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ICH Guidelines on Thalassemia 2025

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CHAPTER

Community Level Screening/Confirmation; Relevant for National Program

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INTRODUCTION

Screening/diagnosis of thalassemia and other hemoglobinopathies at community level is the most challenging one and a need for a different approach in comparison to institutional level. The methodology should be technically correct, practical and sustainable etc. No single strategy can meet the needs of every population. Selection of target population and timing of screening are important determinants for prevention and control strategies as they determine the technical options available for prevention and control, guide community education and counseling needs. Every state can choose the methodology at community level depending on the need and prevailing situation. Screening for early detection of beta-thalassemia (TDT and NTDT) to achieve reduction in mortality and morbidity with improvement in the quality of life of the affected, whereas screening for detection of carrier beta-thalassemia traits to reduce the birth of children affected with thalassemia.

Universal screening for thalassemia major/minor should be done for children (6 months to 6 years). Mass anemia screening will be helpful in identification of thalassemia. Hemoglobin estimation with complete CBC if available/workable could facilitate early diagnosis of thalassemia.

Community screening (Micro Community) by ASHA workers, CHOs and other field workers for severe anemia along with DBS sample collection for HPLC can be the main strategy for early identification/confirmation. Further thalassemia screening/confirmation at facility level can be done through microchip electrophoresis method. However, any alternative viable confirmatory and workable methodology/technology including HPLC/CZE/could be an option depending on the situation.

Population screening for carriers at community level is the mainstay of prevention programs. The greatest challenge in large scale screening is nonavailability of tests with high sensitivity, sustainability, cost effectiveness and implementability at community level. There is no availability of a single screening test which can capture the common hemoglobinopathies prevalent in India i.e., beta thalassemia, HbS and HbE etc. Red cell indices like MCV, RDW, MCH, though sensitive in capturing beta thalassemia trait in institutional laboratories, have missed at community level in 30% of cases due to various reasons. In addition, these parameters are also not available at village and sub center levels due to non-availability of cell counter and lab technicians.

Other screening tests like NESTROFT (Naked Eye SingleTube Red Cell Osmotic Fragility Test), DCIP (Di-Chlorophenol-Indophenol Test, Sickle Solubility Test (Tube Method) meant for beta thalassemia, HbE and HbS respectively are not recommended

at present in community level due to high false positive/negative results and cumbersome process. However, point of care test for SCD like HemoType SC/Sickle SCAN/ Indian POCTs based on lateral flow immunoassay are effective with high sensitivity and specificity, albeit only screening for sickle cell disease and missing other types of hemoglobinopathies.

NEWER TECHNOLOGY[1-6]

Microchip Electrophoresis

This technology offers next generation integrated cost-effective and rapid point-of-care solution for detecting beta-thalassemia, sickle cell and HbE in single multiplex test. Using a finger-prick or heel-prick blood sample, it separates hemoglobin variants based on charge differences. The process involves applying the blood sample to a cellulose acetate paper strip, which is then placed in a cartridge and run through a reader. The reader separates, images, and monitors the hemoglobin variants in real time. The test showed 100% sensitivity and specificity in distinguishing beta-thalassemia major/ intermedia from both healthy individuals and those with beta-thalassemia trait. It also demonstrated 100% sensitivity and 98.3% specificity in identifying beta-thalassemia trait compared to healthy subjects in Indian settings.[1] The system is affordable, compact, and portable, enabling decentralized testing and rapid point-of-care results in less than 10 minutes, and can be performed by minimally trained personnel. This technology is being widely used in facilities level of PHC and CHC across Odisha state.

A field study in Tamil Nadu demonstrated that the POCT is valid for identifying thalassemia trait, with a sensitivity of 92.59% and a PPV of 84.74%. This technology can be used for community level one step screening plus confirmatory tests. This technology is empowered with AI enabled automatic results interpretation which minimize the dependency on expert person/hematologist at community level. All consumables can be stored at room temperature and it doesn't need any ancillary instrument for its operation. Several research papers published reveal that this technology might be used for screening and confirmatory tests of thalassemia, SCD and HbE (both trait and homozygous).

Microchip base electrophoresis is fully automated, battery operated, GPS enabled and can be connected with cloud data/server for automatic uploading of the results. This might help to minimize manual error and create a clean database for the test performed.

The same platform can be used to do quantitative Ferritin test (FIA test) by using whole blood samples. This facilitates an integrated approach for further treatment management of thalassemia patients.

DBS-HPLC System[7-11]

The use of dried blood spot (DBS) samples for HPLC analysis (DBS-HPLC) offer a practical yet technically advanced and accurate one-step screening and diagnostic tool for all clinically relevant hemoglobinopathies in large-scale population studies, especially in resource-poor remote locations.

Conventional HPLC systems which require whole blood samples by phlebotomy, transport and storage of samples with challenging logistics and environment. On the contrary, DBS-HPLC requires blood collected through capillary puncture from finger, heel or toe prick. Blood is blotted onto special filter paper, air dried for 1–2 hours and shipped to the lab at ambient temperature for testing. DBS collection requires minimal training, quick and easy to collect via a finger prick and only a few drops of blood are enough for analysis. DBS samples also have an advantage of being robust, remaining suitable for analysis for weeks at ambient temperatures, eliminating the need for special transport and logistics.

DBS samples for hemoglobinopathy screening can be collected by existing healthcare workers with proper training and can be integrated with other national screening programs utilizing finger prick capillary blood, like Anemia Control Program Malaria Control program etc., optimizing use of government resources.

DBS-HPLC accurately identifies and quantifies HbF, HbA, HbA2, HbS, HbE and other Hb-variants in a single 4 minutes run with very high reproducibility for all age groups.

DBS-HPLC is highly sensitive and specific, requires minimal blood, is easy to operate, highly automated with high throughput, and is cost effective on a large scale. This makes DBS-HPLC an ideal technology for population screening.

Use of DBS for HPLC for screening and diagnosis of hemoglobinopathies for all age groups, i.e., Newborns to adults have been validated in studies worldwide. Recently ICMR has validated use of DBS for sickle cell and thalassemia for newborns, children and adults showing 99.3% sensitivity and specificity as compared to whole blood HPLC analysis for sickle cell, thalassemia and other variant hemoglobinopathies.[11] NHM has recently approved the use of DBS sample for HPLC and capillary electrophoresis for all age groups wide in letter dated 3rd June 2024.

Utilizing DBS samples with HPLC provides a one-step screening cum diagnostic test, not just for SCA but for all clinically relevant hemoglobinopathies especially in field setting involving door to door sample collection more so in remote and tribal regions.

DBS-HPLC has been successfully used in Bastar, Chhattisgarh one of the remotest regions of India and in currently being used in seven districts of Odisha for population screening covering of all clinically relevant hemoglobinopathies, i.e., sickle cell, thalassemia, HbE, HbD, other variant hemoglobinopathies and compound heterozygous cases.

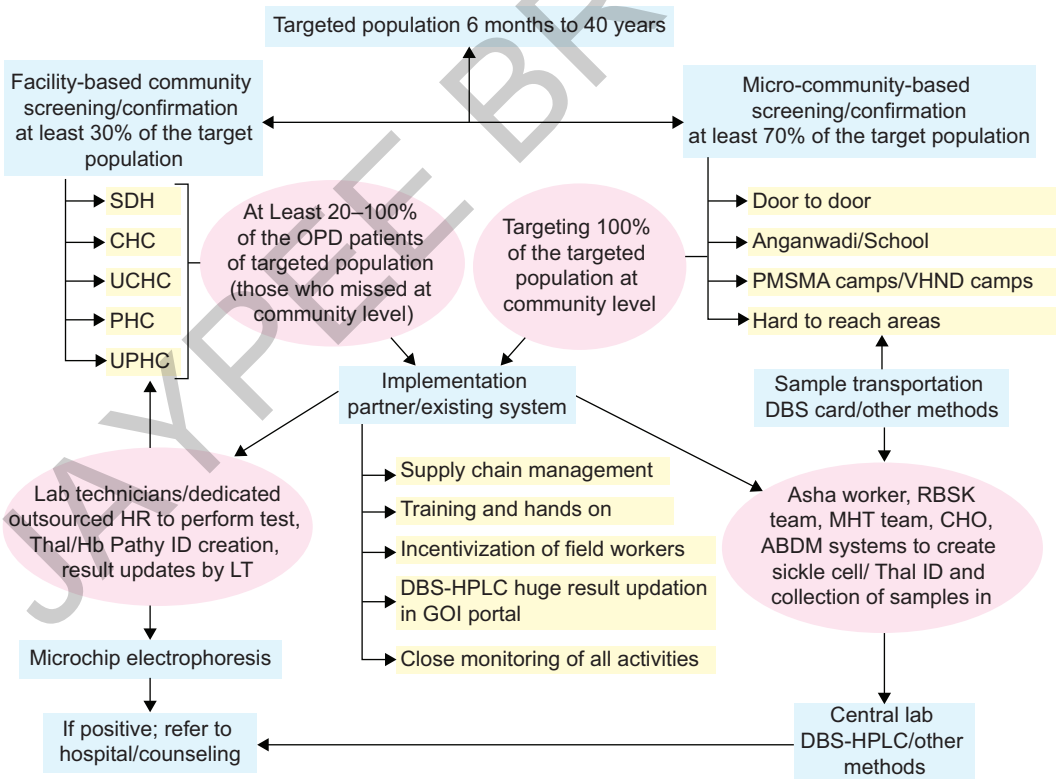
Comprehensive Model of Screening/ Confirmation of Thalassemia and Other Hemoglobinopathies

Beta-thalassemia, HbS and HbE are the major hemoglobinopathies (Hb-pathies) seen in India. It is logical to adopt a method which will capture and confirm all common types of Hb-pathies in one-go for optimal utilization of the resources.

- *Technology used*: **Table 1** summarizes the suggested tests at each healthcare level. **Flowchart 1** shows the stepwise approach for confirmation of thalassemia.
  - *Facility-based community level screening and confirmation*: Facility-based community level screening at institution levels such as PHC, UPHC, CHC, UCHC and SDH to screen and confirm by microchip cartridge-based electrophoresis analyzer (Gazelle Device).
  - *Micro-community based universal /opportunistic screening and confirmation*: At micro-community level DBS-HPLC technology is being used for door to door, school level, at anganwadi center, at PMSMA camps, VHND sessions and also at difficult/ hard to reach areas.
  - *Point of care PCR/other newer technology*: States may consider these options depending on their needs and other factors. However, none of such ideal tests are available to be recommended at present.
- *Adoption of implementation partner (PPP model/existing system)*: Total implementation of the program at community level includes training of the healthcare personnel, counseling, patient's registration, sample collection/ transportation/storage/investigation, interpretation of the results and entry of the data in the government portal. This process has a lot of challenges and barriers in the existing healthcare system

TABLE 1: Suggested screening of POCT/confirmation for each level of healthcare.

Healthcare level	POCT/Confirmation suggested	Infrastructural requirement
AAM-SHC-door to door/universal screening/opportunity screening/ fixed day screening/hard to reach areas (community level)	DBS by HPLC/any other suitable method	Central lab with HPLC/any other suitable equipment
Facilities based community level		
AAM-PHC	Microchip electrophoresis	Lab technician with minimal basic skills
CHC	Microchip electrophoresis	Lab technician with minimal basic skills
SDH	Microchip electrophoresis	Lab technician with minimal basic skills
DH	CZE/HPLC	CZE/HPLC lab technician
Medical College	CZE/HPLC, molecular test	Lab with HPLC, CZE and molecular lab



FLOWCHART 1: Confirmation testing strategy for thalassemia and hemoglobinopathies, highlighting the role of HPLC, CZE, microchip electrophoresis, and molecular mutation testing.

across the country. Each state may adopt PPP mode or existing system for optimal implementation of the program. Government of Odisha has adopted PPP mode for implementation.

Methodology at community level: This programme of screening/confirmation can be done by two ways:

1. *At facilities-based community level*: It includes areas of SDH, CHC, UCHC, PHC, UPHC. It may cover 30% of the target population. The recommended methodology is Microchip Electrophoresis (Gazelle) as depicted in the workflow diagram. However, other newer technologies if found suitable to diagnose beta thalassemia and other Hb Pathies can be considered by the state depending on various factors. Government of Odisha has adopted Microchip based Electrophoresis (Gazelle) at aforesaid facilities across the state.
2. *At micro-community level*: It includes areas; Door to door, Anganwadi/ Schools, PMSMA (Pradhan Mantri Surakhita Matrutwa Abhiyan) Camps/ VHND (Village Heath Nutrition Day) Camps, hard to reach areas. This should achieve 70% of the target population. The recommended methodology may be the DBS-HPLC System. However, states can utilize any competitive alternative option as per their need. The sample collection can be achieved by utilizing the existing healthcare system in the following ways. The laboratory can be centralized for better operability/quality control or at different levels depending on the states need.
    - *Door-to-door universal screening* by ASHA worker/dedicated outsourced HR through sample collection with DBS Technology to test 0–40 years of populations.
    - *Collection of DBS samples through Mobile Health Team (RBSK Team)* is being done at school level and Anganwadi centers.
    - *Fixed day testing*: (i) During PMSMA (Pradhan Mantri Surakhita Matrutwa Abhiyan) Platform for antenatal cases once in a month (9th of each month); (ii) during VHND (Village Health Nutritional Day) session DBS sample of antenatal, postnatal and adolescent cases (if missed during door-to-door campaign) by community health officer and Asha worker twice in a week (Tuesday and Friday).
    - *Hard/difficult to reach areas*: DBS samples are an easy and suitable method and should be collected by the mobile health team.
    - States may adopt alternative suitable methodology as deemed fit after considering all the factors.

Portal Data Entry

- *Facility-based community level*: Patient registration (thalassemia-/Hb-Pathy ID creation) and updating of results in government portal by concern lab technician/trained HR of the facilities (Training has been imparted through Virtual and Physical mode)
- *Microcommunity level*: For Micro-Community level registration (Thal/Hb Pathy ID creation) and updating of results in GOI portal by ASHA workers/trained LTs at Universal screening. Community health officer, RBSK team, Health worker (Female), mobile health team at school, Anganwadi center, PMSMA Camp, VHND session hard/difficult to reach village being done through proper training by Virtual and physical mode.

Supply Chain Management

Implementing a partner/existing system supplies the DBS kits to the District HQ. The district in term supplies the same to CHC HQ.

Health worker (Female) concern, collects the same from the CHC HQ on monthly meeting days. The health worker (Female) distributes the same to selected literate AHAS's who were having android mobile phone for Thal/Hb-Pathy ID creation through Hb-Pathy portal mobile application.

MHU and MHT also collect the DBS kit from CHC HQ and utilize the same for the eligible population. Same distribution Channel is being used to return the DBS sample collected to distribution point (CHC HQ), thereon the implementing partner/existing system collect the DBS sample from the CHC HQ and transport the same to central HPLC lab. The DBS HPLC result of the test entered into the GOI Sickle Cell Portal by the implementing partner/existing system.

Incentives

The fieldworker is being incentivized for portal entry and ID creation @ Rupees five. For transportation of the kit from field to collection point (CHC, SDH, DHS) @Rupees Ten is being given to the AVDM/Non-Android user ASHA's/Health Worker/Community Health Officer. However, the states can modify incentivization as deemed fit.

Confirmation testing: It is preferable to confirm by two alternative confirmatory tests like HPLC/CZE/microchip electrophoresis/molecular mutation testing/any other suitable test whenever required.

- Mutation testing may be needed to confirm the diagnosis if the patient is transfused and both parents are unavailable or if a difficult case for diagnosis. Mutation testing may be required if prenatal testing is being offered.

CONCLUSION

Community-level screening and diagnosis of thalassemia and hemoglobinopathies require a tiered, context-specific approach for effective implementation. Facility-based microchip electrophoresis (e.g., Gazelle device) and micro-community–based DBS-HPLC systems have proven practical, scalable, and effective in the Indian setting. Integration with existing national screening programs and digital data management portals ensures sustainability, while adoption of PPP models can aid in overcoming infrastructure gaps. Confirmatory testing with at least two standardized modalities, including molecular testing when indicated, ensures diagnostic accuracy. Together, these strategies pave the way for large-scale thalassemia control and effective prevention programs across diverse community settings.

SUMMARY

- Community-level screening for thalassemia and hemoglobinopathies requires context-specific, technically accurate, practical, and sustainable strategies tailored to local conditions.
- Universal screening for thalassemia major/minor should target children aged 6 months to 6 years, integrating anemia screening and early diagnosis.
- Facility-based screening leverages microchip electrophoresis (Gazelle device) for rapid, point-of-care detection of β-thalassemia, HbS, and HbE with high sensitivity and specificity.
- Micro-community–level screening employs DBS-HPLC technology, enabling door-to-door, school, anganwadi, and camp-based outreach, particularly in hard-to-reach areas.
- Microchip electrophoresis offers portability, automation, cloud data connectivity, and AI-enabled interpretation, reducing dependency on specialist personnel.

- DBS-HPLC allows robust, ambient-temperature sample storage and transportation, integrating seamlessly with other national health programs, and achieves high diagnostic accuracy for multiple hemoglobinopathies.
- Confirmatory diagnosis should use at least two modalities, with molecular testing reserved for complex cases, transfused patients, or prenatal diagnostic contexts.
- Effective program implementation depends on trained personnel, incentivized field workers, streamlined supply chain management, portal-based patient registration, and the PPP model for bridging infrastructure gaps.

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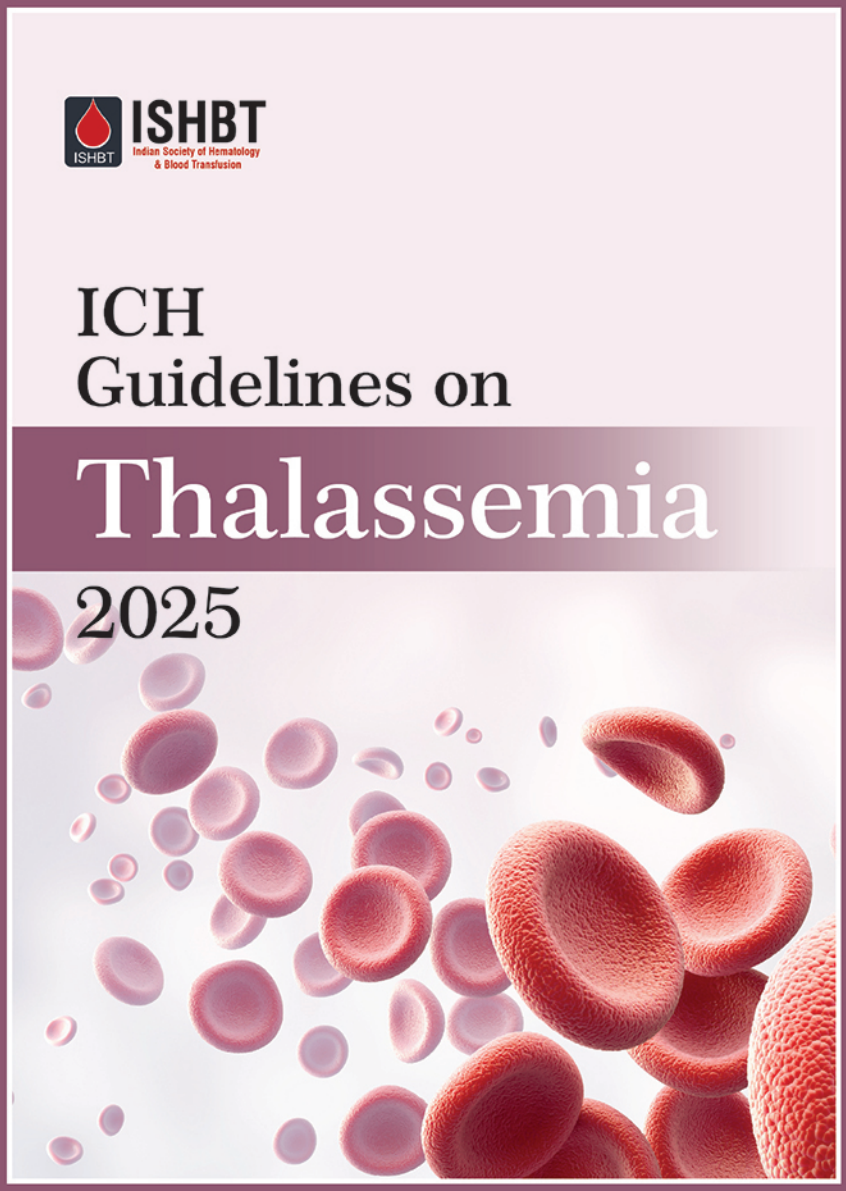

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