Use Cases

Sepsis Diagnostic –
Infection Prevention and Control

1ST EDITION, MARCH 2020
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Acknowledgements
This report was prepared by Rebecca Kirby and Kara Palamountain from Northwestern University with input from UNICEF, Dr. Naomi Spotswood from the Burnet Institute, and Dr. David Goldfarb from the University of British Columbia, and other stakeholders. The document summarizes consensus achieved at a meeting on target product profiles and uses cases for newborn care in low-resource settings, convened by NEST360°. This document was finalized following consideration of all comments and suggestions made by meeting participants at the Consensus Meeting.

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Note to the reader
Because of the richness of the discussion, and in an attempt to keep this report simple and readable, this report aims to convey the themes addressed in each session, rather than attempting to provide a chronological summary of the dialogue.

Disclaimer: The Use Cases do not replace or supersede any existing UNICEF Use Cases. The Use Cases do not constitute tender specifications, nor is UNICEF bound to tender or procure products that arise as a result of these Use Cases. UNICEF may require regulatory approval and proof of compliance to quality management and product-specific international standards for tendering purposes.
INTRODUCTION

Access to diagnostic laboratories remains a key challenge in low-resource settings [1]. Point-of-care diagnostic tests can therefore enable health-care workers to provide more rapid and effective care [2]. Simple, rapid, and affordable point-of-care tests which require minimal or no electricity, a laboratory, or highly trained staff, are now available and widely used for several common conditions in low- and middle-income countries (LMICs) [3]. These point-of-care tests offer an unprecedented opportunity to reduce inequalities in health, and to help LMICs achieve the health-related Sustainable Development Goals (SDGs) [4,5].

Neonatal sepsis is a major cause of newborn mortality and must be identified and treated quickly to ensure survival and minimize morbidity. However, it is not easy to diagnose. Due to the immaturity of a neonatal immune systems, natural history of late deterioration, and high morbidity in the presence of a serious bacterial infection, the standard of care in neonates is to treat while simultaneously screening for sepsis with blood, urine, and spinal fluid cultures and microscopy until studies suggest that infection is unlikely to be present. There are some useful guidelines that help to identify neonates and young infants at risk of sepsis and guide clinical management. However, even when these guidelines are used, many more babies receive antibiotics than those who truly have serious bacterial infections and need antibiotics [6].

DEVELOPING A USE CASE

Overview

The process of developing a TPP for a point-of-care test (POCT) for neonatal possible serious bacterial presented distinct challenges. This is largely because point-of-care testing for neonatal infections is not a currently used diagnostic strategy in clinical practice, in both low-, middle-, and high-income settings. There is thus no similar technology routinely used from which the basics of development considerations and implementation measures can be used as learning points for target product profile development specific for wider use across other settings.

To begin the process of developing a TPP, we worked in partnership with Dr. Naomi Spotswood at the Burnet Institute and Dr. David Goldfarb from the University of British Columbia to develop Use Cases for potential Sepsis Diagnostics. In the first stage, six potential use cases were developed to describe the more likely clinical scenarios where a POCT for neonatal possible serious infections might be used.
Use Case Survey

Researchers around the world are trying to develop a point-of-care test for sepsis. This is a test that can be done by any healthcare worker with a quick result. However, a point-of-care test for sepsis could be used in a number of ways, and it is important that researchers know which way (a ‘Use Case’) will be most helpful to healthcare workers. The following six ‘Use Cases’ were presented in a survey. The purpose of the survey was to evaluate which of these ‘Use Cases’ would be of most practical benefit to clinicians who manage neonates with possible serious bacterial infections. The aim is that a test like this would be used in combination with existing guidelines provided by the World Health Organization [27].

**Use Case 1. Start Antibiotics - Community Referral:** A test that can be used when a baby first comes to a health facility from the community for assessment, and has one or more signs of possible serious bacterial infection. Examples of these include respiratory rate >60 breaths per minute, being unable to breastfeed, or deep jaundice. The test is to help the healthcare worker decide if they should start antibiotics. If the test is positive, this means that the baby is likely to have a serious bacterial infection. The baby needs antibiotics and supportive care. If a blood culture can be sent, this should be collected before the antibiotics are started. If the test is negative, this means the baby is highly unlikely to have a serious bacterial infection. Instead they need careful observation, and the healthcare worker should consider other reasons for their illness.

**Use Case 2. Start Antibiotics - Well Baby with Risk Factors at Birth:** A test that can be used when an otherwise well baby has been born with risk factors for sepsis. Examples of these risk factors are fever in the mother during labour, prolonged rupture of the membranes (>18 hours), or foul-smelling amniotic fluid. Other non-maternal risk factors might include preterm labour. The test is to help the healthcare worker decide if they should start antibiotics. If the test is positive, this means that the baby is likely to have a serious bacterial infection. The baby needs antibiotics and supportive care. If a blood culture can be sent, this should be collected before the antibiotics are started. If the test is negative, this means the baby is highly unlikely to have a serious bacterial infection. Instead they would stay with mother and receive normal newborn care.

**Use Case 3. Start Antibiotics - Unwell at Birth:** A test that can be used when a baby has been born with signs of sepsis with or without maternal risk factors. Signs of sepsis include tachypnea, temperature instability, or tachycardia. The test is to help the healthcare worker decide if they should start antibiotics. If the test is positive, this means the baby is likely to have a serious bacterial infection. The baby needs antibiotics and supportive care. If a blood culture can be sent, the sample should be collected before the antibiotics are started.

If the test is negative, this means the baby is highly unlikely to have a serious bacterial infection. If the baby remains unwell, they need careful observation, and the healthcare worker should consider other reasons for their illness.

**Use Case 4. Start Antibiotics - Small or Premature Baby who becomes Unwell:** A test that can be used for a baby who is already admitted to a health facility because they are small or premature who becomes unwell and has one or more signs of a possible serious bacterial infection. The test is to help the healthcare worker decide if they should start antibiotics. If the test is positive, this means that the baby is likely to have a serious bacterial infection. The baby needs antibiotics and supportive care. If a blood culture can be sent, this
should be collected before the antibiotics are started. If the test is negative, this means the baby is highly unlikely to have a serious bacterial infection. Instead they need careful observation, and the healthcare worker should consider other reasons for their illness.

**Use Case 5. Stop Antibiotics:** A test that can be used for a baby who is already admitted to a health facility and who has already received at least one day of antibiotics for a possible serious bacterial infection. The test is to help the healthcare worker decide if the antibiotics can stop. If the test is positive this means that the baby is likely to have a serious bacterial infection. The baby needs to continue their antibiotics. If there are positive blood or cerebrospinal fluid culture results, the antibiotics may need to change to make sure they are the best antibiotic to treat the infection that has been identified. If the test is negative, this means that the baby is highly unlikely to have a serious bacterial infection. The antibiotics can stop. If the baby is still unwell, the healthcare worker should consider other reasons for their illness.

**Use Case 6. Resistance:** A test that can be used for a baby who is already admitted to a district health facility, has already commenced antibiotics, and remains unwell. The test is to tell the healthcare worker if the baby has an infection resistant to first line (the usual) antibiotics. If the test is positive this means the baby is highly likely to have a serious bacterial infection which is resistant to the first line antibiotics which are usually started. The baby needs a different antibiotic. The test may provide some information which guides the choice of this antibiotic. If the test is negative, this means that either the baby does not have a serious bacterial infection, or that the infection is being appropriately treated by the first line antibiotics which are usually started.

A survey with the six use cases was completed by 33 respondents (see Figures 1 and 2). Respondents were asked questions to prioritize and rank the use cases (see Figure 3). Based on the results presented below, use case 1 and 5 received the highest score despite a wide range (see Table 1 and 2).

**Figure 1: Summary of organizational affiliation for Sepsis Diagnostic from Use Case Survey prior to Consensus Meeting (data as of Oct 25, 2019)**
Figure 2: Summary of response rate by country for Sepsis Diagnostic from Use Case Survey prior to Consensus Meeting (data as of Oct 25, 2019)

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi (7)</td>
<td>21%</td>
</tr>
<tr>
<td>Canada (6)</td>
<td>18%</td>
</tr>
<tr>
<td>USA (5)</td>
<td>15%</td>
</tr>
<tr>
<td>Australia (4)</td>
<td>12%</td>
</tr>
<tr>
<td>Kenya (2)</td>
<td>6%</td>
</tr>
<tr>
<td>UK (2)</td>
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</tr>
<tr>
<td>Botswana (1)</td>
<td>3%</td>
</tr>
<tr>
<td>Ethiopia (1)</td>
<td>3%</td>
</tr>
<tr>
<td>Ghana (1)</td>
<td>3%</td>
</tr>
<tr>
<td>Rwanda (1)</td>
<td>3%</td>
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<tr>
<td>South Africa (1)</td>
<td>3%</td>
</tr>
<tr>
<td>Tanzania (1)</td>
<td>3%</td>
</tr>
<tr>
<td>Uganda (1)</td>
<td>3%</td>
</tr>
</tbody>
</table>

Figure 3: Screenshot of Survey Questions

Q14.2 Question 1: Based upon the Use Case descriptions provided above, please prioritize Use Case 1-6. (drag the indicator to the priority score for each of the 6 Use Cases)

<table>
<thead>
<tr>
<th>Use Case</th>
<th>Low Priority</th>
<th>Medium Priority</th>
<th>High Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use Case 1. Start Antibiotics - Community Referral ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Use Case 2. Start Antibiotics - Well Baby with Risk Factors at Birth ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Use Case 3. Start Antibiotics - Unwell at Birth ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Use Case 4. Start Antibiotics - Small or Premature Baby who becomes Unwell ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Use Case 5. Stop Antibiotics ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Use Case 6: Resistance ()</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
</tbody>
</table>

Q14.3 Question 2: Based upon the Use Case descriptions provided above, Rank Use Case 1-6. (drag the 6 Use Cases below into the appropriate order of rank - 1 being the highest rank, 6 being the lowest rank)

_____ Use Case 1. Start Antibiotics - Community Referral (1)
_____ Use Case 2. Start Antibiotics - Well Baby with Risk Factors at Birth (2)
_____ Use Case 3. Start Antibiotics - Unwell at Birth (3)
_____ Use Case 4. Start Antibiotics - Small or Premature Baby who becomes Unwell (4)
_____ Use Case 5. Stop Antibiotics (5)
_____ Use Case 6: Resistance (6)
### Table 1: Initial Use Case Survey

<table>
<thead>
<tr>
<th>Use Case</th>
<th>Prioritization Score</th>
<th>Rank Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Use Case 1. Start Antibiotics - Community Referral</td>
<td>77.97</td>
<td>(10 - 100)</td>
</tr>
<tr>
<td>Use Case 2. Start Antibiotics - Well Baby with Risk Factors at Birth</td>
<td>69.35</td>
<td>(4 - 100)</td>
</tr>
<tr>
<td>Use Case 3. Start Antibiotics - Unwell at Birth</td>
<td>60.69</td>
<td>(10 - 100)</td>
</tr>
<tr>
<td>Use Case 4. Start Antibiotics - Small or Premature Baby who becomes Unwell</td>
<td>72.72</td>
<td>(15 - 100)</td>
</tr>
<tr>
<td>Use Case 5. Stop Antibiotics</td>
<td>77.26</td>
<td>(22 - 100)</td>
</tr>
<tr>
<td>Use Case 6: Resistance</td>
<td>75.66</td>
<td>(19 - 100)</td>
</tr>
</tbody>
</table>

1 Prioritization takes the average weight assigned to each use case based on the sliding scale. Note that the respondent could assign every use case at the maximum 100 (i.e., no force rank or sum total).

2 Rank takes the average of each assigned rank by use case per submission.
Table 2: Initial Use Case Survey – Detailed Results

<table>
<thead>
<tr>
<th>Use Case 1</th>
<th>Use Case 2</th>
<th>Use Case 3</th>
<th>Use Case 4</th>
<th>Use Case 5</th>
<th>Use Case 6</th>
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<td>60</td>
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Survey respondents were asked whether there are any other Use Cases or situations where a point-of-care test could help healthcare workers to manage young infants with possible serious bacterial infections. The following comments were received:

1. "Standards around neonates is that the majority of the time we are treating when infection is highly improbable. Hard to imagine something that can replace cultures"
2. "Use Case 3 + would ideally say which antibiotic to start; Use Case 6 should tell you which bacteria is resistant; all of these tests would depend on sensitivity or specificity"
3. "A) Umbilical cord dx - I believe this is often discarded but several studies have studied biomarkers in cord blood and seen promising results. B) I’m not sure how realistic this would be, but a diagnostic for resistance at the time of diagnosis of sepsis could help guide treatment in one visit. I know the mortality rate of neonatal sepsis is very high, and I wonder if that means that use cases 1-4 should be prioritized over use case 5/6. In my mind, a baby who is unwell (use cases 3/4) will be started on antibiotics anyways so I had those at a lower priority, but of course there are issues of resistance and misdiagnosis there too. I believe a large burden of neonatal mortality occurs soon after birth, which was my justification for putting use case 2 at the highest priority"
4. "If the test is low-cost and simple to use by community health workers, then it could be used during community outreach activities to identify a patient at the community level and refer to the nearest health facility for Abx initiation. This is similar to case #1, but starts from the community level for early identification at community/household level -> referral -> and early/immediate initiation."
5. "A baby who had other problems at admission and becomes unwell after admission (diagnosing hospital-acquired sepsis)"
6. "Treatment response: a use case that enables clinicians to non-clinically monitor response to treatment for diagnosed septic neonates. This use case could herald possible antibiotic resistance and rationalize / prioritize blood culture usage"
7. "Test to guide other intervention (e.g. supporting, referral to a higher level center)"
8. "Surgical patients those who have gone through major operations and some patients with Gastrochisis, open spina bifida. Many of these later develop signs and symptoms of sepsis. Some babies are delivered at home under unsterile procedure. Need proper tests to guide on use of antibiotics"
9. "Hospitalized premature infant with respiratory worsening (increase in ventilation or oxygenation needs)"
10. "If there are signs of infection healthcare workers will start antibiotics - hence less useful. However a more pertinent question would be what antibiotics to start - if the diagnostics could identify the bacteria that would be extremely helpful in all cases"
Consensus Meeting

On November 20 - 22, 2019 over 69 stakeholders gathered in Stellenbosch, South Africa to focus on building further consensus on the Use Cases for a Sepsis Diagnostic. The results of the Use Case survey were shared and discussed.

Consensus Meeting Summary: Sepsis Diagnostic

It was clear in the time available for group discussion at the Consensus meeting that further analysis and consultation will be required to formulate a TPP, particularly to delineate the practicality and clinical impact of each Use Case. Give this, a data-based analysis of potential use cases and further survey process are planned.

Developing a Target Product Profile for a Neonatal Sepsis Point-of-Care Test: Next Steps

Initial discussion in the Consensus Meeting focussed on whether the first four use cases (starting antimicrobials) could be condensed into one use case. While collapsing use cases one to four into a single use case may be simpler conceptually, it was noted that each use case would have different microbiology, immunology and epidemiology, each of which will affect the pre-test probability of infection in the target population. Further, clinical thresholds for starting antimicrobials for the same use case may differ between settings. Overall it was agreed that reducing unnecessary antimicrobial use would be a key attribute of a neonatal sepsis POCT.

Moving forward, relevant questions are below. Each would ideally be estimated for the setting of interest. 1(c) and 2(c) require pre-defined target sensitivity and specificity:

1. For the first four use cases:
   a. How frequently are neonates evaluated for possible serious bacterial infections?
   b. What is the frequency of confirmed serious bacterial infection?
   c. Based on 1(a) and 1(b), how many antimicrobial courses could be avoided with use of a POCT?
2. For use case five:
   a. How frequently do hospitalised neonates receive antimicrobials?
   b. Amongst these neonates, what is the frequency of confirmed serious bacterial infection?
   c. Based on 2(a) and 2(b), how much excess antimicrobial exposure could be avoided with use of a POCT?
3. For each of use cases one to five, what is the frequency of confirmed infection with a pathogen resistant to first line antimicrobials?

The next steps for the Sepsis Diagnostic TPP are to:

- Conduct an analysis of currently available data to provide estimates for the above questions. This will allow clearer evaluation of the potential clinical impact of a POCT for each use case.
- Formulate and distribute an extended survey to finalise the TPP for a neonatal sepsis POCT. This is planned to reach beyond the original group: the WHO possible Serious Bacterial Infections
Community of Practice group and Medicins Sans Frontiers have been identified as examples of groups to contact given their practical knowledge and experience relevant to this process.

- Given the wide relevance of a TPP for a neonatal sepsis point-of-care test, the group will consider publication of the TPP development process and final results in a peer reviewed journal.
REFERENCES


APPENDICES

Appendix A: Consensus Meeting Participation

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Bentry Tembo (Kamuzu Central Hospital)
Bev Bradley (UNICEF)
Casey Trubo (D-Rev)
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Emmie Mbale (PACHA)
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Guy Dumont (The University of British Columbia)
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Ronald Mbwasi (Kilimanjaro Christian Medical Centre)
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Sara Liaghati-Mobarhan (Rice University)
Sona Shah (Neopenda)
Steffen Reschwamm (MTTS)
Steve Adudans (CPHD/MQG)
Thabiso Mogotsi (University of Botswana)
Walter Karlen (ETH Zurich)
Zelalem Demeke (Clinton Health Access Initiative)
Appendix B: Abbreviations

°C  Degrees Celsius
bCPAP  Bubble continuous positive airway pressure
bpm  Beats per minute / Breaths per minute
CE Mark  Conformité Européenne – certification mark
cm  Centimeters
cm²  Centimeter squared
CRP  C-reactive protein
CPAP  Continuous positive airway pressure
DHS  Demographic and health survey
FDA  Food and Drug Administration
HIS  Health information system
Hz  Hertz
IMR  Infant mortality rate
ISO  International Standards Organization
IV  Intravenous
KMC  Kangaroo Mother Care
kg  Kilogram
LPM  Liters per minute
LRS  Low-resource settings
MCH  Maternal and child health
MDG  Millennium Development Goal
Mg/dL  Milligrams per deciliter
mL/hr  Milliliters per hour
mmol/L  Millimoles per liter
µmol/L  Micromoles per liter
MMR  Maternal mortality rate
MNCH  Maternal, newborn, and child health
MNH  Maternal and neonatal health
nm  Nanometer
NMR  Neonatal mortality rate
PCT  Procalcitonin
PEEP  Positive end-expiratory pressure
PR  Pulse rate
RDS  Respiratory distress syndrome
ROP  Retinopathy of prematurity
SpO2  Peripheral saturation of oxygen
SDG  Sustainable Development Goal
TFR  Total fertility rate
U5MR  Under-5 mortality rate
UNFPA  United Nations Population Fund
USAID  U.S. Agency for International Development
uW  Micro Watts
W  Watt
WHO  World Health Organization