Human Biology Review (ISSN 2277 4424) 12(1) 2023
Human Biology Review
Brief Report (Singh et al. pp. 13-21)
www.humanbiologyjournal.com
Accepted on December 1, 2022

Highly stratified population sickle cell frequencies and prevention in India

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Citation: Singh RK, Alur S, Jain S and Rao VR. 2023. Highly stratified population sickle cell frequencies and prevention in India. Human Biology Review, 12 (1), 13-21.

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ABSTRACT

Sickle cell (HBS) is a blood genetic disorder with morbidity and mortality affecting large number of tribal population. Universal screening programs are still cost intensive. The present short communication is an attempt to provide an anthropological method for estimating HBS spread and identifying hot spot regions in Indian population to aid prevention.

The Indian population is largely structured into four broad geographical-linguistic (GL) administrative categories, states. Each GL further divided into eco-cultural zones (ECZ), comprising 3-5 districts within state. Further, each ECZ comprise local hierarchical ethno-linguistic-clusters (ELCs). Tribes occupy lowest ELC substratum followed by lower, middle and higher castes. Sickle cell is confined to tribal ELCs of Dravidian GL. Within the geographical areas of these tribal ELCs, HBS gene flow to other caste GLCs is evidenced, inferring historical and socio-cultural processes underlying the highly stratified HBS population frequencies. We attempt to evaluate these processes, based on anthropological literature, to interpolate published HBS population frequencies. THREE high risk tribal ELC foci corresponding to sickle cell spread in 31 districts as core ECZs are identified. Further, 98 districts are considered as extensions of core ECZs providing a contour of sickle cell spread in India. Disease burden for total HBS spread,129 districts estimated population in 2020, stands at around 3 lakh sickle cell anemia (SCA) homozygote sufferers with an increment of around 4-5000 births per annum. We map the HBS spread to the district level with estimates of disease burden to aid prioritization of public health efforts in these areas.

Key Words: *Sickle Cell. Hot spot regions. India.*

Decrease in child mortality all over the world witnessed increase in relative numbers of sufferers with genetic disorders. Survival of SCA children mark highly heterogeneous epidemiological transition. Granularity of local historical, environmental and cultural factors weigh heavily on effectiveness of prevention programs. Relevant options include premarital screening, education, awareness and management of children from birth. Universal newborn screening programs are still economically not viable in India. Highly stratified HBS frequencies provide an opportunity for long-term sustainability and feasibility of such newborn screening. This short communication is a contribution, supported by historical, anthropological and epidemiological data in identifying THREE high risk regions of ethno-linguistic-clusters (ELCs) for prevention.

We have included 192 tribal population studies for HBS distribution with sample size (n)=>50 with local ethnic group subpopulation identification that comprised data published during 1950 to 2000, including extensive screening by the Anthropological Survey of India (1960-1965) (Negi,1972). Large number of these population studies were done by reduction test and cannot distinguish homozygotes. For the purposes of the present study, these data sets are useful in terms of prevalence of HBS in a particular subpopulation. Besides, wherever same subpopulation sampled multiple times from same region (ex. Pradhan) frequencies were in range validated by electrophoresis/ HPLC.

Tribes (7.8%) of total Indian population comprise ELCs of broad linguistic category Dravidian GL, as source subpopulations for HBS. Diagrammatic representation of Indian population structure and distribution of HBS, other hemoglobin variants and G6PD deficiency distribution is depicted in figure 1. HBS largely confined to Dravidian GL is shown along with its spread to caste cluster. Highly stratified HBS frequencies within an ELC explained more by historical-social processes theorizing that the '*formation of local endogamous subpopulations not due to fission but lack of fusion'* (Karve 1978). Indian population ancient genomic substratum dates back to >50 years (Reich et al. 2009) creating a flux of gene pools, later ordained by highly structured hierarchal caste system imposed by Manu around 400 years back (Encyclopedia Britannica 2015), resulting in tribe-caste continuum (Sinha1965). HBS spread to caste populations is reported by several micro-profiling studies (Kar et al. 1986; Patra et al. 2015) and extensive review (Rao 1998). Further, genetic and clinical findings confirm severe SCA disease in castes due to lack of α-thalassemia co-existence unlike tribes (Mukherjee et al. 1997). Taken together, it is imperative that programs addressing control of SCA targeting only tribes holds the peril of failure. To understand spread, in the context of Indian population structure, the concept of eco-cultural- zones (ECZs) is relevant, defined as 'contiguous geographic area within which most societies share many traits in common and were not coincident with divisions of linguistic categories' (Singh, 1996). The distribution of HBS among Dravidian tribes show THREE FOCI (HBS >30%): ELCs i.e. PANIYAN-IRULA, GOND and BHIL southern, central and western regions of India (Figure 2). These correspond to core and extended ECZs areas spread to 20 States and 1 Union territory comprising 129 districts (Figure 3, Table 1), which can be taken as the extent of spread of HBS to all segments of population in these regions. Disease burden (SCA, homozygotes) for 129 districts HBS spread estimated for 2020 population is 4-5000 births per annum. Piel et al (2013a, 2013b)

modelling based on geo-statistics and demographics estimated 42-44000 births per annum is an overestimate, since local granularities of Indian population structure was not considered.

SCA requires seamless dedicated medical services from birth (Serjeant, 2006) possible only with creation of special sickle cell clinics (SSCCs) for newborn screening, identification of cohorts for long term follow-up with simultaneous education, awareness of parents, families and society at large. Further, a strategic bottom-up approach, with components of step 1: documentation of existing SCA cases and building newborn screening cohorts for continuous surveillance, besides cascade carrier screening of extended relatives of SCA patients and heterozygotes and step 2: comprehensive screening of hemoglobin disorders by HPLC and G6PD deficiency of a representative un-related sample (n=100) of each local endogamous subpopulation. This will help in creating SCA cohorts for long term follow-up and clinical management from birth and establish HBS allele frequencies along with co-occurrence of other hemoglobin disorders and G6PD deficiency and identification of hot spot endogamous subpopulations /regions in the district. Both steps need to include simultaneous undertaking of KAPS (knowledge, attitude, practice study) and Re-KAPS for long term impact. Besides, impact evaluation, work-audit of these programs with defined out-come variables in a *program research mode* is the need of the hour. The ultimate targeted outcomes will be increase in pre-marital, parental pre-conception, antenatal testing and number of eligible couples opting for prenatal diagnosis. Each SSCC can be responsible for a group of districts in the implementation of HBS control and prevention programs following the ingredients of the district model with uniform internationally accepted protocols for impact evaluation. We also provide in Table 1 the existing programs being funded by government (state, central) institutes, non-government organizations (government funded or self- financed) being undertaken in different HBS high-risk regions. It is high time for harmonizing all the efforts of SSCCs with uniform internationally accepted guidelines.

Genetics in public health is an emerging field and considered as the new revolution in health care (Yusuf et al. 2011). Bottom-up approach with community participation is crucial in the delivery of public health as a product than equally important medical services. SCA require seamless service (Serjeant GR, 2006) and the most appropriate approach need to be development of surveillance systems with “Family education, routine immunization, malaria prevention, nutrition and hydration, prophylactic antibiotics, folic acid supplements, transfusion when required, support groups for children and their families, protocols for the management of acute events by health workers and—most importantly—regular follow- up” (McCavit, 2012).

Funding: No funding Received

Conflict of Interest: The authors declare that they have no conflict of interest.

Acknowledgements: The authors acknowledge the support from the affiliating organizations Thalassemia & Sickle Society and Genome Foundation in facilitating this work.

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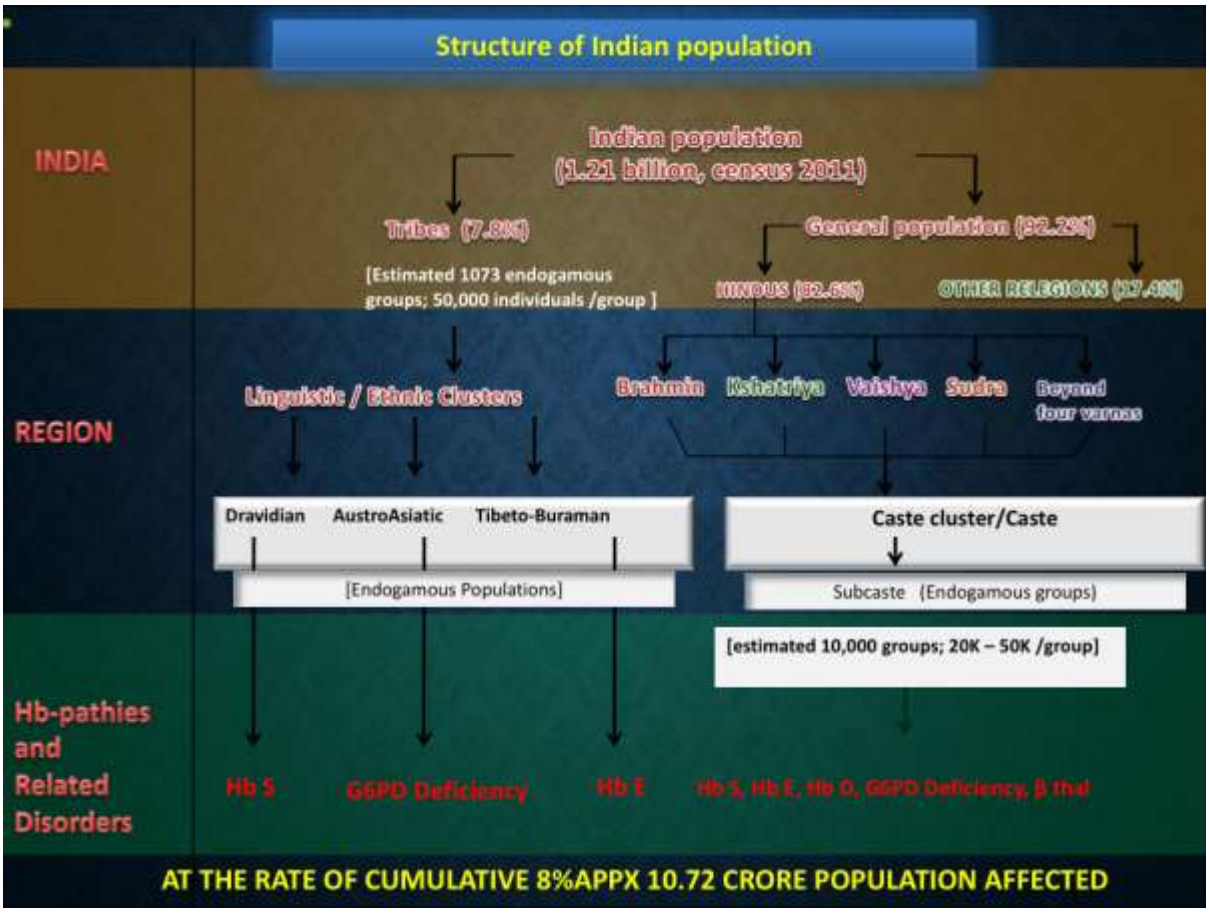

Fig. 1 Indian population structure and distribution of HBS, other hemoglobin disorders and G6PD deficiency.

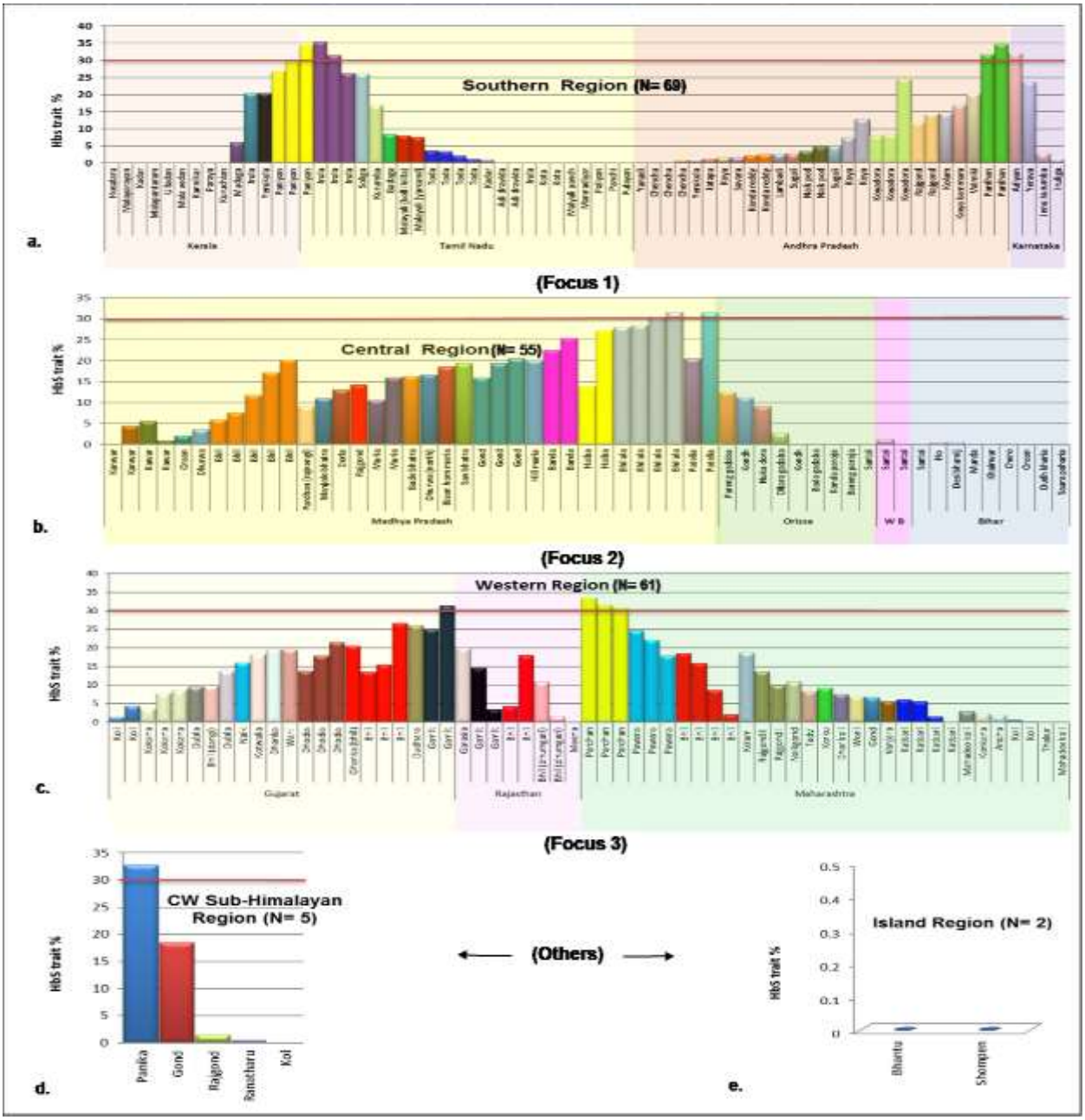

Fig. 2 HbS percent frequency distribution in Indian Tribes from various regions showing 3 ELGs (N=192). Note: Where, Fig. 1 a, b, and c indicate THREE FOCI a). Paniyan-Irula ELG , b) Gond ELG c). Bhil ELG and other regions d) CW Sub-Himalayan region and e) Island region

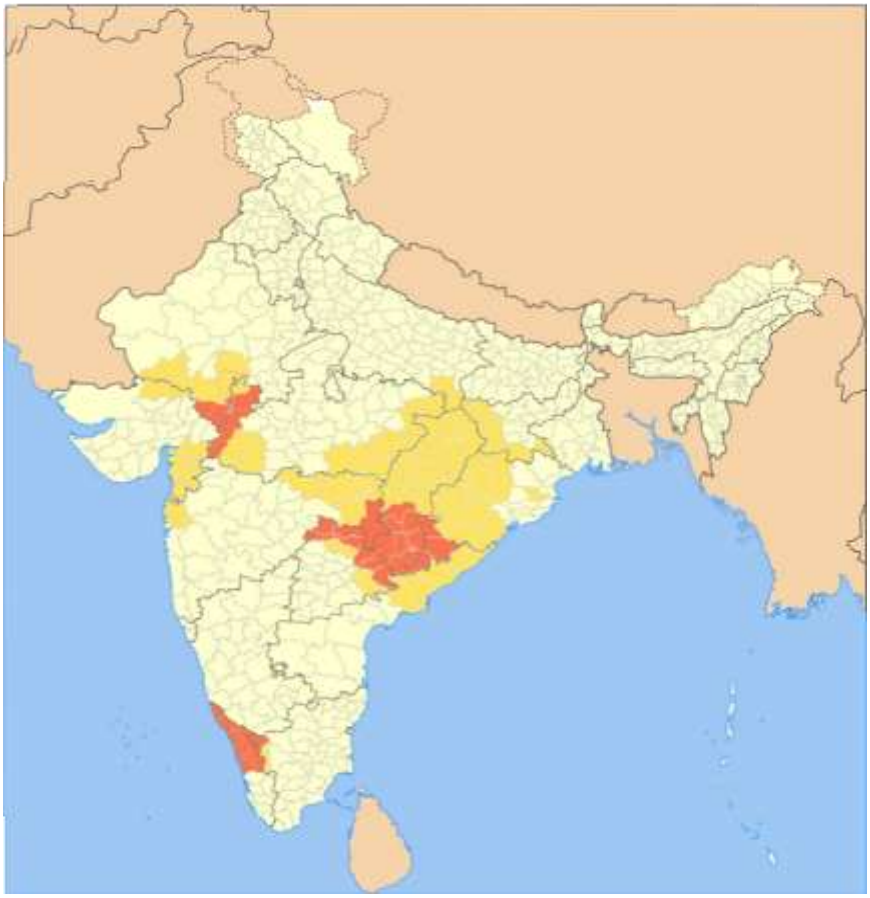

Fig. 3 India district map showing the Three ECZs (core) regions of sickle cell district wise distribution (red coloured) and extended areas (light colored) of PANIYAN-IRULA (south), GOND (centre) and BHIL (west) ELGs.

Table 1: HbS High risk ethnic milieu, eco-cultural geographic zones, population size and sickle cell centers existing and proposed.

Foci (With Highest Hb S Carrier Frequency >30%)	Eco-Cultural Geographic Zones(ECZ) (Core or Extended)	State/Districts	Total Population Size*	Estimated Sickle Cell Heterozygotes and Homozygotes**	Existing Sickle Cell Activity in Respective Regions.	Remarks
Focus 1	**Core** (Cheranadu& Malabar)	*Kerala*: Kannur, Kesargad, Khozikhode, Mallapuram, Palghat, Trichur, Wynad. *Tamil Nadu*: Nilgiri.	18513539 (2011) 1975583 (2020)	No of Districts: 8 2011: Hetero-1758786 Homo-46284 2020: Hetero-1876804 Homo-49390 Yearly Increment: Hetero-11802 Homo-311	<u>*Tamilnadu*</u> 1)Sickle Cell Disease Center, Gudalur Adivasi Hospital, Gudalur. -Diagnosis, Treatment, Community Screening and Education.	In view of the location of the 9 districts and number affected it is essential to have another center at Kozhikode.
	Extended	*Tamil Nadu*: Coimbatore.	3458045 (2011) 577629 92020)	No f Districts: 1 2011: Hetero-168579 Homo-2161 2020: Hetero-196739 Homo-2522 Yearly Increment: Hetero-2816 Homo-36		
Focus 2	**Core** Bastar plateau, Dandakaranya.	*Chhattisgarh:* Bastar, Sukma, Dakshina Bastar (Dantewada), Bijapur, Narayanpur, Kondagaon, Uttara Bastar (Kanker). *Maharastra:* Gadchiroli *Orissa:* Malkajgiri, Koraput, Nabarangapur. *Telangana:* Bhadradri, Jayashankar, Mancherial, Komaram Bheem, Adilabad, Nirmal.	11420605 (2011) 12073000 (2020)	No of Districts: 17 2011: Hetero-1084957 Homo-28552 2020: Hetero-1146935 Homo-30183 Yearly Increment: Hetero- 6198 Homo-163	<u>*Chattishgarh*</u> 2)Sickle Cell Center, Pt. JNM Medical College, Raipur. - Diagnosis, Treatment, Community Screening and Education. <u>*Orissa*</u> 3)Sickle Cell Clinic, Veer Surendra Sai Institute of Medical Sciences and Research, Sambalpur. - Diagnosis, Treatment, Community Screening and Education. <u>*Telangana*</u> 4)Thalassemia & Sickle Cell Society, Hyderabad. -Diagnosis, Treatment, Education. 5)Thalassemia & Sickle Cell Center, Red Cross Society, Mancherial. -Diagnosis, Treatment, Education. <u>*Maharastra*</u> 6)ICMR Sickle Cell Center, Chandrapur. -Community Screening and Education. 7)Sickle Cell Association, Nagpur, Maharashtra. - Diagnosis, Treatment, Education. 8)Thalassemia and Sickle Cell Unit, Rughvani Child Care Center and Hospital, Nagpur. - Diagnosis, Treatment, Education. 9)Sickle Cell Society of India, Nagpur. -Education.	In view of large extent of geographical area it is required that Chattishgarh, Orissa need to have 2 centers each and Jharkhand, Andhra Pradesh and Maharastra one each.
	Extended					

		Chattishgarh: Balod, Dhamtari, Gariaband, Rajnandgaon, Durg, Raipur, Mahasamund, Balodabazar, Bemetra, Kabeerdham, Janjirchampa, Raigarh, Jashpur, Balarampur, Surajpur, Surguja, Koriya, Kobra, Mungeli, Bilaspur. *Maharastra:* Wardha, Nagpur, Bhandara, Gondia, Yavatmal, Chandrapur, Wardha, Amravati. *Orissa:* Gajapati, Ganjam, Kalahandi, Rayagada, Kandhamal, Sambalpur, Subrnapur, Angul, Balangir, Baudh, Bargah, Debangarh, Jajapur, Jharsaguda, Naupada, Sundargarh. *Telangana:* Nirmal, Jagtial, Peddapalle, Warangal(R), Mahabubabad, Khammam. *Andhrapradesh:* West Godavari, East Godavari, Visakhapatnam, Vijayanagaram, Srikakulum. *Jharkhand:* Purba Singbhum, Paschim Singbhum, Simdega, Gumla, Lohadaga, Latehar, Garhwa, Palamu. *Uttarprdaesh:* Sonbhadra, Mirzapur. *Madhyapradesh:* Singrauli, Sindhi, Shahdol, Annupur, Dindori, Mandla, Balaghat, Seoni, Chindwara.	108861304 (2011) 122737806 (2020)	No of Districts: 74 2011: Hetero-5306989 Homo-68038 2020: Hetero-5983468 Homo-76711 Yearly Increment: Hetero-67648 Homo-867		
Focus 3	**Core** Malwa, Nimar, Bagelhkand	*Madhya Pradesh:* Jhabua, Ratlam, Mandsaur. *Rajasthan:* Banaswara, Dungarpur, Pratapghar.	10848250 (2011) 1293144 (2020)	No of Districts: 6 2011: Hetero-1030584 Homo-27120 2020: Hetero-1228487 Homo- 32329 Yearly Increment: Hetero-19790 Homo-521	Gujarath Sickle Cell Anemia Control Society, Valsad Rakta Dan Kendra, Valsad, Gujarath. -Community Screening and Education.	Though Sickle Cell work published from Medical Colleges in Rajasthan, no sickle cell center either in Government or Private Sector. One center may be established in Rajasthan.
	Extended	*Madhyapradesh:* Neemuch, Dhar, Indore, Barwani, Khargove. *Rajastan:* Udaipur, Sirohi, Chattarpore, Bilwara, Jalor. *Maharastra*: Thane, Palghar. *Gujarath:* Valsad, Navsari, Surath, Tapi, The Dangas, Banaskanta, Baroch, Narmada, Vadodara, Chota Udaipur. *Union Territory:* Dadra & Nagar Haveli.	152996151 (2011) 196185457 (2020)	No of Districts:23 2011: Hetero-7458562 Homo-95623 2020: Hetero-9564041 Homo-122616 Yearly Increment: Hetero-210548 Homo-2699	National Institute for Research in Tribal Health (ICMR), Jabalpur, Madhya Pradesh. -Community Screening and Education.	
		All Districts:		No of Districts (129) 2011: Hetero-1680857 Homo-267778 2020 Hetero-19996474 Homo- 313751 Yearly Increment: Hetero-1831562 Homo-4597		

*Population size: 2011 is Census Figure; For 2020 extrapolated from District Population of 2011 Census and Decadal Growth rate as given in www.mapsofindia.com/districts-india/

**based on assumed 10% and 5% carrier frequencies for core and extended regions respectively and Hardy-Weinberg Expectations.