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Use of Point-Of-Care Cholesterol Testing in Population Based Non-Communicable Disease Surveillance: Caveats and Challenges

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ABSTRACT

Introduction: Point of care testing (POCT) for total cholesterol (TC) is invaluable in non-communicable disease (NCD) surveillance programs, as it may permit rapid risk stratification for efficient channeling of limited finances in resource constrained settings. Nevertheless, one needs to be aware of some caveats to the dependability of POCT results for TC in high load situations. **Aims & Objectives:** To evaluate the analytical performance of POCT for TC in a population-based NCD surveillance study, by comparing its results with a laboratory assay, and to identify sources of error. **Place and duration of study:** Mangamandi, Lahore (sampling); Services Institute of Medical Sciences, Lahore (laboratory), from December 2019 to March 2020. **Material & Methods:** POCT for TC was done as part of CVD risk stratification in a large NCD surveillance project. Lower than expected readings of TC on POCT were flagged during routine data quality checking, and this prospective study was designed to determine accuracy of POCT readings by testing the same sample in a laboratory. Mean ±SD of two methods were compared in overall sample and in subgroups. Linear regression analysis was done to determine correlation between the two methods. After a significant disparity was confirmed, POCT process was scrutinized to identify its cause, and re-testing after its correction confirmed the source of interference. **Results:** Mean TC level in overall sample (n= 699) by POCT was significantly lower than that of laboratory method: 2.80 (±0.30 SD) mmol/l vs. 5.28 (±1.27 SD) mmol/l ($p < 0.0001$) R^2 0.085. This trend persisted in subgroup analysis. A significant difference between the two methods was seen in a Bland Altman plot. POCT process evaluation identified optical window interference as a possible cause of the discrepancy, and after this was corrected, POCT results started showing a higher trend and became comparable with laboratory: 4.67 (±1.50 SD) vs. 5.45 (±1.89 SD) mmol/l, R^2 0.9157.**Conclusion:** Even though the utility of POCT for CVD risk stratification in NCD surveillance programmes is undeniable, some caveats and challenges remain. Non-compliance with device maintenance protocols in high throughput situations encountered in field testing may contribute to inaccurate results. Cholesterol POCT requires careful operator training, technical support and strong quality assurance backup.

Key words: point-of-care cholesterol testing, optical window interference, non-communicable disease screening

INTRODUCTION

The 21st century has witnessed a paradigm shift in the global burden of disease from communicable to non-communicable diseases (NCD). According to the 2017 Global Burden Disease (GBD) study of WHO, 73.4 % of all deaths in 2017 were due to NCDs; an increase of almost 22.7% over the preceding decade.[1]Recognizing this fact, WHO has included NCD control in its Sustainable Development Goals for 2030.[2]A substantial number of these deaths (17.8 million in the 2017 survey) occur due to premature CHD in lower middle income countries (LMIC) like Pakistan, where NCD programmes are still in infancy.[1,3] In resource constrained settings, it is cost-effective to focus on primary prevention, using a two-pronged approach of disease surveillance and population based low cost interventions like the WHO Package of

Essential Non communicable Disease Interventions (WHO PEN), delivered though frontline workers.[4]

The Global Health Research Unit (GHRU) on Diabetes and Cardiovascular Disease in South Asia is an international collaborative project between UK and four South Asian countries including Pakistan, funded by National Institute for Health Research (NIHR), UK. Details of the collaboration and current projects can be found on the project website: (https://fundingawards.nihr.ac.uk/award/16/136/68). Under the umbrella of this project, a NCD surveillance study was started in the Punjab province in Pakistan in 2019, with the aim of ascertaining the true prevalence of NCD in the province.

Blood cholesterol level, as an important marker of CHD, was among the various parameters being recorded in this population based surveillance study. Point of care testing (POCT) for total cholesterol was done to help in risk stratification using CVD risk prediction tools, for inclusion in the participant health assessment report. Based upon risk stratification, participants could then be channeled towards ensuing NCD control projects.

While POCT for estimation of blood glucose and glycosylated hemoglobin has been a part of clinical management of diabetes for a long time,[5] POCT for cholesterol in whole blood has become widely available relatively recently.[6,7,8] The advantage of including POCT for TC in NCD surveillance programmes lies in that it may be used for early detection of elevated cholesterol allowing risk stratification and timely institution of risk mitigation measures like statin therapy.[6] However, this is a relatively new technology, and while it offers advantage of speed and convenience, the caveat lies in the fact that in a population-based screening setting, POCT has a high usage load and is mainly performed by front-line workers with little technical background, who are usually not well-versed in the technical details of the device and testing process.[9] This may be an even greater challenge in low resource countries like Pakistan where availability of technical and quality control support is minimal particularly in remote locations. Indeed, concerns have been raised about reliability of POCT results compared to the conventional laboratory testing, which may be ascribable to operator dependent issues rather than a limitation of POCT per se, as the reliable operation of the device requires an understanding of the principle of colorimetric detection, and ability to service the device optical window regularly. Proper operator training, and continuous quality control (QC) checks are a mandatory requirement for dependable POCT testing in high throughput settings.[10]

In the GHRU surveillance project, POCT for TC was performed for immediate CHD risk assessment, while blood was collected for complete biochemistry as a batch in a central lab at a later date. To select a suitable TC POCT device for use in the project, a range of available devices were compared on the basis of reliability of results, live data capture and stability of performance in high ambient temperatures likely to be encountered in field testing in South Asian countries including Pakistan. The Aina POCT device (Jana Care Inc, USA) was selected by the central steering committee, as it fulfilled above mentioned criteria.[11] A pilot study was done to compare the device results with laboratory findings, and showed comparable results (unpublished data, available on request). Frontline community health workers were trained in Aina device usage as per documented standard operating protocols of the surveillance project, and a detailed operations manual was made available to each of them. For quality assurance, the central project team was running continuous quality control (QC) checks on the collected data of the Aina POCT device. The device continued to perform well for several months into the surveillance project, however, after performance of almost 2200 tests on the Aina device, routine QC checks identified that measured TC levels were showing a consistent drift towards low values.

The rationale of present study was to identify practical issues in the implementation of a new smart phone linked cholesterol POCT device as a cost effective tool for population based surveillance studies in limited resource settings like Pakistan. TC results of POCT were evaluated by comparing its analytical performance with TC measured in a clinical laboratory, in the backdrop of lower than expected TC levels, in the first instance, to confirm this finding, and if confirmed, to critically evaluate the POCT process to detect the source of any disparity, institute remedial measures, followed by re-testing to verify improvement in performance. The objective of this exercise was to identify the challenges and to suggest practical ways to overcome these difficulties.

MATERIAL AND METHODS

As mentioned previously, the present study was conducted on a subset of the participants in the ongoing GHRU surveillance study which aims to screen 150000 adults for NCD in four South Asian

countries, out of which 30000 would be from Pakistan. The project has been approved by National Bioethics Committee (Ref: No.4-87/NBC-347/19/1506 dated 01.31.2019) and the hospital Institutional Review Board (Ref: IRB/2018/461/SIMS dated 09.24.2018).

Equipment used in the study included Aina POCT lipid device (Jana Care Inc, USA) for cholesterol POCT and Cobas c311 analyzer (Roche Diagnostics GmbH, Germany) for laboratory assays as a standard for comparison. The Aina POCT device has a reported clinical accuracy of 100% samples within 20% bias and a good correlation (R^2= 0.973) with Dimension RxL Max Analyzer (Siemens, USA) and a measuring range of 2.59 to 10.34 mmol/l for TC working at 10 to 40° C with test time of 2 minutes. In addition, it has an advanced feature of cloud readiness i.e. safe transfer of data to central databases.[11] Cobas c311 is an automatic clinical laboratory analyzer which was based in an ISO 15189 accredited laboratory with internal and external quality controls.

Participants were enrolled and given a translated information sheet one day before the surveillance activity, and fasting venous samples were collected next day after their written informed consent. While serum was stored for a wide range of biochemical tests to be run as a batch at a later date, POCT for blood glucose and TC were done to be included in the participant health assessment report. In December 2019, the continuous QC checks identified that the POC cholesterol results had drifted well below expectations over a four week period immediately preceding this study (October, 2019: range 2.59-5.67 mmol/l, mean 3.23 (±0.54 SD) mmol/l vs November/December, 2019: range 1.71-4.68 mmol/l, mean 2.92 (±0.35 SD) mmol/l. To determine if this inconsistency was a chance occurrence or was due to a malfunction of the POCT, a cross-sectional, prospective study was conducted to compare the POCT results with laboratory analysis results. Sampling was done in the area of Mangamandi, in suburbs of Lahore, over a four week period from mid-December 2019 to January 2020. POCT was performed in a Mobile Health Unit (MHU) specially designed for NCDs surveillance, with a mini-laboratory set up for POC testing, sample processing and storage. The average ambient daytime temperature during this time ranged between 16.1°C-19.5°C with 75% humidity.[12,13] A total of 699 participants were included in the study, with 455 females (65.1%) and 244 males (34.9%). Venous blood sample, of participants fasting for 8-14 hours, was collected from a single venipuncture into 2 ml EDTA and 3.5 ml serum gel tubes through multi-sample needles. For POCT, 15 µL whole blood was pipetted onto the cholesterol test strip of Aina device. For laboratory testing, serum was separated within 4 hours, and was evaluated in clinical laboratory of Services Institute of Medical Sciences, Lahore. TC was measured by an enzymatic colorimetric method using Cobas c311 analyzer (Roche Diagnostics GmbH, Germany). The results of the two methods were compared overall, as well as in subgroups based on gender, age and laboratory cholesterol level.

Further course of action was to be determined by the results of the first phase. It was planned that if on initial testing, POCT cholesterol readings differed significantly from the laboratory results, POCT process would be evaluated to identify the source of the error, and testing would be repeated after the fault had been eliminated, to confirm that this was the cause of the anomaly.

Statistical analysis:

Data analysis was performed using Microsoft Excel (2013). Mean ± SD of two methods was obtained, and % bias calculated. Bland-Altman plot was used to assess agreement between two methods. Statistical significance calculated by Student's t-test, was defined at $p< 0.05$. Linear regression analysis was done to determine the existence of correlation between two methods.

RESULTS

1. Initial comparison of POCT cholesterol results with laboratory testing:

In the overall population, mean (± SD) TC by laboratory method was 5.28 (±1.27) mmol/l and by POCT device method it was 2.81 (±0.30) mmol/l. Overall bias and % bias was -2.47 and -46.78 respectively while R^2 was 0.085. Bland Altman plot showed significant negative bias (Fig-1).

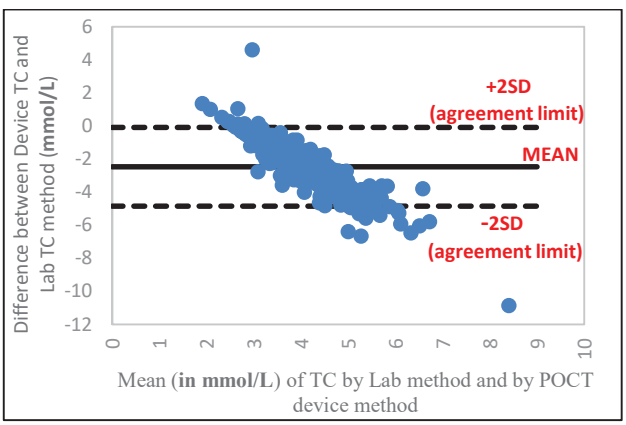

Fig-1: Bland Altman Plot for the difference between the POCT device and the laboratory for TC

On gender specific analysis, TC mean (±SD) in females was 5.32 (±1.23) mmol/l, and in males was 5.19 (±1.33)mmol/l by laboratory method, while by POCT, it was 2.83 (±0.31) mmol/l in females and 2.74 (±0.28) mmol/l in males.
The % bias, p-value and correlation between POCT and laboratory method based on gender is given in (Table-1) and (Fig-2)

Sex	n	%	% Bias	p-value
Female	455	65.1	0.00103	<0.0001
Male	244	34.9	0.00194	<0.0001
Note. n=number of participants				

Table-1: Analysis of groups by gender

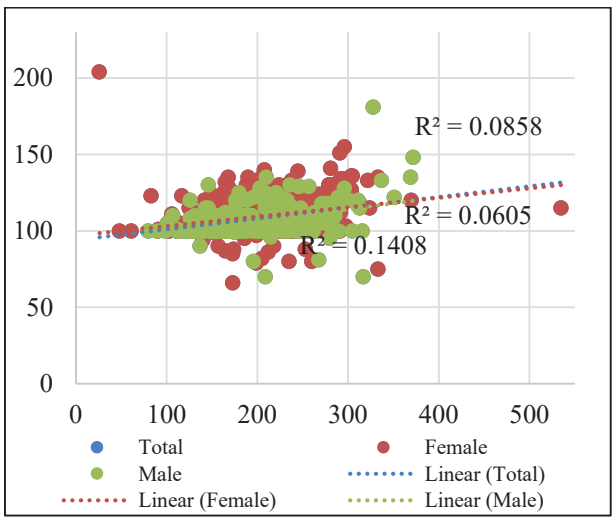

Fig-2: Correlation between device method and laboratory method according to gender

Analysis of subgroups based on age for TC by POCT method vs cholesterol by laboratory method can be seen in Table-2 and Fig-3.

Age group (years)	n	Total Cholesterol Device (mmol/l) Mean ±SD	Total Cholesterol by automation (mmol/l) Mean ±SD	% Bias	p-value
i. 18-35	202	2.77±0.28	4.86±1.24	0.00213	<0.0001
ii. 36-59	463	2.82±0.31	5.45± 1.23	0.00104	<0.0001
iii. >60	32	2.76±0.32	5.39± 1.51	0.01525	<0.0001
Note. n=number of participants. SD=standard deviation					

Table-2: Total Cholesterol by device versus laboratory estimation according to age groups

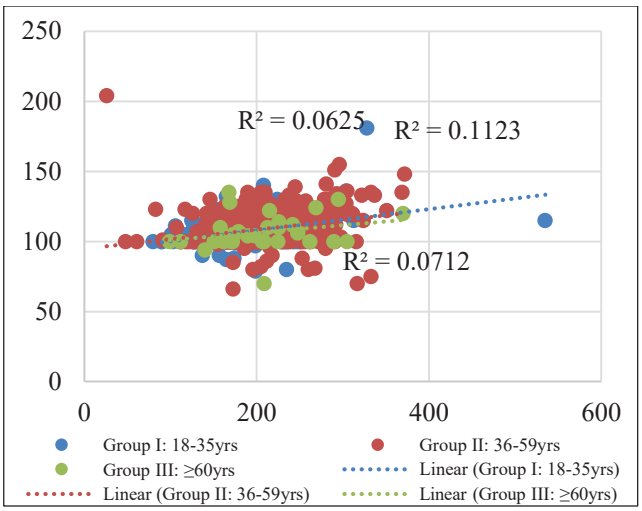

Fig-3: Correlation between Device method and laboratory method according to Age

Table-3 and Fig-4 details analysis of TC measured by POCT and laboratory method based on cholesterol levels by laboratory method.

Cholesterol Level (mmol/l)	n	TC Device (mmol/l) Mean±SD	TC by automation (mmol/l) Mean±SD	% Bias	p-value
a) < 5.147	333	2.73±0.27	4.28±0.69	0.00109	<0.0001
b)5.147- 6.18	226	2.79±0.25	5.63±0.30	0.00222	<0.0001
c)≥6.19	138	2.98±0.30	7.09±0.94	0.00421	<0.0001
Grand Total	699	2.80±0.30	5.28±1.27		
Note. n=number of participants. TC=total cholesterol. SD=standard deviation.					

Table-3: Comparison of Device versus laboratory estimation according to Cholesterol Level

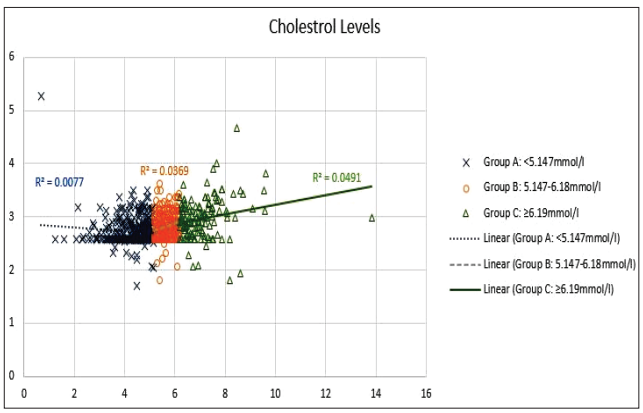

Fig-4: Correlation between Device method and laboratory method according to Cholesterol level

2. Identification of the source of error

As the anomaly identified on QC was confirmed by the result of the first phase of testing, a biomedical engineer scrutinized the POCT process and found that the sample collection and processing operating

protocols were being followed correctly. However, it was identified that while the device was cleaned externally with isopropyl alcohol on a daily basis, as per protocol, the optical window was not being serviced as this needed to be exposed by opening the device body. Once the optical window was exposed by opening the device body (Fig-5), it was cleaned with 70% isopropyl alcohol, and device performance was retested after cleaning.

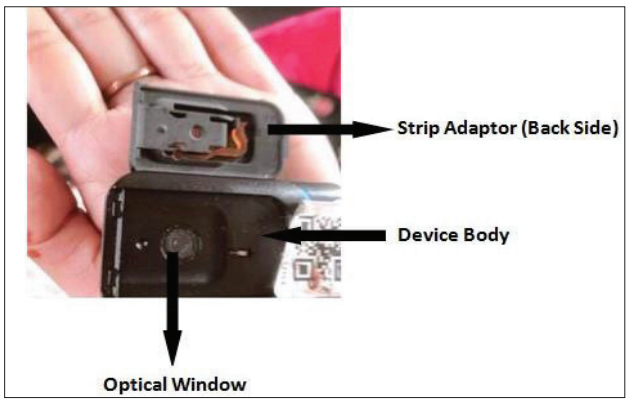

Fig-5: Optical window exposed after sliding strip adaptor from the device body

Retesting after optical window servicing:
After the device optical window was cleaned, a series of duplicate tests were run on randomly selected samples over a three week period (February-March 2020). It was immediately apparent that the range of POCT results had increased beyond the low values seen in the preceding period (range: 2.59-7.42 mmol/l, mean 3.99 (±0.81 SD) mmol/l. The results of the POCT compared to the laboratory testing are given in (Table-4) and (Fig-6). This confirmed that the device performance issue had been due to optical window interference.

Cholesterol Level	n	Device Method (mmol/l) Mean	Lab Method (mmol/l) Mean	Correlation	R^2	P- value
a) < 5.147	11	3.26± 0.80	3.72±0.6	0.785	0.61632	0.1429
b) 5.147-6.18	2	5.21± 0.55	5.59±0.55	1	1	0.3845
c) ≥ 6.19	10	5.96± 0.68	7.33±0.86	0.904	0.8173	0.00098
Overall	23	4.67±1.5	5.45±1.89	0.9569	0.9157	0.099
Note. n =number of participants. SD=standard deviation. R=coefficient of determination.						

Table-4: Correlation between Device method and laboratory method according to Cholesterol level after optical window cleaning. (overall R^2=0.9157)

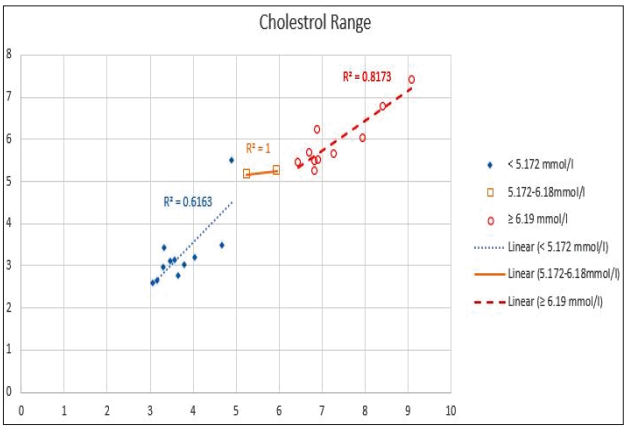

Fig-6: Correlation between Device method and lab method according to Cholesterol level after optical window cleaning (overall R^2=0.9157)

3. Retraining and remediation:
As remedial measures, the operating technicians were retrained in the device maintenance procedure, and the operations manual was expanded to include a section on routine device maintenance, emphasizing the technique of opening and cleaning the optical window.

DISCUSSION

Knowledge of the patient's cholesterol levels is invaluable in risk stratification for focusing preventive measures and directing risk mitigation programmes like the WHO PEN intervention, deliverable by trained frontline workers. POCT for TC offers an attractive solution, whereby patients can be triaged and assigned to a particular intervention in a single encounter, minimizing loss to follow-up. However, in order to be a useful part of clinical assessment, POCT systems should yield results which are accurate and comparable with laboratory analysis.[14]

Cholesterol POCT technology became generally available around the year 2000, but devices were initially large and cumbersome. Over time, devices have become more portable and compact and capable of integration with data servers.[15] The Aina POCT device offers the advantage of both being very compact and directly pluggable into a smartphone for live data capture by the central server[11] The present study was the first time it had been used in population based screening in Pakistan. The device showed accurate results compared with laboratory assays in the pilot study, and in the first three months of the surveillance project, as confirmed by regular quality assurance checks. However, in the period immediately preceding this study, lower than expected readings had been

flagged by these checks. During the initial phase of this study, meant to confirm the low readings, it was seen that the POCT cholesterol results were significantly lower than those from the laboratory cholesterol assay ($p < 0.001$), with very low correlation between the two ($R^2 = 0.085$). This was of great concern to us, as it was likely to have an impact on the validity of the health report given to the participants. Even more worrying was the fact that this was at odds not only with the pilot study, but also the device performance in the initial three months. The second part of the study focused on a step by step analysis of the testing process to pinpoint the source of the disparity, which identified the device optical window to be responsible, and this was confirmed when POCT result correlation with laboratory assay increased significantly after its correction ($R^2 = 0.916$).

As the availability of POCT for cholesterol is a relatively new development, there is a paucity of external validation studies, especially for the newest generation of smartphone compatible devices. Some of these studies have raised concerns about lack of accuracy of cholesterol POCT devices, with a bias towards an underestimation of TC.[16] Similar trend was quantified in the initial phase of our study; the negative bias of -2.46 showed that POC device values were less than those of the gold standard laboratory method indicating accuracy issues, however the bias was eliminated after the removal of the source of interference. The difference in the overall sample mean of TC by the two methods in our study was almost 2.47 mmol/l (95.5mg/dl). This difference was plotted in the Bland Altman plot (Fig-1) showing several readings lying outside $\pm$ 2SD limits of agreement which seemed to indicate significant measurement bias between the two methods.[17,18] In fact such a difference had been previously reported by Park et al in a POCT TC validation study with -15.9% bias[14] whereas standard for accuracy set by NCEP guidelines is $\leq \pm$ 5%.[19] In another study of 111 cases, Xavier et al reported moderate correlation between POCT device and clinical laboratory for TC values ($R^2 = 0.796$).[20] Whitehead et al, reported that the POCT analyzer showed a negative bias for TC of -17.6±13.4% when compared to the laboratory method.[21] In a study by Matteucci et al. POCT also underestimated TC (bias 6.5%).[22] Other studies have, however, shown satisfactory correlation between POCT and laboratory values of TC. Ferreira et al, reported good correlation between POCT and laboratory method for TC: (R^2 0.879, average bias 4.0 %) in a study on 516 participants.[23] Indeed, the differences in the experiences of different groups of researchers suggest that something beyond a limitation of the device technology is involved here.

Clearly, it is a matter for concern that, while the device performance in device validation studies usually correlates highly with laboratory data, when testing in field conditions, a significant difference between cholesterol results on POC testing and laboratory readings has been noted by many authors.[8,20,21] Our study highlights the fact that falsely low cholesterol readings may be due to operational factors, reflecting the difficulty in running simple but sensitive technology in field conditions, where the operators are often non-technical personnel,[21,24] and technical support may not be immediately available. Such user dependent challenges were identified by O'Kane and colleagues as a major source of quality errors in POCT.[25] Furthermore, it highlights the need for rigorous quality control measures, to detect any deviation from expected trends.[8,9,22,23] Extrapolating from our results, we can speculate that the accuracy issues observed in other POC cholesterol devices could be attributed to a similar issue. Inaccuracy in POCT results can be an operator dependant issue due to a failure to follow device maintenance protocols, rather than a limitation of device per se.[22,23] This was also noted by Whitehead et al in the field setting of the outreach NHS health screening clinics in England.[19] It is important to raise this issue because in actual field testing, with a large number of samples being handled in circumstances, these best practices are frequently ignored.[10,19,23]

Although cholesterol POCT devices are simple to use, they utilize a sensitive technology that requires careful and regular device maintenance by trained operators. These devices, including the one used in our study, are based on optical bio-sensing technique, which uses enzyme catalyzed color reaction[24] for cholesterol identification and reflectance photometry for changing the chemical signal into an optical signal.[25] Cholesterol concentration is then quantified through photometric detection.[28] The reaction area, where test strip/cassette is inserted, is a removable part of the device and lies directly above the optical system which is a non-removable intrinsic part of the device body. The optical window is made from optical material with specific qualities tailored for reflected light transmission into the optical system.[29,30,31] Changes in the optical properties of this window due to contamination (dust, dirt, blood etc) or abrasion can cause distortions in reflected light or interference with its transmission leading to erroneous results.[32] The optical window needs to be

exposed by opening the device body, to be cleaned regularly. Although this is not a complicated step per se, it may be omitted by the field operators who are usually not from a technical background, and may be unable to understand the technical requirements of the system.[21,25,28]

Operator factors were recently reported as a reason of resistance towards POCT system acceptance in workflow by a large primary care CVD risk assessment program in New Zealand and it was suggested that continuous training and support could help in achieving the recognized benefits of POCT.[10] Indeed, technical support may not always be available in field screening, and such remediable sources of error may go unnoticed. This highlights the importance of careful training and re-training of field operators, and indeed their supervisors, who may themselves be unaware of the technical requirements of the system.[24,25] Furthermore, the importance of quality control checks cannot be overemphasized, as these are able to flag potential sources of error, and indicate the need for remedial measures.[24,25,28]

In our study, we were fortunate to have both technical support and a rigorous quality assurance system in place, because of which we were able to quickly identify and correct the issue. In low resource countries like Pakistan, in particular where cholesterol POCT is being used in population screening in remote locations, this issue may become very relevant.

It is noteworthy that interference due to dirty window can be an issue in all optical biosensors, including those in glucose POCT devices. However, in contrast to cholesterol POCT devices, the newer generation glucose POCT devices have resolved this issue by using electrochemical bio-sensing.[33] Technology for cholesterol POCT devices is in emerging state, with optical biosensors being the most cost effective solution for the time being.[34] If cholesterol POCT is to be successfully incorporated into population based screening programs, devices which are less dependent on technical maintenance need to be developed. Furthermore, thorough operator training, robust technical support as well as rigorous quality assurance with periodic evaluation of results against laboratory cholesterol assays are essential to maintain validity of results.

CONCLUSION

In conclusion, operator training in technical aspects of POCT device maintenance is an essential part of the internal quality control (IQC) protocols. It is important to highlight this issue because in field testing for population screening, where a large number of samples are handled in less than ideal circumstances, these best practices may not be followed due to inadequate operator training or the high workload. Clearly, while the ease of use and speed of results for POCT is undeniable, unless these devices are operated with careful adherence to operating and maintenance protocols, with appropriate technical support, device accuracy may become compromised.

Limitations:

As this was not a formal validation study, it was not possible to control for every factor that might have an impact on the results. The study was designed in the context of an ongoing surveillance project with narrow focus on the study's own POCT accuracy concerns raised by routine QC. However, we wanted to share our experience so that public health researchers especially in low resource countries may be aware of difficulties in POCT device usage in high load settings and can take suitable measures to avoid these for a reliable and cost effective data output.

Conflict of Interest:

The authors have no conflict of interest to declare.

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https://fundingawards.nihr.ac.uk/award/16/136/68

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