UPDATE

Choice of point of Care diagnostic device in anemia prevalence surveys: policy-level Implications in monitoring progress and guiding further action.

Preetam B Mahajan[1], Newtonraj A[2], Joy Bazroy[3], Anju Sinha[4], Umesh Kapil[5], Anil Purty[6]

[1]Associate Professor, Department of Community Medicine, Pondicherry Institute of Medical Sciences, Pondicherry;[2]Assistant Professor, Department of Community Medicine, Pondicherry Institute of Medical Sciences, Pondicherry; [3]Professor, Department of Community Medicine, Pondicherry Institute of Medical Sciences, Pondicherry; [4]Deputy Director General, Division of Reproductive and Child Health, Indian Council Medical Research, New Delhi; [5]Professor and Head, Public Health Nutrition, Human nutrition Unit, AIIMS Delhi; [6]President IAPSM-India, Professor & Head, Department of Community Medicine, Pondicherry Institute of Medical Sciences, Pondicherry

Corresponding Author

Address for Correspondence: Dr Preetam B Mahajan, Associate Professor, Department of Community Medicine, Pondicherry Institute of Medical Sciences, Pondicherry.
E Mail ID: preetam3879@gmail.com

Citation

Mahajan PB, Newtonraj A, Bazroy J, Sinha A, Kapil U, Purty A. Choice of point of Care diagnostic device in anemia prevalence surveys: policy-level Implications in monitoring progress and guiding further action. Indian J Comm Health. 2018; 30, Supp: 80-85.

Source of Funding: Nil **Conflict of Interest:** None declared

Background

Anemia is highly prevalent disease of global concern. Childhood anemia can result in irreversible damage to brain and affect cognitive, intellectual, and pyscho-motor development. In pregnant women, it is a significant contributor to adverse maternal outcome (1–4). In 2011, alone it was responsible for loss of 42 million Disability adjusted life years and among the top three causes of disability worldwide (5). In an attempt to address this huge public health problem, guidelines have been issued by various leading international organizations and targets have been set to monitor progress towards its control. One such indicator is 50% reduction of anemia in women in reproductive age group (WRA) between 2011 and 2025 (6). This makes it necessary to carry out huge population-based anemia prevalence surveys repeatedly, to measure the progress and guide policy makers in carrying out specific interventions needed to reduce its prevalence.

Anemia is often defined employing hemoglobin (Hb) measurement and world health organization (WHO) criteria to determine the cut-offs after adjusting for smoking status, altitude etc (7). Most recent estimates of prevalence of anemia in specific age groups like under five children, WRA, pregnant and non-pregnant women, for all states in India were available from the 4th National Family Health survey (8).

The most convenient way of measuring the prevalence in such surveys is by using a point of care testing/diagnostic (POCD/POCT) device as it allows rapid assessment of hemoglobin using capillary blood with a high degree of quality and can be operated using battery or mains electricity. Reference methods utilize automated hematology analyzers, these entails extra costs, greater volumes of venous blood, and a longer turnaround time, making it unsuitable for prevalence studies.

Wide variety of both invasive and non-invasive POCDs are available (9). These include Hemocue system, STAT–Site MHgb (Stanbio Laboratory, Boerne, TX), Hgb Pro Professional Hemoglobin Testing System (ITC, Edison, NJ), D-10 Hemoglobin Testing (Bio-Rad Laboratories, Hercules, CA), CompoLab HB system (Fresenius Kabi AG, Bad Homburg, Germany), Pronto 7 (Non-invasive (SpHb)

rainbow 4D sensor, rev E, Masimo Corp., Irvine, CA, USA), Sahlis method, WHO Hemoglobin colour scale, digital hemoglobinometry devices using colorimetry, indirect cyanmethemoglobin method using elution techniques, True Hb, Touch Hb etc. We have provided comparisons with respect to certain limited variables for some of these devices easily available for use in India in Table 1.

How to select between different POCDs?

Since a number of POCDs are available in the market, researchers and policy makers are often faced with the challenge of recommending and choosing the most suitable device. Certain factors are required to be taken into consideration while comparing the available options. These include the accuracy parameters like sensitivity, specificity, predictive values, likelihood ratios; reliability measures like Intraclass correlation coefficient for consistency and agreement, limits of agreement; cost-effectiveness ratio; ease of operation of the device; acceptability by consumers and providers; non-invasive v/s invasive; stability under different environmental conditions.

We will discuss few of these factors further. The foremost is agreement between the test device and gold standard. Since Hb is a continuous variable, the most suitable method for its analysis is Bland- Altmann plot which compares the difference in readings on two devices plotted on y axis with average of the same two values on the x axis. Here we can also plot limits of agreement based on standard error of these differences and an average line for all such differences can be computed provided values are normally distributed. This line gives the extent of systematic bias that exist. A device is said to have acceptable reliability if 95% of these values fall within $\pm$ 1g/dl of reference values. Sometimes, the extent of differences between values measured on two devices vary according to the underlying true value. For e.g. from an unpublished report of the first author, it was seen that values obtained on one such POCD agreed with minimal differences (Average difference of -0.2g/dl) for Hb values < 10g/dl as compared to Hb values >10g/dl (Average difference of -0.4g/dl). So, the extent of misclassification is unlikely to be consistent for any possibility of correction and this is certainly not a very desirable trait. We therefore need devices that have similar disagreements across the range of Hb values.

Unlike previously thought, besides predictive values, even the sensitivity and specificity parameters are expected to vary along with prevalence of disease (16,17). Other determinants of sensitivity and specificity would include the population composition on which these parameters are estimated, and the distribution of Hb values in these populations. In other words, the prevalence of the disease would determine what proportions of subjects have Hb values around the clinical cut-off used for defining anemia for a particular population sub-group. The possibility of misclassification (FP v/s FN) as a result of instrument error, both random as well as systematic is more significant for subjects having Hb values around the cut-offs. It is intuitive that if more people have values around the cut-offs (i.e. high prevalence situations) more chances of misclassifications and these will automatically affect the sensitivity and specificity estimates of that device. A number of other factors have been identified (17) which are responsible for variations in estimation of accuracy parameters like differences in demographic features (age and sex composition) of study populations, disease severity, interobserver variability, availability of clinical information, test technology, test execution etc.

Another important consideration while selecting between different devices is their overall cost-effectiveness. To determine the same, certain considerations are important as mentioned while designing studies on diagnostic test accuracy, as data needs to be generated to simultaneously compare various devices. A community-based study aiming to cover a huge population would not be complete without an economic evaluation. Ultimately the decision by the policy makers depend on the proper

economic evaluation which should be locally relevant. There are many ways to do economic evaluation. One of the way is measuring the cost effectiveness of two tests. While calculating the cost bottom to top or top to bottom approach can be carried out.(18) Discounting factor needs to considered while calculation.(18) Both direct and indirect costs to be ideally considered for better estimation. (18) Sensitivity analysis will help the investigator to give a comprehensive picture on what would happen if the dependent parameters changes.(19) Effectiveness in terms of QALY(quality adjusted life year) or DALY(disability adjusted life year) could be measured using Markov model. (20,21) While comparing two or methods an incremental cost and effectiveness will help to determine the addition effect on changing the diagnostic tool.(18) for example we can calculate cost and effectiveness of diagnosing anemia with Sahli's haemoglobinometer and now we can calculate what would happen if the diagnostic tool changed from Sahli's to Hemocue or auto analyzer at the POCD in terms of incremental cost and effectiveness in terms of QALY and DALY. Another way could be calculating the effective cost of a diagnostic test, which is the money spent per unit of diagnostic performance. This can be measured as diagnostic utility (DU), the probability-weighted sum of the utilities of the four test outcomes True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN): DU = U(TP)P(TP) + U(TN)P(TN) + U(FP)P(FP) + U(FN)P(FN). In this model of comparing effective costs compares actual direct cost with clinical measures of test performance and utility values. This model offers a more clinically realistic setting than models based on costs alone.(22)

Having said that, once we narrow down on our choice about any one particular device and policy decisions are taken for utilizing a particular device in disease burden estimation study, we need to keep in mind two important factors that can have huge policy implications. Firstly, the extent of over or under estimation of true disease burden will depend on the underlying sensitivity and specificity of the measuring device. We will illustrate this with an example subsequently. Secondly, the sensitivity and specificity of the selected device will vary from place to place in the country due to differences in distribution of underlying clinical trait i.e. Hb values, and from period to period as with time continuous efforts to control the disease will also result in change in prevalence and thus change in accuracy statistics and thus also influence the extent of under or over estimation. Which means we need to estimate these parameters each time we carry out a prevalence study and use this information to get a correct estimate of the disease burden.

What are the implications of accuracy and reliability on true estimates of anemia burden?

Whenever, we use a POCD to determine the prevalence of any disease, the numerator of prevalence formula (all those diseased/all those tested) will include all those people tested positive (i.e. diseased) for a given POCD. This includes both TP and FP. While the true prevalence will have TP+FN in the numerator (figure 1). It is obvious that unless the false positives are equal to false negatives the prevalence estimates are unlikely to be accurate.

In-order to illustrate the impact on disease burden estimate we will illustrate the concept discussed thus far with an example from prevalence estimates for WRA calculated using Hemocue 201+ for selected states in NFHS 4 survey. Here we will need information on the sensitivity, specificity for Hemocue 201, which we have acquired from an unpublished report of first author for the sake of illustration. Once we know the sensitivity and specificity we can derive the true prevalence and estimated prevalence using an excel calculator and make comparisons. We have demonstrated the Gaps in prevalence in figure 2.

Word of caution while interpreting figure 2. The Gap estimation is based on an assumed fixed value of sensitivity and specificity across

different prevalence ranges across different states for the same population subgroup. We have already discussed that accuracy parameters cannot be same across population subgroup from different geographical locations due to variations in distribution of underlying Hb values leading to different true prevalence values. But we have attempted to demonstrate that the true picture will vary depending upon the accuracy parameters of the device being used.

It has been shown earlier by other researchers (23) that If the disease prevalence is below 50%, we will require a device with specificity greater than sensitivity. Conversely for diseases with prevalence above 50%, sensitivity will have to be higher in order to get accurate estimates. With lower true prevalence, Specificity of the instrument tends to be higher and the gap between calculated and true value a bit smaller, unlike what we see for the state of Manipur in the figure 2.

So, the solution lies in either choosing appropriate POCDs for a given true prevalence or estimating the necessary test statistic each time on a carefully selected subsample from a study population of ongoing disease prevalence study and provide corrected estimates based on the distribution of variables in figure 1.

We therefore conclude that there is urgent need to revamp the guidelines for carrying out prevalence studies in India especially the ones designed to capture anemia prevalence across the country in different clinically relevant subgroups. There is need to estimate the accuracy parameters of POCDs used for the study each time a prevalence study is planned, in order to determine the true anemia prevalence and guide action accordingly. The choice of POCDs for this kind of surveys will mainly depend on the reliability parameters i.e. extent of fluctuations around the true values; stability of the instrument across different climatic conditions; possibility of committing errors while estimating the value; cost involved, ease of operation etc. It is important to carry out comparisons within a few shortlisted POCDs on paired samples to generate robust evidence, which has apparently not been attempted till date and needs to be addressed by the research agencies of our country. Only then we can inform key policy decisions with this regard. Unless we know the truth, we will not achieve success.

Acknowledgement

We would like to thank 1st Year Postgraduate student Dr Sumedha Kesavan, Department of Community Medicine, Pondicherry Institute of Medical Sciences for her contribution in preparing the content for Table 1 in this article.

References

1. Zavaleta N, Astete-Robilliard L. [Effect of anemia on child development: long-term consequences]. Rev Peru Med Exp Salud Publica [Internet]. [cited 2018 Mar 16];34(4):716–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29364424
2. Walter T. Effect of Iron-Deficiency Anemia on Cognitive Skills and Neuromaturation in Infancy and Childhood. Food Nutr Bull [Internet]. 2003 Oct 2 [cited 2018 Mar 16];24(4_suppl2):S104–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17016952
3. Basu S, Kumar D, Anupurba S, Verma A, Kumar A. Effect of maternal iron deficiency anemia on fetal neural development. J Perinatol [Internet]. 2017 Dec 12 [cited 2018 Mar 16]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29234149
4. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev [Internet]. 2006 May [cited 2018 Mar 16];64(5 Pt 2):S34-43-91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16770951
5. Mathers C, Stevens G, Ho J, Fat DM, Mahanani WR, Andreev K, et al. WHO methods and data sources for global burden of disease estimates 2000-2011 [Internet]. Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2013.4. 2013 [cited 2018 Feb 23]. Available from: http://www.who.int/gho/mortality_burden_disease/en/index.html
6. The Global Nutrition Report 2016 [Internet]. [cited 2018 Apr 10]. Available from: http://www.globalnutritionreport.org/the-report-2016/
7. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1) [Internet]. [cited 2018 Feb 24]. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf
8. International Institute for Population Sciences (IIPS) and ICF. 2017. National Family Health Survey (NFHS-4), 2015-16: India. Mumbai: IIPS. [Internet]. [cited 2018 Apr 10]. Available from: http://rchiips.org/NFHS/NFHS-4Reports/India.pdf
9. Sanchis-Gomar F, Cortell-Ballester J, Pareja-Galeano H, Banfi G, Lippi G. Hemoglobin Point-of-Care Testing. J Lab

Autom [Internet]. 2013 Jun 6 [cited 2018 Apr 10];18(3):198–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22961038
10. HemoCue Hb 201 + System [Internet]. [cited 2018 Apr 10]. Available from: http://en.esbe.com/Customer/esscin/specpages/Hb201.pdf
11. Whitehead RD, Zhang M, Sternberg MR, Schleicher RL, Drammeh B, Mapango C, et al. Effects of preanalytical factors on hemoglobin measurement: A comparison of two HemoCue® point-of-care analyzers. Clin Biochem [Internet]. 2017 Jun [cited 2018 Apr 10];50(9):513–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28412284
12. Masimo International. Pronto 7, A New Solution for Haemoglobin Spot-Check Testing [Internet]. [cited 2018 Apr 10]. Available from: https://pdf.indiamart.com/pdfim/?url=https://4.imimg.com/data4/OJ/RX/MY-4849193/pronto-7-pulse-oximeter.pdf
13. Paddle JJ. Evaluation of the Haemoglobin Colour Scale and comparison with the HemoCue haemoglobin assay. [cited 2018 Apr 10]; Available from: http://www.who.int/bulletin/archives/80(10)813.pdf
14. Howard Haskins BD. A NEW PERMANENT STANDARD FOR SAHLI'S HEMO- GLOBINOMETER. [cited 2018 Apr 10]; Available from: http://www.jbc.org/content/57/1/111.full.pdf
15. S.K. Kapoor, Umesh Kapil, Sada Nand Dwivedi, K. Anand, Priyali Pathak, Preeti Singh. Comparison of HemoCue Method with Cyanmethemoglobin Method for Estimation of Hemoglobin. Indian Pediatr [Internet]. 2002 [cited 2018 Apr 10];39:743–6. Available from: https://www.indianpediatrics.net/aug2002/aug-743-746.htm
16. BRENNER H, GEFELLER O. VARIATION OF SENSITIVITY, SPECIFICITY, LIKELIHOOD RATIOS AND PREDICTIVE VALUES WITH DISEASE PREVALENCE. Stat Med [Internet]. 1997 May 15 [cited 2018 Mar 11];16(9):981–91. Available from: http://doi.wiley.com/10.1002/%28SICI%291097-0258%2819970515%2916%3A9%3C981%3A%3AAID-SIM510%3E3.0.CO%3B2-N
17. Whiting P, Rutjes AWS, Reitsma JB, Glas AS, Bossuyt PMM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med [Internet]. 2004 Feb 3 [cited 2018 Mar 8];140(3):189–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14757617
18. Prinja S, Bahuguna P, Faujdar DS, Jyani G, Srinivasan R, Ghoshal S, et al. Cost-effectiveness of human papillomavirus vaccination for adolescent girls in Punjab state: Implications for India's universal immunization program. Cancer. 2017 Sep;123(17):3253–60.
19. Smith RD, Slenning BD. Decision analysis: dealing with uncertainty in diagnostic testing. Prev Vet Med. 2000 May;45(1–2):139–62.
20. Prinja S, Bahuguna P, Rudra S, Gupta I, Kaur M, Mehendale SM, et al. Cost effectiveness of targeted HIV prevention interventions for female sex workers in India. Sex Transm Infect. 2011 Jun;87(4):354–61.
21. Manji RA, Witt J, Tappia PS, Jung Y, Menkis AH, Ramjiawan B. Cost-effectiveness analysis of rheumatic heart disease prevention strategies. Expert Rev Pharmacoecon Outcomes Res. 2013 Dec;13(6):715–24.
22. Patton DD, Woolfenden JM. A utility-based model for comparing the cost-effectiveness of diagnostic studies. Invest Radiol. 1989 Apr;24(4):263–71.
23. Campbell H, Biloglav Z, Rudan I, (CHERG) on behalf of CHERG. Reducing bias from test misclassification in burden of disease studies: use of test to actual positive ratio--new test parameter. Croat Med J [Internet]. 2008 Jun [cited 2018 Mar 1];49(3):402–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18581619

Tables

TABLE 1 DEVICES EASILY AVAILABLE FOR USE IN INDIA

Sl. No	Name of the instrument	Battery or electricity operated	Invasive or non-invasive	specimen	Reading Direct/ indirect	Point of care (i.e. place of survey) Diagnosis
1.	HemoCue Hb 201+ System (10)	AC adapter / 4 AA batteries	Invasive	Capillary / venous/arterial	Direct (Digital result)	Yes
2.	HemoCue® Hb 301 System (11)	AC adapter / 4 AA batteries	Invasive	Capillary / venous/arterial	Direct (Digital result)	Yes
3.	Pronto-7 (12)	Electricity and Battery	Non - invasive	----	Direct (Digital Result)	Yes
4.	WHO Haemoglobin colour scale (13)	Manual	Invasive	Capillary	Direct (subjective comparison)	Yes
5.	Sahli's haemoglobinometer (14)	Manual	Invasive	Capillary	Direct (subjective assessment)	No (Requires to be carried out in a facility)
6.	Filter Paper Cyanmethemoglobin (15)	Manual	Invasive	Capillary/ Venous sample	Indirect method, but objective assessment	No (requires processing in a Lab)

Figures

FIGURE 1: TWO BY TWO TABLE COMPARING TEST METHOD WITH GOLD STANDARD IN A TYPICAL DIAGNOSTIC ACCURACY STUDY.

	Gold standard		
	Diseased	Not diseased	
Screen test positive	TP	FP	TP+FP/ total Population **will provide the** **Estimated Prevalence**
Screen test Negative	FN	TN	
	TP+FN/ total Population **will provide the** **True Prevalence**		Total Study Population

FIGURE 2: COMPARISON BETWEEN TRUE ANEMIA PREVALENCE AND NFHS 4 CALCULATED PREVALENCE (USING HEMOCUE 201) AMONG WOMEN BETWEEN 15-49Y IN SELECTED STATES ASSUMING SENSITIVITY OF 92.82% AND SPECIFICITY OF 75%.