a more moderate relative impact of approximately 8·2% in the community cohort. This difference reflects our inclusion of additional parameters, such as clinician adherence and referral success, as well as a more granular accounting for the health burden of HAI and antibiotic-related complications. By incorporating these dimensions, our study provides a complementary perspective that reinforces the high value of TPP-compliant diagnostics while adopting a conservative approach to clinical impact across diverse epidemiological landscapes.

Importantly, this analysis was designed as a global early-HTA model rather than a setting-specific economic evaluation. This structure enables jurisdictions, particularly LMICs, to adapt and parametrize the framework with country-level epidemiology, care-seeking patterns, local treatment pathways, unit costs, and health system constraints. This enables locally contextualized value evidence to inform reimbursement, procurement, and donor investment decisions.

Additionally, this study extends beyond direct treatment effects to include system efficiency, antimicrobial stewardship, and downstream morbidity avoidance. By capturing these broader externalities within a unified decision model, this work provides a quantifiable and decision-relevant justification for diagnostics funding that is typically absent from conventional prioritization approaches.

The 2025 WHO TPP was published to promote the development of a rapid and accessible test that could reduce the discrepancies in health outcomes and reduce the economic burden between LMICs. The findings of this study illustrate the mechanisms through which improvements in health outcomes and costs reductions can operate, resulting in prompt treatment of NS cases and reduction in the risk of HAI, AMR and complications as well as resource use in patients without NS. Which, consequently, frees resources for other patients.

This study has several limitations. There is limited LMIC-specific evidence for some parameters, particularly the AMR DALY burden, the incidence of long-term complications, and stratifications by

early and late onset sepsis. We adopted cautious assumptions to avoid overstating benefits. Whereby direct costs associated with AMR externalities were excluded, which results in an underestimation of total economic gains. Additionally, we did not select the societal perspective as the definition varies widely across LMICs. Including societal costs such as those attributed to caregiver time lost could build a more favourable case toward the implementation of the POCT. However, real-world impact will depend on local implementation, health system capacity, and clinician adherence to diagnostic guidance. Despite these constraints, the PSA confirmed the robustness of the POCT's dominance in most simulations.

Conclusion

A rapid triage point-of-care diagnostic for NS has the potential to deliver robust health and economic gains in LMICs. These findings provide an evidence-based benchmark to align diagnostic innovation with the clinical realities of neonatal care. Our results should inform investment from global health donors and manufacturers to accelerate the transition of these diagnostics from the TPP stage into development, prioritizing neonatal point-of-care triage as a component of global newborn care strategies.

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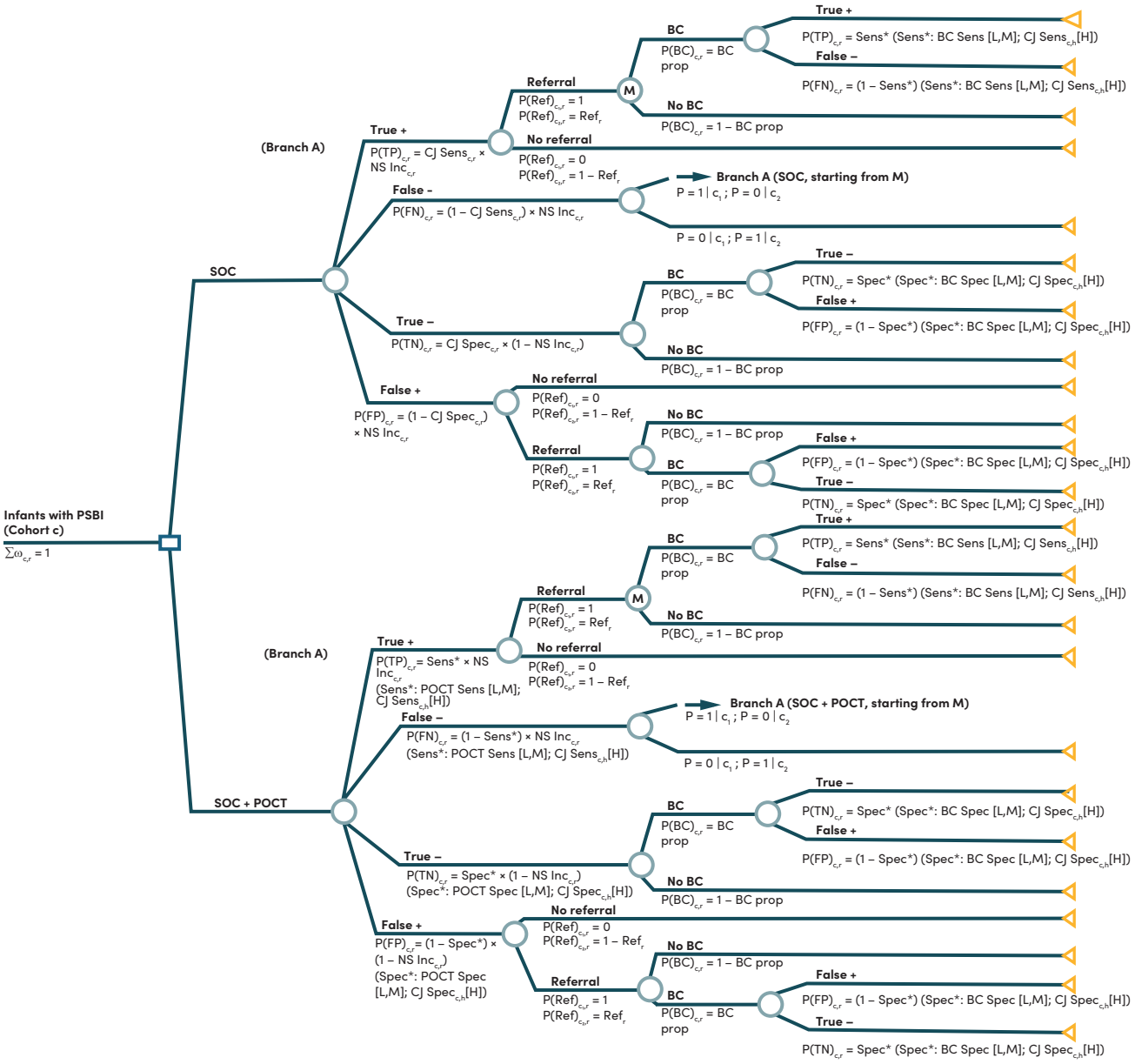
Figures and Tables

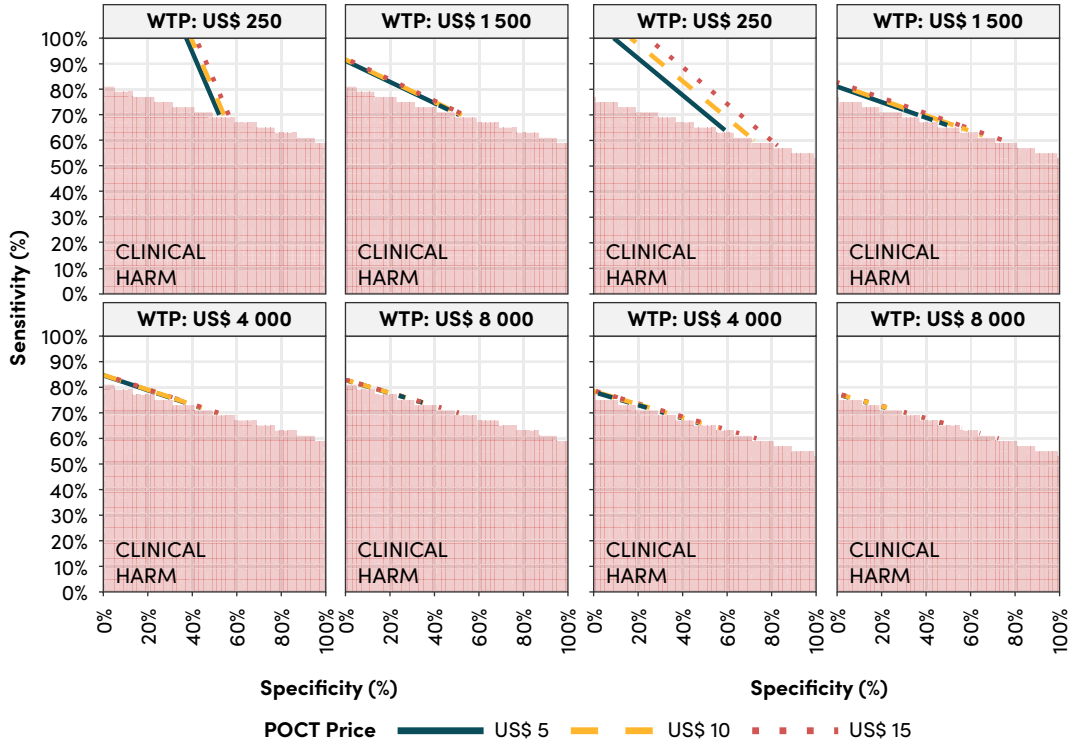
FIGURE 1. Clinical pathways of an infant with possible serious bacterial infection (PSBI) engaging with the healthcare system



Notes: Illustrates the clinical pathways of an infant with possible serious bacterial infection (PSBI) engaging with the healthcare system. The figure focuses on diagnosis and referral. Antibiotic treatment was omitted because sensitivity and specificity directly translate into treatment decisions. Before entering the model, infants are distributed into three risk groups (L, M, and H) based on presenting symptoms. In c1, the referral pathway is bypassed. The outcome is determined by antibiotic duration and length of stay (LOS), which depend on diagnostic results (SOC ± BC, POCT ± BC). High-risk infants are defaulted to treatment for safety reasons.

Abbreviations: SOC, standard of care; SOC + POCT, standard of care plus point-of-care test; c1, facility-of-birth cohort; c2, community cohort; c, cohort index; r, risk stratum; L, low risk; M, moderate risk; H, high risk; PSBI, possible serious bacterial infection; NS, neonatal sepsis; NS Inc, neonatal sepsis incidence; CJ, clinician judgment; POCT, point-of-care test; BC, blood culture; BC prop, proportion receiving blood culture; Ref, referral; P(·), probability of event; Sens, sensitivity; Spec, specificity; Sens*, effective sensitivity used in the model; Spec*, effective specificity used in the model; TP, true positive; FP, false positive; TN, true negative; FN, false negative; ω, branch weight (with $\Sigma\omega(c,r) = 1$).

FIGURE 2. Minimum accuracy requirements for cost-effective POCT use across cohorts and willingness-to-pay thresholds



Notes: Divided into panel (A) facility-of-birth cohort (c_1) and panel (B) community cohort (c_2). Panels are stratified into four boxes representing different willingness-to-pay (WTP) thresholds, defined as the maximum amount LMIC societies are WTP per DALY averted. Straight and dashed lines indicate minimum POCT accuracy requirements for the unit prices shown in the legend. The red shaded area denotes the net clinical harm zone, where adoption of POCT results in DALY loss. POCT is cost-effective for combinations of sensitivity (y-axis) and specificity (x-axis) that fall within the regions defined by these lines and outside the clinical harm zone.

TABLE 1. Input variables of the deterministic and probabilistic cost-effectiveness analysis

	Notation	Inborn (c_1)	Community (c_2)	Dist.
Cohort Distribution	$\omega_{c,r}$			
Prevalence of low risk PSBI (r=L)	$\omega_{c,L}$	0·67[EO]	0·55[1,2]	β
Prevalence of moderate risk PSBI (r=M)	$\omega_{c,M}$	0·22[EO]	0·35[1,2]	β
Prevalence of high risk PSBI (r=H)	$\omega_{c,H}$	0·11[EO]	0·10[1,2]	β
Epidemiology	NS $Inc_{c,r}$			
Incidence of NS (low risk)	NS $Inc_{c,L}$	0·23[3,4,EO]	0·08[5,EO]	β
Incidence of NS (moderate risk)	NS $Inc_{c,M}$	0·47[3,4,EO]	0·17[5,EO]	β
Incidence of NS (high risk)	NS $Inc_{c,H}$	0·93[3,4,EO]	0·34[5,EO]	β

(Continued)

TABLE 1. (Continued)

	Notation	Inborn (c_1)	Community (c_2)	Dist.
Diagnostic Accuracy				
POCT Sensitivity	POCT Sens	0·90[6]	0·90[6]	β
POCT Specificity	POCT Spec	0·80[6]	0·80[6]	β
CJ Sensitivity (r∈{L,M})	CJ $Sens_{c,r}$	0·70[EO,7]	0·65[EO,7]	β
CJ Specificity (r∈{L,M})	CJ $Spec_{c,r}$	0·50[EO,7]	0·50[EO,7]	β
CJ Sensitivity (r=H)	CJ $Sens_{c,H}$	1·00[EO,7]	1·00[EO,7]	Fixed
CJ Specificity (r=H)	CJ $Spec_{c,H}$	0·00[EO,7]	0·00[EO,7]	Fixed
Secondary Testing (BC)				
Fraction receiving BC	BC prop	0·06[8]	0·06[8]	β
BC Sensitivity	BC Sens	0·69[9]	0·69[9]	β
BC Specificity	BC Spec	1·00[9]	1·00[9]	β
Referral Pathway (c_2 only)				
Low risk referral (r=L)	Ref_L	NA	0[1,10]	Fixed
Moderate risk referral (r=M)	Ref_M	NA	0·30[1,10]	β
High risk referral (r=H)	Ref_H	NA	0·60[1,10]	β
Clinical Outcomes				
CFR treated NS (L/M/H)	—	0·04/0·09/0·20[11,EO]	0·04/0·09/0·20[2,EO]	β
CFR untreated NS (L/M/H)	—	0·11/0·26/0·57[2,EO,12]	0·11/0·26/0·57[2,EO,12]	β
CFR for non NS	—	0·02[5]	0·02[5]	β
RR mortality (treated/untreated)	—	0·35[12]	0·35[12]	ln
HAI risk target (per inpatient stay)	—	0·06[13]	0·06[13]	β
HAI risk (per inpatient day)	—	0·0058[13,14]	0·0058[13,14]	β
CFR for HAI (inpatient case)	—	0·12[13]	0·12[13]	β
Costs (US$)				
Cost of POCT device/reagents	—	5·00[6]	5·00[6]	γ
Hospital bed per day	—	41·55[15–18]	41·55[15–18]	γ
BC test	—	9·09[16–19]	9·09[16–19]	γ
Outpatient visit	—	NA	5·81[20,21]	γ
Antibiotics per case (outpatient)	—	NA	6·30[30]	γ
Antibiotics per day (inpatient)	—	1·07[23]	1·07[23]	γ
DALYs				
DALYs per death	—	31·10[24]	31·10[24]	γ
DALYs for AMR	—	0·13[25–32]	0·07[25–32,EO]	γ
DALYs for NS NEC Complication (inpatient)	—	0·01[33–35]	0·01[33–35]	γ
DALYs for NS IBD Complication (inpatient)	—	0·00006[36–39]	0·00006[36–39]	γ

Abbreviations: c_1, inborn cohort; c_2, community cohort; c, cohort index; r, risk stratum; L, low risk; M, moderate risk; H, high risk; PSBI, possible serious bacterial infection; NS, neonatal sepsis; CJ, clinician judgment; POCT, point-of-care test; BC, blood culture; Sens, sensitivity; Spec, specificity; BC prop, proportion receiving blood culture; RefL/RefM/RefH, probability of successful referral for low-/moderate-/high-risk infants (c_2); CFR, case fatality rate; RR, relative risk; HAI, healthcare-associated infection; NEC, necrotizing enterocolitis; IBD, inflammatory bowel disease; AMR, antimicrobial resistance; DALY, disability-adjusted life year; US$, United States dollars; Dist., probability distribution; β, Beta distribution; γ, Gamma distribution; ln, log-normal distribution; EO, expert opinion; Comp., complications; NA, not applicable.

TABLE 2. Distribution of final status for 1 000 infants with PSBI

	Inborn Cohort (c_1)			Community Cohort (c_2)		
	SOC (n)	SOC and POCT (n)	Increment (n)	SOC (n)	SOC and POCT (n)	Increment (n)
TP	285	333	48	102	128	26
FN	78	30	–48	37	11	–26
TN	334	512	178	400	637	237
FP	304	126	–178	461	224	–237

Abbreviations: PSBI, possible serious bacterial infection; c_1, inborn cohort; c_2, community cohort; SOC, standard of care; POCT, point-of-care test; TP, true positives; FN, false negatives; TN, true negatives; FP, false positives; n, number of cases.

TABLE 3. Cost-effectiveness analysis of management of 1 000 infant with PSBI

	Inborn Cohort (c_1)			Community Cohort (c_2)		
	SOC	SOC and POCT	Increment	SOC	SOC and POCT	Increment
Deaths						
Total Deaths	61	55	–6	49	45	–4
NS Deaths	45	39	–6	33	30	–3
HAI Deaths	5	4	–1	1	1	0
DALYs						
Total DALYs	1 964	1 758	–206	1 109	982	–127
NS DALYs	1 396	1 228	–168	577	474	–103
AMR DALYs	77	60	–17	48	31	–17
HAI DALYs	148	129	–19	23	19	–4
Comp. DALYs	7	6	–2	7	4	–3
Resource use						
Total LOS (Days)	7 613	6 628	–985	1 208	984	–223
Costs (US$)						
Total cost (US$)	323 245	285 904	–37 342	60 102	54 387	–5 715

Notes: Components may not sum to totals due to rounding. PSBI, possible serious bacterial infection; c_1, inborn cohort; c_2, community cohort; SOC, standard of care; POCT, point-of-care test; NS, neonatal sepsis; HAI, healthcare-associated infection; AMR, antimicrobial resistance; DALY, disability-adjusted life year; Comp., complications; LOS, length of stay; US$, United States dollars.

Appendix E. Comparable Diagnostics

TABLE E.1 Description of selected comparable diagnostics

TEST NAME/COUNTRY OF DEVELOPER	INDICATION	WHAT IT MEASURES	PLATFORM	COST PER TEST	ANNUAL SALES VOLUME	SOURCES
careHPV (QIAGEN), the Netherlands	High-risk HPV	Measures several different strains of HPV (DNA)	Molecular diagnostic with benchtop instrument, signal amplification hybrid capture	About US$4.95 (reagents); all-in modeled about US$9.34, including consumables/ logistics		WHO pricing slides
Cepheid GeneXpert, United States	Tuberculosis (TB) and drug resistance	DNA	Molecular test with benchtop, RT-PCR	TB cartridges: US$7.97 in Global South	Tens of millions a year	Price negotiated through Global Fund
Molbio, India	TB and drug resistance, flu panels, sexually transmitted infections panels	DNA/RNA	Molecular diagnostic with benchtop instrument	US$4–$10; US$5,000–$10,000 for instrument	Unclear	Private information from firm
Huwel influenza panel, India	Influenza panel	Looks for different influenza strains (RNA)	Molecular diagnostic with a benchtop instrument, RT-PCR	US$3 per test; instrument costs US$2,000, which could fall by 30%–40% at scale	Hundreds of thousands within India	Private information from firm
CueReader	SARS-COV2	DNA	Molecular test, isothermal NAAT	CueReader costs US$200, retail cost is US$50 per test; industry expert says could sell for US$5–$10 at scale	Unclear	Private information from firms
Wondfo	HIV/HCV/HBV test	Antigens	Immunoassay, multiplex with instrument	<US$1; US$1,000 per instrument	Unclear	Commercial websites
SD Biosensor, Dual HIV/syphilis RDT, South Korea	HIV and syphilis	Antibodies	Lateral flow strip (immunoassay) without an instrument	<US$1 with global access deals	More than 5 million in 2020	WHO news; MedAccess/ CHAI announcement
Haemocue, Sweden	Hb level, anemia screening	Hemoglobin concentration	Photometer reading instrument	Microcuvettes cost about US$0.35; analyzer costs about US$547 (one-time purchase)	Manufacturer claims about 140 million microcuvettes sold annually	Haemocue UNICEF page
Malaria RDT, globally manufactured	P.f HRP2 + Pan pLDH	Lateral flow	No instrument	US$0.30	345 million	UNICEF market update; WHO malaria RDT page. (World Health Organization)

Appendix F. Components of and Rationale Behind Mechanism Design

Section 6 introduces the NeoTest facility and provides an overview of the market frictions addressed. This appendix provides a deeper rationale behind the NeoTest facility's design, documenting the specific design choices at each decision point, the alternatives that were considered and rejected, and the safeguards that protect the mechanism against gaming.

COMPONENTS

The milestone

To participate in the facility, a firm must satisfy all of the following:

- **TPP compliance:** Meets minimum TPP specifications. Firms are not preferentially rewarded for going above and beyond the minimum criteria.
- **Regulatory approval:** Received approval through at least one of the following: a pre-approved Stringent Regulatory Authority (SRA), or WHO Prequalification.
- **COGS audit:** Independent audit of the cost of goods sold (COGS) covering the entire test (including platform/instrument where applicable) conducted by independent auditor with contractual access to firm's production data. The audit must result in a marginal cost of the cartridge and platform that meets the TPP minimum requirements.
- **Commitment to commercialize in low- and middle-income countries (LMICs):** Binding commitment to commercialize in LMIC markets within a defined window; licensing obligations (or repayment of the milestone) triggered on failure. The nature of the licensing obligations and period of the commercialization window are to be defined.
- **Provision of units for pilot studies:** Provision of test units, which will be delivered to LMIC facilities for use in pilot studies. Representative numbers are provided below; final values are still to be determined:
  - Non-platform based: 25,000–50,000 units
  - Platform-based: 5–10 instruments and 10,000–25,000 cartridges
  - Wearable and/or clinical algorithm: Negotiated with the firm, which will provide enough to run pilot studies in at least 10 secondary and/or tertiary centers over at least a one-year period.

Units delivered for pilot studies are eligible for AMC top-up payments. Where a firm licenses manufacturing to a partner, production by the licensee satisfies the condition, as long as the licensing agreement is executed and the licensee produces the required volume.

The first firm to develop a test receives an immediate payment of $5 million. A 12-month eligibility window commences after this payment, during which additional firms may qualify. At the end of the 12-month period, the remaining $15 million is distributed equally among all eligible winners.

Example: The first firm to qualify receives $5 million immediately. If no subsequent firm qualifies, the first firm receives an additional $15 million at month 12. If three subsequent firms qualify, these firms receive $3.75 million at month 12, while the first firm receives an additional payment of $3.75 million. If the milestone is not rewarded within a set number of years after the announcement of the facility, the milestone, along with the rest of the funds in the facility, is returned to donors. The number of years that the milestone remains open to firms after the announcement of the facility is to be finalized.

Implementation support

The implementation support fund is a flexible pool of capital designed to bridge the gap between regulatory approval and commercialization. Its use is intentionally left open-ended, as spending priorities will be driven by LMICs seeking to adopt a neonatal sepsis diagnostic. This country-led approach enables governments to address context-specific uncertainties and market failures that may hinder diagnostic uptake.

The fund will likely be allocated through a competitive request for proposal process open to LMIC applicants (including governments, NGOs, implementers, and multilateral partners). Maintaining flexibility is essential to accommodate the heterogeneity of market failures across geographies and health systems.

Potential uses of implementation support include the following:

- sponsoring clinical utility or pilot studies (e.g., an ICMR–supported trial in India)
- country-level competitive grants
- guideline and procurement facilitation (e.g., support for updating national clinical guidelines, essential diagnostic lists, and procurement processes)
- AMC administrator fees.

The advance market commitment

Any firm is eligible for the AMC, provided that it

- meets TPP specifications
- self-declares its COGS and gives the AMC administrator the contractual right to verify its COGS before tenders are conducted (up to a maximum of once a year; number to be finalized)
- permits the AMC administrator to view its purchasing and production data.

Firms do not need to have received the milestone or have satisfied the other milestone conditions to be eligible for the AMC.

Distributors and procurers must register with the AMC administrator in advance for purchases to be eligible. To maintain their eligibility, they must retender at a minimum frequency of at least once every three years (frequency to be finalized).

If a firm creates a platform-based diagnostic, it must do so on an all-inclusive pricing basis (a single per-test price covering instrument placement, reagents, consumables, maintenance, and training).

The AMC is structured as a $30 million shared subsidy pool. Each unit sold in an eligible LMIC market triggers a "top-up" payment to the firm, paid in addition to a "country copay" self-financed by in-country procurers. The firm receives the copay plus top-up per unit used.

The AMC fund will be open for four years starting with the closing of the milestone competition (this time window is to be finalized). If funds from the AMC have not begun to be disbursed within this time window, they will be returned to donors.

The top-up pool covers 6 million units on a declining schedule: $7 per unit for the first 2 million units, $5 for the next 2 million, and $3 for the last 2 million. The top-up is paid on a per-use basis, calibrated to the diagnostic format:

- **Non-platform based:** $3–$7 top-up per test used, verified by purchase data
- **Platform-based:** $3–$7 top-up per cartridge used on the platform, verified by instrument log or purchase data
- **Wearable and/or clinical algorithm:** Top-up paid based on verified monthly use. Verification method to be specified by the mechanism administrator in collaboration with the firm; must be independently auditable.

The country copay is the private price negotiated between the procurer and the firm. The AMC top-up is paid to the firm on top of this copay; the firm receives the copay plus a top-up per unit used. For the AMC top-up to be awarded, the country copay must be equal to or greater than the price floor, which will be set individually for each firm at its marginal cost of production, based on the most recent COGS audit.

The floor does not cover the landed price. We expect procurers to negotiate a copay above the floor to cover these

incremental distribution and last-mile delivery costs, or alternatively for the AMC top-up to implicitly subsidize this gap.

Updated COGS audits can be requested by procurers in advance of tender decisions or auctions. The AMC administrator bears the cost of COGS verification.

The AMC is restricted to LMICs, as defined by the World Bank for the 2026 fiscal year. Under this definition, eligible countries are countries with per capita Gross National Income (GNI) below $13,935. Eligibility is fixed under the FY2026 World Bank LMIC definition and remains unchanged thereafter, even if a country is subsequently reclassified. The AMC subsidy applies only to tests procured for use in public sector healthcare facilities (any healthcare facility that is owned, operated, or directly administered by a national, regional, or local government authority in a LMIC).

DESIGN JUSTIFICATION

Market frictions and gaming issues

Various market frictions undermine the development of a neonatal sepsis diagnostic, justifying the creation of this facility. Table F.1 summarizes them.

Gaming issues are distinct from market failures and challenges: They are moral hazard concerns about how firms or procurers might exploit the mechanism's rules to capture value without delivering the intended outcome. Table F.2 summarizes them.

TABLE F.1 Market frictions preventing development of a diagnostic and ways to circumvent them

MARKET FAILURE	PROBLEM DESCRIPTION	HOW THE DESIGN CIRCUMVENTS IT
Weak market-fit and use-cases	A diagnostic test that achieves regulatory approval and satisfies the TPP may nonetheless fail in practice because it struggles to fit into clinician workflows, lacks a compelling use-case in LMIC neonatal care settings, and/or proves difficult to integrate into existing clinical protocols. The characteristics that solve for these and other potential end-user challenges are not straightforward to incorporate into a TPP.	The AMC pays per unit procured and used. Because obtaining the AMC subsidy is the primary means by which firms recoup their development costs, firms have a strong incentive to ensure their diagnostic is incorporated into routine, clinical care in LMIC markets. This forces them to build for real-world use throughout development.
Fragmented demand	LMIC diagnostic markets lack a central global procurer. Individual country procurers represent small, uncertain volumes across different regulatory systems and tender processes. Without a credible demand signal, firms cannot reliably invest in the manufacturing scale-up needed to reduce the unit cost of the test.	The milestone provides up to $20 million at regulatory approval, reducing dependence on early LMIC revenue to fund scale-up investment. The AMC also provides a demand signal. Neither feature guarantees that a certain volume of the test will be purchased, however. To address this residual gap, in countries in which demand credibility is the binding constraint, implementation support can fund volume guarantees or work with the AMC implementor to develop centralized procurement mechanisms. Where there is an absence of clinical evidence for the local context, it can sponsor clinical utility studies; where guidelines or procurement processes are the bottleneck, it can fund technical assistance to update essential diagnostic lists and tender frameworks.

TABLE F.1 Continued

MARKET FAILURE	PROBLEM DESCRIPTION	HOW THE DESIGN CIRCUMVENTS IT
Low willingness to pay	The cost of a neonatal sepsis diagnostic may exceed what LMIC public sector procurers are willing or able to pay. Health budgets are constrained and diagnostic procurement often lacks the political salience of vaccines or therapeutics. Together with the demand-fragmentation failure, low willingness to pay can create a "valley of death" between regulatory approval and commercialization.	The design seeks to bridge the gap between the price procurers can pay and the price firms need to recoup their development costs and sustain commercialization efforts. The lump-sum milestone allows firms to immediately recoup some of their development costs; the AMC top-up further narrows this gap. The price floor on the country co-pay grounds a long-term exit price. The implementation support fund can increase countries' willingness to pay, including by sponsoring health-economic evidence (e.g., health technology assessments) or pilot studies, which may build the political will to reprioritize budgets toward diagnostic expenditure.
Copycats and competitors	Follow-on entry can take two forms: (a) copycats replicating the original innovators' approach, typically entering at lower cost because they free ride on the original R&D or (b) "true" competitors developing a novel diagnostic that may offer clinical and/or operational advantages. Both are valuable: Copycats can drive down the price, as they do not need to recoup R&D costs and may have a comparative advantage in manufacturing innovation; "true" competitors can improve quality and expand the range of settings and use-cases the diagnostic can serve. If adequate incentives are not provided for both, a single-supplier structure can emerge, with little to no pressure on price or innovation. This problem can be acute in diagnostics, where platform-based formats can embed incumbencies if switching costs are high.	The AMC is firm-agnostic: any firm meeting TPP specifications is eligible, whether or not it received the milestone. Unlike other market-shaping mechanisms (e.g., non-agnostic procurement guarantees), subsidies are not pre-committed to any particular firm, keeping the door open for future entrants that can provide a better or cheaper product.

TABLE F.2 Gaming issues and ways to prevent them

ISSUE	RISK	HOW THE DESIGN REDUCES IT
Capture of a share of the milestone by copycats	A firm observes the first winner and rapidly reverse-engineers the test to claim a share of the milestone.	The 12-month eligibility window is short enough that a rival firm cannot reengineer a test from scratch after observing the first winner, ensuring that the milestone rewards genuine innovation rather than rapid imitation. At the same time, it is long enough that developers working on parallel approaches can qualify.

TABLE F.2 Continued

ISSUE	RISK	HOW THE DESIGN REDUCES IT
Failure to commercialize in LMICs following capture of the milestone	A firm meets the milestone conditions, collects the payment, and either pauses commercialization entirely or pursues it only in high-income (HIC) markets, where profit margins are higher.	The milestone is sized so that a firm cannot break even on it alone: recouping full development costs requires capturing AMC revenue, which can be obtained only by making sales in LMICs. A firm might argue that the milestone defrays enough development cost to make a HIC commercialization strategy viable. Three factors reduce this possibility: • The clinical landscape suggests that the use-case is overwhelmingly concentrated in LMICs. • If a highly profitable HIC use-case existed, the test would likely be under development without a pull incentive. • The AMC's size and LMIC restriction implicitly pulls firms toward LMIC commercialization as the primary revenue opportunity. Beyond these structural incentives, the access terms attached to the milestone require a commitment to LMIC commercialization within a defined period, with licensing obligations or milestone repayment triggered on failure. We think it is possible that a firm could pursue a dual launch strategy or adapt its test to HIC markets. Provided this does not delay rollout of a test in LMICs, commercialization in HIC markets could help offset development costs and sustain ongoing commercialization efforts in LMICs.
Procurement distortion	Three forms of price manipulation can undermine the mechanism: • Knowing the AMC top-up exists, country procurers or distributors may extract artificially low base prices from the firm (effectively leveraging the AMC contract). • Firms (particularly first-movers) may inflate their reported COGS to raise the price floor that procurers must meet. • Follow-on entrants may understate their COGS to price below competitors, win tenders, and quickly capture market share.	Every firm accessing the AMC may self-declare their COGS, or permit the AMC administrator to undertake a COGS audit. The co-pay floor would be tied to the marginal cost reported by the self-declared COGS or audited COGS. The administrator also retains a contractual right to access production data. To ensure that the audit requirement does not become a barrier to entry for lower cost follow-on firms, the mechanism administrator may subsidize audit costs for qualifying small and medium-size enterprises and LMIC manufacturers from the implementation support fund.
Targeting of facilities with high willingness to pay over facilities with high need	A firm prioritizes private hospitals and urban tertiary centers (where procurement is easier and volumes more predictable) over public-sector primary and secondary facilities, where the burden of neonatal sepsis is highest.	The AMC is a finite, shared pool. This means firms must compete to capture the subsidy before competitors do. This creates an incentive to position the test in places with high throughput, which should correlate with high sepsis burden. However, market forces may misalign with burden if the profit margins at lower-burden facilities are higher. Accordingly, we restricted the AMC subsidy pool to tests sold to public facilities.

Other design choices

The mechanism structure includes both intensive and extensive decisions—for example, the decision to have a milestone at all, and if so, the share of the total funding facility that will go toward it. Table F.3 summarizes some of these decisions.

TABLE F.3 Alternative design choices considered and rationale for rejection

DECISION POINT	CHOICE ADOPTED	ALTERNATIVE REJECTED	RATIONALE
Whether to use a pull mechanism at all	A pull mechanism rewarding delivery	Push (grant) funding only	Push funding reduces private capital at risk during R&D but gives no assurance an LMIC market will exist at the end of the pipeline. It does not reward delivery or use, so it cannot address demand or appropriability failures, and other funders (CARB-X, BARDA, the Gates Foundation) already perform this function. Developers told us repeatedly that they needed a clear demand signal to justify shifting development priorities, given the opportunity cost of doing so.
Whether to include a milestone at all	Include a milestone alongside an AMC	Create only an advance market commitment (AMC), or a pure AMC	A pure milestone rewards proof of feasibility but is untied to uptake, so firms may optimize for the milestone criteria over real-world adoption, with no ongoing affordability bridge and no incentive to keep improving the product. A pure AMC protects funders by paying only on use, but may under-reward the first mover where weak IP lets later entrants free-ride and quickly capture the subsidy, and it defers reward given slow adoption. Splitting the reward hedges against both failure modes: the milestone supplies liquid capital for early commercialization, while the AMC rewards use.
Split between milestone and AMC	Roughly equal split in present value terms ($20 million milestone $30 million AMC)	Concentrate the reward in either the milestone or the AMC	The milestone must be smaller than the AMC so that firms cannot break even on approval alone and must pursue AMC revenue to recoup costs completely. The AMC's larger size offsets its later, discounted disbursement.
Distribution of the milestone	Equal split among all firms qualifying within a 12-month window, with $5 million paid to the first qualifier on qualification	Winner-takes-all	Equal distribution avoids over-rewarding speed and the corner-cutting it invites; the 12-month window is short enough to defeat reverse-engineering yet long enough to admit genuine parallel efforts. The $5 million advance spares the first qualifier a 12-month wait without creating a clawback risk.
TPP reward structure	Binary threshold: qualify on meeting the TPP minimum	Sliding scale rewarding performance beyond the TPP minimum	By construction, the TPP minimum is the clinically functional standard. A sliding scale may invite marginal improvements of diminishing value, add costly performance monitoring, and slow time to market. The AMC's market test will reward superior products through the mechanism of greater uptake (and a larger share of the subsidy).
AMC top-up schedule	Declining per test price across successive 2 million-unit tranches	Flat per-unit subsidy	A declining schedule concentrates support early, where affordability gaps and unit costs are largest; signals a credible path to unsubsidized pricing; and shortens the payout period, reducing the fund's present-value cost. It may also have tax advantages.

TABLE F.3 Continued

DECISION POINT	CHOICE ADOPTED	ALTERNATIVE REJECTED	RATIONALE
Co-payment floor	Floor on each firm's co-pay at its audited marginal cost (COGS)	No floor	A floor prevents procurers from bargaining the base price down to below cost in anticipation of the subsidy and prevents follow-on entrants from understating cost to dump product and capture share. Both practices would undermine the post–AMC exit price.
COGS verification	Self-declared COGS with contractual right to independent audit (maximum of once per firm per year)	Mandatory audit of every firm at every tender	Universal mandatory audits are slow and costly and could deter low-cost entrants. A right-to-audit preserves the floor's integrity at far lower administrative burden; the administrator may subsidize audit costs for small and medium-size enterprises and LMIC manufacturers from the implementation fund.
Geographic concentration of the AMC	Limited to LMICs	Per-country caps or geographic restrictions	Geographic mandates could delay launch or force firms into markets they are not best placed to serve. The advantage of a firm-agnostic subsidy that is paid only on procurement is that countries decide which tests they want to use and reward; not donors.

Why not incorporate a volume guarantee?

A volume guarantee commits a funder to purchase a minimum quantity from a selected supplier over a set period, often at a ceiling price. It is the closest single-instrument alternative to the milestone/AMC structure: like the milestone, it offers a firm financial certainty ahead of sales; like the AMC, it rewards supply rather than mere technical achievement. It is therefore worth setting out why a volume guarantee was not chosen, but where it nonetheless retains a role.

Why not replace the milestone with a volume guarantee?

The milestone is designed to serve as a liquid, upfront reward for the first innovator(s), regardless of their size. A volume guarantee is similar in that it is also a guaranteed financial reward, but it is paid out over a longer period and made contingent on manufacturing and supply commitments. While that conditionality has the appeal of securing a deliverable for donors, it defers the reward and ties it to obligations a first-mover may not yet be positioned to meet. These obligations are precisely the constraint the milestone exists to relieve. The milestone instead provides immediate, flexible capital that firms can direct toward the barriers they perceive as binding, whether manufacturing scale-up, licensing, or early commercialization.

Why not replace the AMC with a volume guarantee?

The fundamental difference between a volume guarantee and an AMC is in how they allocate risk: a volume guarantee shifts risks onto the funder by guaranteeing revenue to the firm, while an AMC shifts risk onto the firm by tying revenue to a market test. This distinction matters when the real-world use-case of a test has yet to be proven (such as a de novo, neonatal sepsis diagnostic). Unlike a vaccine, whose efficacy is largely established at approval, a diagnostic's value depends on how it performs in practice – whether clinicians trust and act on its results, whether it fits facility workflows, and whether it is robust to the constraints of low-resource settings. A volume guarantee pays out against a contracted quantity regardless of whether these conditions are met, so a firm has no reason to optimize for them (or to continue innovating for them). An AMC, by tying revenue to units actually used, makes real-world performance the thing firms compete to deliver.

Additionally, the AMC preserves competitive dynamics by maintaining the market test: since any qualifying firm can capture the subsidy, firms are incentivized to compete with each other on price and quality. It also preserves optionality across expected entrants. AMCs perform well under both single-firm scenarios (in which the absence of competition means the firm can capture the full subsidy, giving it de facto revenue certainty) and multi-firm scenarios (in which competitive dynamics drive price and quality improvements). A volume guarantee, by contrast, can be extended to multiple entrants, but if each is assigned a supplier base and recoups its development costs in full through the guarantee, none has any incentive to compete with the others. For platform-based diagnostics, assigning a supplier base may also have the unintended consequence of creating an installed-base monopoly that deters follow-on entry.

Volume guarantees can smooth out the price of a test and allow COGS to fall more rapidly, addressing the willingness-to-pay gap earlier in the product lifecycle. They can also expand procurer choice: by bringing down the upfront price of a more expensive but clinically superior test to parity with a cheaper but inferior alternative, volume guarantees enable procurers to select on quality rather than defaulting to the lowest-cost option. As such, implementation support funds can be allocated to volume guarantees where appropriate. Of note, similar effects are achieved via the milestone providing the upfront funds for manufacturing scale-up and the AMC's creation of competitive conditions under which firms race to capture the subsidy, which drives costs down and widens the range of viable products.

Appendix G. Rationale for the Mechanism's Sizing

The facility was sized using the framework set out in the Market Shaping Accelerator's Pull Incentive Sizing Tool. The logic behind this tool is that a pull mechanism must offer an expected reward that is at least as large as the expected cost a firm bears in attempting the innovation, scaled up to attract enough firms that at least one is likely to succeed.

The tool includes four steps:

1. Estimate per-stage costs, durations, and probabilities of success.
2. Compute the expected cost and overall success probability of a single attempt.
3. Determine the program size needed to hit a target probability of at least one success.
4. Convert that net present value (NPV) into a nominal facility size and net out other funding.

INNOVATION COSTS AND RISKS

We triangulated across 783 data points—developer interviews, white papers, National Institute of Health grant funding patterns, company websites, and the literature—constructing weighted averages across firm archetypes and diagnostic complexity. Accounting for existing development and "push" funding in the space, we parametrized the cost side (Table G.1).

From each stage's gross cost, we subtracted the share already covered by other sources—including push grants (from CARB-X, BARDA, the Gates Foundation, PACE) and any expected market returns a firm might extract from LMIC markets.

TABLE G.1 Projected development costs, durations, and probabilities of success

STAGE	COST ($M)	DURATION (YEARS)	PROBABILITY OF SUCCESS (PERCENT)	EXPECTED COSTS ($M)	DISCOUNTED EXPECTED COSTS ($M)
Biomarker validation and clinical feasibility	6.3	2.4	18	6.3	6.3
Platform adaptation	3.9	1.6	80	0.7	0.9
Larger clinical validation	4.1	1.5	60	0.6	0.9
Regulatory approval	0.6	0.8	90	0.1	0.10
Total to product launch	14.9	6.3	8	7.6	8.1
Clinical utility studies	1.4	1	–	0.1	0.1
Commercialization	6.3	3	70	0.0	0.0
Total	22.6	10.3	5	7.8	8.3

Note: Costs were discounted at the firm's hurdle rate of 9.8%.

EXPECTED COST AND SUCCESS PROBABILITY PER ATTEMPT

Firms choose to enter markets based on the expected cost at the time of entry, not the all-in cost of a successful product. Because a firm stops incurring costs the moment an attempt fails—and most attempts fail at the early, cheaper stages—the expected cost is often lower than the cost of seeing an attempt through to launch.

Formally, with k stages, a vector of stage costs $\mathbf{C} = [c_1, ..., c_k]$ and conditional success probabilities $P = [p_1, ..., p_k]$, the expected cost of an attempt before discounting is:

$$\sum_{i=1}^{k} c_i \prod_{j=1}^{i-1} p_j \qquad \text{G.1}$$

The cost of each stage is weighted by the probability of reaching it. Each stage's expected cost is then discounted at the firm's hurdle rate to reflect the time value of money.

For NeoTest, this estimate yields an all-in cost to launch of roughly $14.9 million and an expected cost per attempt of about $7.6 million ($8.1 million after accounting for the timing of when costs fall). The per-attempt probability of reaching launch is about 8% (Figure G.1). The implied expected developer net present value (NPV) under base-case private revenue is negative. This result is consistent with the absence of observed market entry despite technical feasibility.

PROGRAM SIZE FOR A TARGET PROBABILITY OF SUCCESS

A firm enters this market only if the expected reward at least covers its expected cost. As a firm wins the reward only if it succeeds, the NPV incentive needed to attract one firm is its expected cost divided by its probability of success (at an 8% success rate, roughly 12 times the expected cost). This multiple is the cost of shifting development risk from the funder to the firm. The funder commits the full sum but pays only on success; in the roughly 92% of cases in which the firm fails, the funds are released for other uses.

To raise the probability that at least one firm succeeds, the funder must attract multiple entrants. With a per-attempt success probability p, the minimum number of entrants n needed to reach a target probability θ that at least one succeeds satisfies the following expression:

$$n \geq \frac{\ln(1-\theta)}{\ln(1-p)} \qquad \text{G.2}$$

Each additional entrant raises the chance of success but is increasingly expensive to attract, because every firm now faces the risk of splitting the reward with other winners. Assuming that firms are identical and independent, enter simultaneously, and share the reward equally, the required present-value pull size is given by

$$PV(Incentive) \geq \frac{\ln(1-\theta)}{\theta \cdot \ln(1-p)} \cdot E[c] \qquad \text{G.3}$$

FIGURE G.1 Expected probability of success at each stage of the process

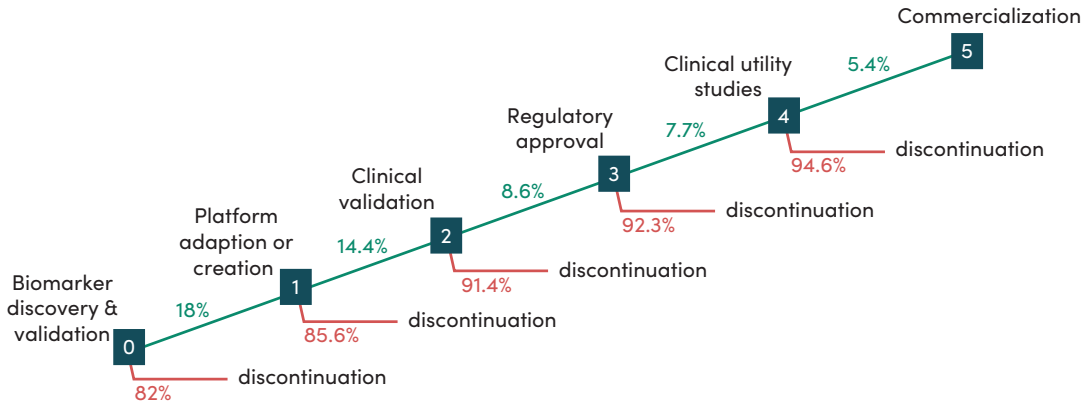
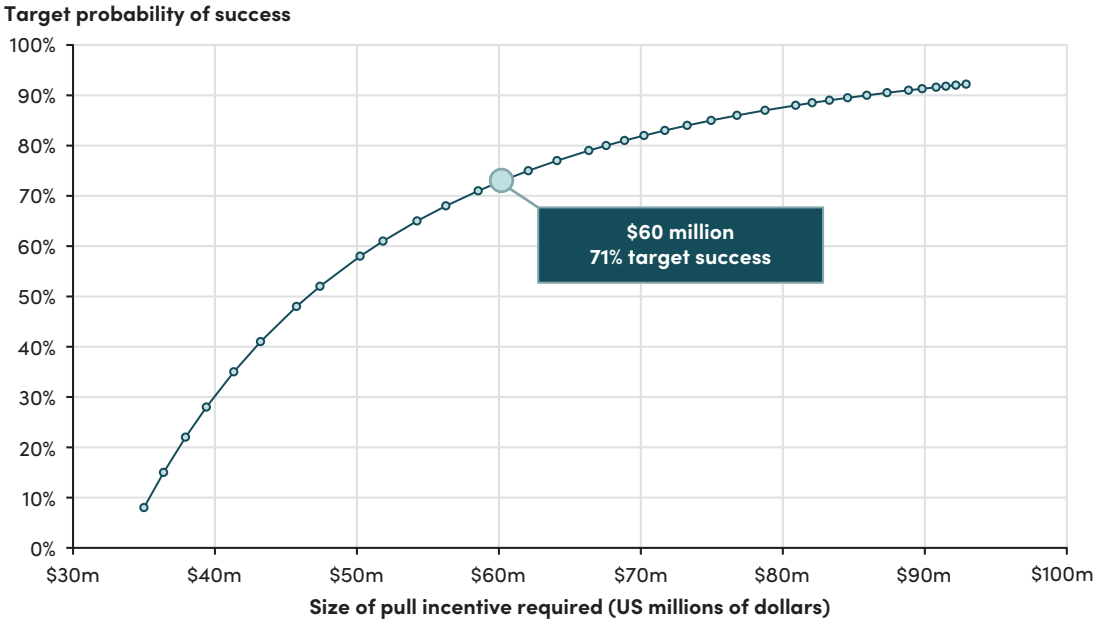


FIGURE G.2 Probability of at least one successful product launch given a target pull size



where E[*c*] is the discounted expected cost per attempt. The marginal cost of inducing one more attempt rises with *n* and asymptotes to the expected cost of an attempt itself.

For NeoTest, a per-firm launch probability of about 8% and a target of 70% probability that at least one firm reaches launch imply that roughly 15 firms must find entry rational (Figure G.2).

Expression G.3 shows the reward a firm needs for entry to be rational. This reward is the target the facility must deliver, valued at the time of regulatory approval. Commercialization costs incurred after approval are amortized back into this figure, so the target reflects all the costs a firm must recoup. All values are discounted to the point of regulatory approval.

NeoTest splits that target in two. Roughly half is paid as the milestone in present value terms and is disbursed at regulatory approval; the other half is delivered through the AMC, paid out as a per-unit top-up over the adoption trajectory of the test. Appendix H describes the adoption trajectory.

Because the AMC half is paid over time rather than at regulatory approval, delivering a given target value through it requires committing more than that value in nominal terms: each year's payment is worth less to the firm than a payment at regulatory approval, so the stream must be larger to compensate. We project sales onto the adoption trajectory, discount them to regulatory approval-equivalent units at the firm's hurdle rate, and then set the per-unit top-up so that the discounted stream equals the half the AMC's target.

The headline facility size is therefore larger than the target valued at approval. The milestone delivers its half one-for-one; the AMC half is grossed up to offset the discounting of payments spread across the adoption period. At the target probability of success—a 70% probability that at least one firm reaches regulatory approval—the facility size is approximately $59 million, which we round to $60 million. Figure G.2 shows how the size responds as the target probability and other inputs are varied.

Appendix H. Benefit–Cost Ratio Calculations

The benefit–cost ratio (BCR) compares the present value of the health and economic benefits that NeoTest is expected to generate with the present value of the funds donors commit to the facility. Both are projected over a 15-year time horizon (2030–45) and discounted to present value at a 2% social discount rate.

We calculate benefits and costs as follows:

1. We estimate demand for the test (D) through adoption modeling.
2. We estimate the per-test impact (I), including DALY benefits and savings to the healthcare system.
3. We apply the per-test impact to demanded tests to estimate the total benefit (B = D x I).
4. We calculate the present value of the funds committed by the funder and costs incurred by the healthcare system (C).
5. We divide total benefits by total costs (B/C).

Steps 1, 3, 4, and 5 are detailed below; step 2 comes from our Health Technology Assessment, which can be found in Appendix D. The model is hosted in a Google Spreadsheet (click here).

A defining feature of pull mechanisms is that benefits and costs are realized together—and only upon success. The AMC and milestone pay out only if a qualifying test is developed and used; the events that trigger disbursement are the same events that generate health benefits. As a result, the probability that the facility's funds are spent is, by construction, close to the probability that its benefits are realized. The two move in lockstep, separated only by the opportunity cost of holding committed capital in escrow.

Estimating adoption

Before valuing benefits and costs, we estimate how many tests would be used over a 15-year period. We build this figure bottom up across six country and regional tiers (India, Ghana, Kenya, Brazil, Ethiopia, Nigeria, and a residual LMIC basket), in four steps. We draw on the academic and grey literature; case studies; and interviews with developers, in-country stakeholders, and other market-shaping implementors to inform our parameter choices:

1. **Population size.** For each country, we start with a projected number of annual live births (from the UN World Population Prospects' 2024 medium variant), split into facility and home births, and apply the setting-specific incidence of possibly serious bacterial infection (PSBI), per the WHO case definition, to estimate the number of neonates presenting with signs of sepsis each year. This pool of neonates with PSBI is the total addressable market (TAM). We count each eligible neonate once and exclude plausible expansions from repeat testing during inpatient monitoring or screening of at-risk neonates at birth, both of which would increase the size of the eligible patient population.
2. **Market penetration.** A test does not reach the entire TAM. We apply a peak penetration ceiling to each market (15%–40% of the TAM, highest in Brazil and India, lowest in the residual LMIC basket), reflecting the possible long-run uptake given health-system reach and donor support.
3. **Diffusion over time.** Uptake toward that ceiling follows a logistic (S-shaped) adoption curve, $P(t) = \frac{Peak}{1+e^{-k(t-t_{mid})}}$, where t is years since launch, t_{mid} is the time to reach half of peak penetration, and k governs steepness. Launch is

staggered by tier (India in 2031, other priority markets in 2032, later entrants in 2034). Curve parameters are calibrated to observed roll-outs of comparable point-of-care diagnostics—malaria RDTs (WHO World Malaria Report 2024) and molecular TB testing/GeneXpert (FIND, UNITAID)—which reached roughly half of their addressable uses over five to eight years.

4. **Commercialization risk.** Each market's adoption is multiplied by a country-specific probability that a launched test is successfully commercialized there (50%–72%, conditional on a product reaching launch at all). These probabilities capture the risk that a test clears regulatory approval but fails to penetrate a given market; they are conditional on a test successfully getting to product launch. The 15%–40% penetration probabilities and the 50%–72% commercialization probabilities have isomorphic effects: both are multiplicative scalars on demanded tests. If one treats the penetration probabilities as implicit commercialization discounts, the "true" effective commercialization probability is therefore lower than the 50%–72% stated above, closer to 7.5%–24.0% once both are combined.

The result is a probability-adjusted stream of tests used per country per year, which drives both the benefit numerator and the AMC component of the cost denominator. (A second, independent risk adjustment—the 65%[ii] probability that any qualifying product reaches launch—is applied at the BCR level, as discussed below.)

Total benefits: The BCR numerator

Benefits accrue from three sources:

1. **The value of more disability-adjusted life years (DALYs):** We model the increase in DALYs from reduced mortality, long-term complications, antimicrobial resistance, and hospital-acquired infections. The per-test DALY reduction (0.167) is taken directly from our Health Technology Assessment (see Appendix D), which estimates DALY benefits separately for neonates born in a facility and neonates brought in from the community. To generalize to a single test, we weight the two cohorts 50/50. (This split likely varies by country, but data on the share of PSBI arising before versus after discharge is limited, so we hold it constant for simplicity.) The per-test reduction is applied to the probability-adjusted test volumes from the adoption model. We value each DALY at the relevant country's per capita GDP.
2. **Health-system cost savings:** Fewer treatment episodes and inpatient days reduce healthcare costs. The per-test saving ($22) comes from the HTA under the 50/50 weighting. These savings are included in the BCR but excluded from the headline cost-per-DALY figure (so that the cost-effectiveness estimate is not flattened by them). The HTA's cost figures include the price of the test, so the cost-saving benefit reported by the HTA already subtracts the country co-payment.
3. **Returned funds in failure states:** Because committed capital is held and released only upon verified success, where no product launches (or launches but fails to commercialize), the unspent milestone and AMC funds return to the funder. The numerator credits these returned funds, net of the opportunity cost of holding them in escrow rather than deploying them elsewhere.

The shape of the adoption curve is depicted below in Figure H.1, which applies the HTA per-test mortality reduction to estimated demand for tests to arrive at lives saved per geography by year.

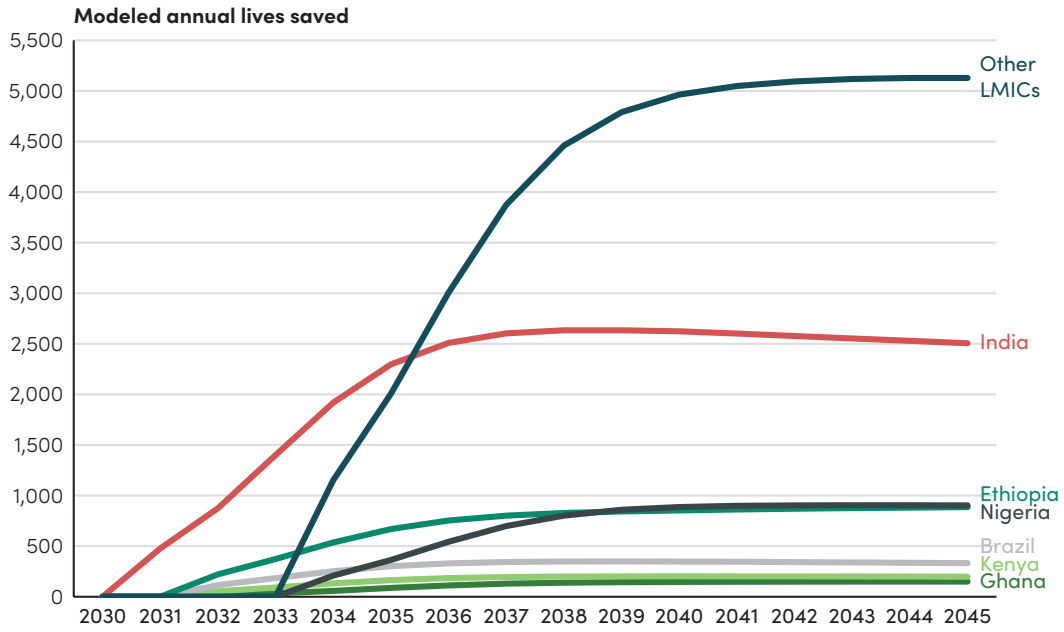
Total costs: The BCR denominator

The denominator is the present value of all funds committed to the facility, discounted at a social discount rate of 2%. We use total committed budget rather than expected expenditure, because the probability that funds are spent is already mirrored in the numerator, as the same success events drive both.

One asymmetry is worth noting: the 65% launch probability applies symmetrically to the milestone payment and milestone-linked benefits, but the AMC carries additional

ii Note that this is 5 percentage points below the 70% target success probability used to size the facility. We adopt the lower figure to err on the side of conservatism; raising it to 70% would raise the probability that committed funds are deployed against realized benefits, increasing the BCR.

FIGURE H.1 Modeled lives saved per geography over a 15 year time horizon, based on estimated demand for tests and estimated per-test mortality reduction



commercialization risk, which lowers the probability of the AMC being paid out relative to the milestone. Despite this difference, we treat the probability of spending the AMC the same way we treat the milestone, which makes the ratio more conservative (as it increases the costs).

The BCR calculation

We calculate the BCR as follows:

$$\frac{(1-P(S))(1-P(C))\cdot d\cdot(Ms+Amc)+P(S)P(1-C)\cdot d\cdot(Amc)+P(S)P(C)\cdot Benefits}{PV\,of(Amc+Ms)},$$

where $P(S)$ is the probability of a successful product launch; $P(C)$ the probability of successful commercialization; d the opportunity cost of tying funds held in escrow; Ms the cost of the milestone; Amc the cost of the AMC; and $Benefits$ the total benefits of the test.

The numerator is a probability-weighted sum across three states of the world:

1. **No launch:** Both the milestone and the AMC return to the funder, adjusted for the time value of money held in escrow.
2. **Product launch, but no commercialization:** The milestone is disbursed, but the AMC is returned to the funder, adjusted for the time value of money.
3. **Full success:** Both the milestone and AMC are paid out.

The denominator is the present value of the committed facility.

Risk adjustments

The risk adjustments—launch probability (65%), commercialization probability (50%–72%), market penetration probability (15%–40%)—affect the BCR in the following ways:

1. **The launch probability is essentially neutral to these risk adjustments, because it scales both the numerator and denominator.** Its effect runs entirely through how much a funder cares about committing capital ahead of a payout that may not occur. If a funder places no cost on having funds committed to a future contingency, the launch probability has no effect on the BCR. If tying up capital in the milestone or AMC carries a meaningful opportunity cost, a lower launch probability—a higher chance that funds are never deployed—reduces the BCR; the more heavily the funder weights that opportunity cost, the larger the reduction.

TABLE H.1 Benefit–cost ratio of selected valuations of disability-adjusted life years

VALUATION OF DISABILITY-ADJUSTED LIFE YEAR (DALY)	BENEFIT–COST RATIO
GDP per capita	78
$100,000 per DALY	2,025
Coefficient Giving (CG) Units ($100,000 per DALY + health-system savings valued in $CG)[a]	2,087

Note: [a]For an explanation of how Coefficient Giving yields cost-effectiveness estimates, https://coefficientgiving.org/research/cost-effectiveness/#2-how-this-works-in-practice.

TABLE H.2 Comparison of NeoTest and counterfactual scenarios

FEATURE	NEOTEST SCENARIO	COUNTERFACTUAL SCENARIO	EFFECT
Launch timing	India 2031, other priority markets 2032, later entrants 2034	Each launch delayed by seven years	Pushes entire adoption curve later, so fewer test-years fall within the 2045 window
Speed of diffusion	Time to 50% peak penetration as calibrated (2–3.5 years by tier)	Time to 50% peak doubled; curve steepness held constant	Flattens the ramp, so penetration accumulates more slowly toward the same eventual peak
Commercialization	Country-specific success probabilities (50%–72%)	Probabilities scaled down by a factor of 0.8	Fewer markets successfully take up the test, lowering realized volumes

2. **The commercialization and market penetration probabilities affect the BCR,** because they act on benefits that accrue only after the milestone has been paid. A test can clear regulatory approval and trigger the milestone yet still fail to commercialize in a given market. The higher the commercialization risk, the more often the milestone is disbursed without the accompanying health benefits that successful uptake would deliver.
3. **The AMC is essentially neutral to these risk adjustments,** because its costs and benefits move one-for-one: it pays out only on verified sales, and those sales are what generate the health benefits. A test that never commercializes triggers no AMC outlay and no AMC–linked benefit. As with the launch probability, the AMC affects the BCR only to the extent a funder cares about its capital being committed to the facility in the interim.

Cost per DALY

We report cost per DALY separately from the BCR. Under conservative assumptions, the facility costs approximately $39 per DALY averted, excluding health-system cost savings. Including those savings, it saves roughly $91 per DALY averted. These figures include the co-payment, as the HTA's cost figures net out the test price.

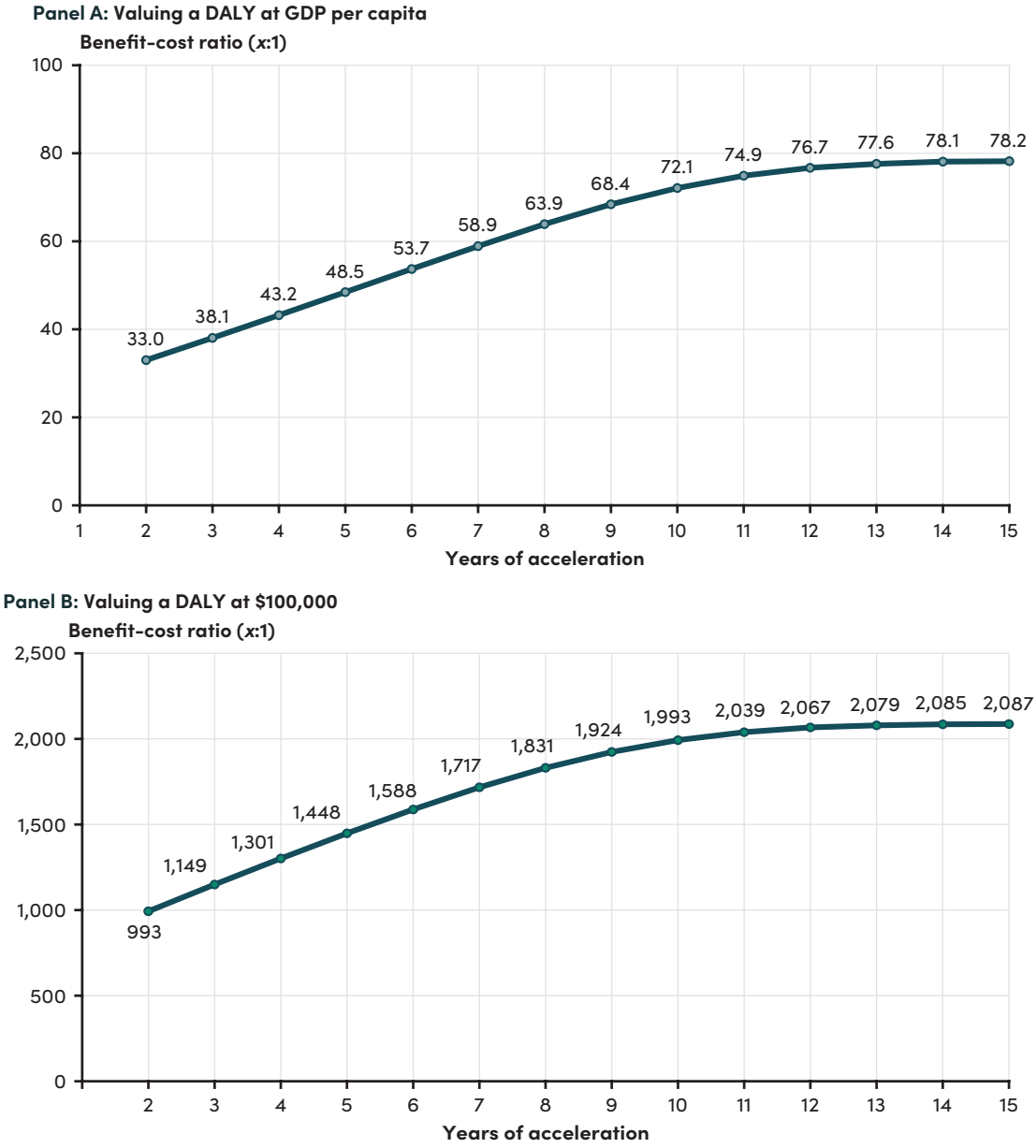
The cost per DALY depends on assumptions. We anchor the central estimate to the most conservative convention—valuing a DALY at GDP per capita—and report alternatives based on the monetary value aligned to a DALY saved (Table H.1).

The central BCR treats NeoTest as the difference between the BCR given the existence of a test and the BCR in the absence of a test, in effect crediting the facility with the full 15 years of benefits that it models. Given the severity of the market failures, we deem this a defensible assumption.

We also model scenarios, in which a test would have entered the market without NeoTest (our counterfactual) and subtract this counterfactual from the benefits we attribute to NeoTest. These scenarios assume that the only function of NeoTest is to accelerate the adoption and roll-out of a product that would have emerged eventually.

We model a world in which a qualifying test is developed without NeoTest but arrives later, diffuses more slowly,

FIGURE H.2 Benefit–cost ratio under different assumptions about the launch year



and commercializes less reliably (Table H.2). We hold constant the benefit per test, the DALY valuations, the discount rate, and the 2045 benefit cut-off across the two scenarios, altering only the adoption trajectory. The facility's marginal value is then the difference between the two benefit streams (the world with NeoTest and the world that would have existed without it).

Peak penetration is left unchanged, so the counterfactual eventually reaches the same long-run equilibrium; the facility's value comes from getting there sooner and with greater certainty, not from a higher steady-state patient population. Under these assumptions, the BCR becomes 58.9 (using the per capita GDP valuation), and the cost per DALY rises to $47.69. Even on this more conservative basis the facility remains highly cost-effective.

Assuming different changes in launch timing but holding the other two parameters constant changes the BCR valuation (Figure H.2).