Research Article

A pilot survey on quality control and method evaluation practices in clinical laboratories in Nepal

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Keywords
Internal Quality Control; Method Evaluation; Laboratory Survey

Abstract

Background
There is a lack of systematic collection of information on the quality control practice and method evaluation approach in clinical laboratories in Nepal. Such data is important to formulate educational activities and policy that may address any potential knowledge and practice gap identified.

Method
The pilot survey included twelve questions regarding quality control practice and method evaluation approach and was distributed among the laboratory medicine professionals in Kathmandu, Nepal. Data were collected using a structured self-reported questionnaire on the Google Docs platform. A total of 43 responses were received.

Results
Internal quality control and method evaluation practice varied considerably in terms of the number of levels of material used, frequency of analysis, type and source of material and acceptance criteria among responding laboratories.

Conclusion
The variability in quality control practice and method evaluation approach highlights need for augmentation of knowledge, attitude, and practice behavior among laboratory professionals in Nepal.

Background
Laboratory medicine in Nepal started with the establishment of the first medical laboratory in 1960. After 1990, the private sector began to assume a more significant role in laboratory service provision. As a result, several private laboratories were established throughout the country. Eventually Nepal got its first ISO 15189: 2012 accredited laboratory in 2015[1]. At present the numbers of services and professionals in laboratory medicine have increased. However, the laboratory quality practice and method evaluation approach in Nepal remain areas that requires substantial development. This is in part limited by the lower prioritization for quality and lack of trained laboratory professionals in quality management system given the resource limitation [2]. The clinical laboratory practice is moving toward harmonization globally,

and it is possible to achieve this in a small country like Nepal through the cooperation of clinical laboratories, professional and regulatory agencies, invitro diagnostic industries and metrological institutes. There is currently a lack of systematically collected information about the quality control practice and method evaluation approach in Nepal. Such information is necessary to identify potential knowledge and practice gaps and allow formulation of appropriate educational activities and policy to address them. The goal of this pilot study is to survey the referral clinical laboratories in Kathmandu, Nepal, to identify quality control and method evaluation practices currently in use.

Method

This cross-sectional survey was undertaken in November 2023 among the registered laboratory professionals working in different clinical laboratories in Kathmandu. A structured and self-reported survey questionnaire containing informed consent and other measures was published on the Google Docs platform. Data were collected using the same platform. The respondents provided informed consent for publication of de-identified, aggregated data prior to the start of the survey. Survey of this nature was exempted from ethics approval at the institution where this survey was performed. This study strictly maintained the anonymity and confidentiality of the data. The questionnaire consisted of 12 questions in total. After reviewing the literature in this area and several questionnaires used for an online survey, a questionnaire was designed, and it was reviewed and approved by an independent expert in laboratory medicine. The questions were multiple choices and respondent were allowed to select more than one answer. The questionnaire used in this study was developed for this study. The survey was sent via email to the laboratory personal, representing clinical laboratories in Kathmandu, who registered themselves for a workshop focusing on quality control. There were 48 recipients resulting in 43 responses received. Data were summarized using descriptive statistics and all calculations were done using Microsoft® Excel® 2019. Subsequently a one-day workshop was organized, and survey results were summarized and presented. Additionally, the comments made by the laboratories about their practices in the local setting were qualitatively recorded and presented below.

Results

The survey contained questions on internal quality control and method evaluation. There were 43 responses where 27 were from private standalone tertiary laboratories including nationally recognized accredited laboratories, six were from medical colleges and ten were hospital based laboratories. There was no participation from government laboratories. The individual questions along with the findings of this survey are discussed below. The number of answers is not equal to the number of respondents because option for choosing multiple answers was provided. Thus, the resulting percentage of answers can exceed 100%.

Section 1. Quality Control Practice

1. Which of the following QC material is used in your laboratory?

A. Quality control material from reagent manufacturer
B. Quality control material different from reagent manufacturer (third-party)
C. Leftover patient samples
D. Others

Results

All the participating laboratories are using QC material in one way or other. Most of them, 51%, are using QC material from reagent manufacturers as well as third party QC material. Around 10% and 35% of laboratories are using QC material from reagent manufacturers and third party QC material, respectively.

Table 1: Results for the type of QC material used in clinical laboratories in Nepal.

QC Material	Number	Percentage of laboratories
From Reagent Manufacturer	28	65.1
Different from Reagent Manufacturer	38	88.4
Leftover Patient sample	1	2.3
Other	1	2.3

Comments

The use of QC materials from the reagent manufacturer is suboptimal since they may be produced under the same condition and may mask changes in the analytical performance. The use of retained patient samples provides a cost-effective alternative and is considered generally commutable, although the retained samples should be kept in a condition that ensures their integrity and the target values and control limits need to be established by the laboratory.

Recommendation

The ISO 15189:2022 standard recommends QC material independent of the assay manufacturer to control the risk of non-detection of drift when changing reagent lot. For some tests, laboratories may have limited alternatives to QC material from the assay manufacturer. In these circumstances, the use of alternate/ additional forms of QC should be considered, e.g. retained patients sample or patient-based real time quality control.

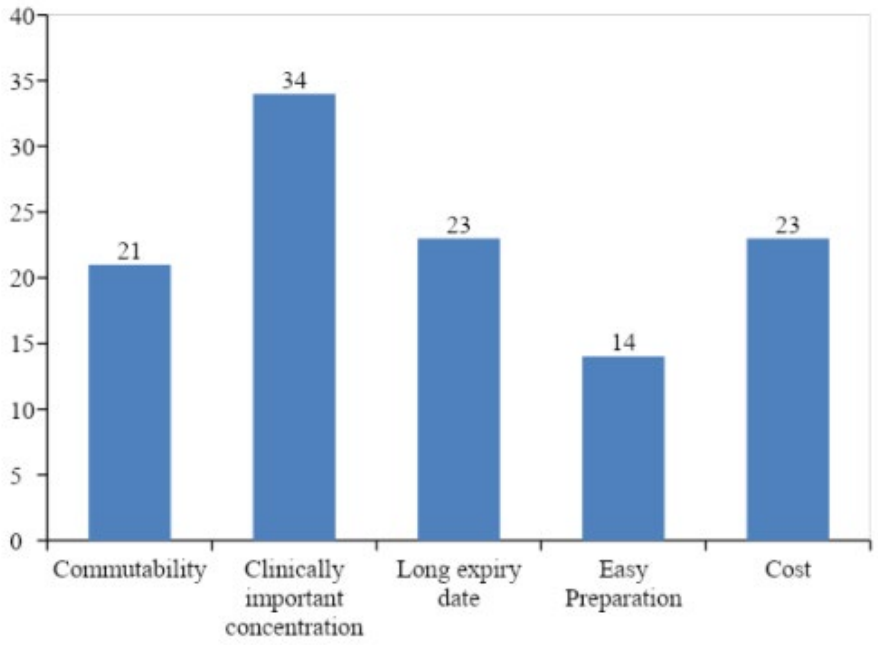
2. What are your main considerations when selecting quality control materials?

A. Commutability of the quality control material
B. Quality control material covering clinically important concentration
C. Long expiry date
D. Easy preparation
E. Cost

Results

Around 20% of participating laboratories consider all considerations equally important. A majority of laboratories primarily consider the availability of QC material at clinically important concentration while the ease of material preparation is least likely to be a main consideration.

Figure 1: Factors considered while selecting QC material (X-axis) versus number of laboratories (Y-axis).



Comments

All factors listed above are important considerations when selecting QC materials. The prioritization of the specific considerations will depend on local circumstances. The emphasis on clinically important concentrations suggests an appreciation for monitoring the performance of the assay at these high-risk concentrations. Having a long expiry and low cost of QC material are operational and financial consideration of equal importance to the survey respondents. Commutability status of a QC material is often uncertain, it is nevertheless important to use QC materials with appropriate matrix for the sample types encountered clinically. Ease of QC material preparation is generally a compromise the laboratory is most willing to make.

Recommendation

National regulatory body should encourage local proficiency testing providers to provide affordable QC materials. It is recommended that laboratories use QC materials that are commutable and covering clinically important concentrations that are within the limits of the analytical measuring range of the assay, without dilution.

3. In general, how many concentrations (levels) of quality control material are used in your laboratory for each assay?

A. One concentration
B. Two concentrations
C. Three or more concentrations

Results

Almost 50% of laboratories use two levels of QC. Just over a quarter (28%) of laboratories uses three or more concentrations. One in ten (10%) laboratories use one level of QC for analytes with low volume of requests and two levels of concentration for those with high volume of requests. A minority (~5%) of laboratories use only one level of QC.

Comments
The surveyed laboratories refer to the various sources the number of level of QC used, including National Accreditation Board for Testing and Calibration Laboratories (NABL), India (Document 112) and peer reviewed literature. Most of the laboratories use at least two levels of QC, which meet the regulatory or accreditation requirements.

Recommendation
Experts in laboratory medicine of Nepal in collaboration with national regulatory body and Accreditation Education Research & Scientific Services Center (AERSSC), an accreditation body in Nepal, should establish a consensus on the number of level of QC that are appropriate for the local laboratory practice.

4. What are the desired concentrations of quality control in your laboratory?

A. Near the lower limit of reporting/ functional sensitivity of the assay
B. Near the reference intervals/ medical decision limits
C. Near mid-point of the assay range
D. Near the upper limit of assay range

Table 2: Results for the number of QC levels used in clinical laboratories in Nepal.

Number of QC levels	Number	Percentage of laboratories
One concentration	6	14
Two concentrations	29	67.4
Three or more concentrations	17	39.5
Other	1	2.3

Results
Only 35% of laboratories use QC materials with concentrations covering the reference interval or medical decision limit for the analyte. The other laboratories consider a mix of functional sensitivity, midpoint, lower and upper limit of assay as the desirable concentrations to be monitored by the QC.

Comments
While having QC material covering clinically important concentrations is the most commonly cited emphasis when selecting QC materials (see Question 2), there is a lack of consensus on what constitute desirable concentration. Most laboratories did not consider reference limits or medical decision limits as desirable concentrations to be monitored by QC.

Recommendations
Choosing QC material with analyte levels which are close to the reference limit and/ or medical decision limit is recommended. These are the concentrations that are liable to affect clinical interpretation of the laboratory results should there be a change in analytical performance. Ideally, at least one QC concentration should cover the reference limit/ medical decision limit while another may cover concentration within the pathological range for the analyte.

5. How does your laboratory establish the quality control target value and control limits?

A. Use manufacturer's target value and control limits
B. Establish in-house target value and control limits

Table 3: Results for the concentration of QC material used in clinical laboratories in Nepal.

Concentration of QC	Number	Percentage of laboratories
Near the lower limit of reporting/ functional sensitivity of the assay	7	16.3
Near the reference intervals/ medical decision limits	22	51.2
Near mid-point of the assay range	18	41.9
Near the upper limit of assay range	16	37.2

Result
Most of the laboratories use QC manufacturer's target value and control limits (82%) while the others established these parameters in-house.

Comment
Laboratories using manufacturer's target value and control limits may do so for a combination of reasons including unfamiliarity with the procedure to derive these parameters themselves, a lack of resources or for convenience.

Recommendation
Target values and control limits provided by manufacturers are often wider than those found within the laboratory. This may

lead to overly lenient control limits, which can compromise the detection of analytical errors. Laboratories should establish its own target value and control limits for QC material using long-term data. The target value and control limits should be reviewed periodically and judiciously adjusted where appropriate to ensure optimal error detection performance.

6. How often is quality control testing performed in your laboratory?

A. Once a day
B. Twice a day
C. Three times a day
D. Before running a batch of samples
E. After running a batch of samples
F. Before and after running a batch of samples

Results

Around 60% of laboratories perform QC testing once a day. Only 18% perform QC testing twice a day. 5% of them run QC once or twice a day depending upon the number of test request for the analyte.

Comments

Laboratories testing QC once a day may do so due to operational (e.g. low test request) or financial reasons. In laboratories analyzing large number of clinical samples between QC testing, there is an increased risk of missed error.

Recommendation

The frequency of QC testing should consider the stability of the analytical performance of the analyzer and method along with reagents, the workload and frequency of the assay and the risk of harm to patients from an erroneous result. It is important to consider testing QC sample before (and ideally, after) patient sample analysis as well as following daily maintenance, calibration and any troubleshooting procedures.

7. Which of the following quality control interpretative rules are being used in your laboratory?

A. 1:2S (1 QC result outside of 2SD)
B. 2:2S(2 consecutive QC results outside of 2SD)
C. 1:3S (1 QC result outside of 3SD)
D. 4:1S (4 consecutive QC outside of1SD)
E. $10\bar{x}$ (10 consecutive QC results to the same side of mean)

Table 4: Results for the frequency of QC testing in clinical laboratories in Nepal.

Frequency of QC	Number	Percentage of laboratories
Once a day	32	74.4
Twice a day	10	23.3
Three times a day	2	4.7
Before running a batch of samples	5	11.6

Results

Only 14% of laboratories are using all the interpretative rules for acceptance of QC results. However, all laboratories are using at least one QC rule. The most commonly applied QC rule is 2:2S followed by 1:3S,1:2S and $10\bar{x}$ respectively.

Comments

Among the survey participants, nearly all are using Levy-Jennings chart for reviewing the QC results. The 4:1S and $10\bar{x}$ rules are less commonly applied and are helpful for detecting systematic changes (bias).

Recommendations

It is recommended that laboratories establish a policy for interpreting QC results, including the setting of QC rules. The 1:2S rule is generally regarded as a warning rule and is associated with approximately 5% false flagging/ alarm rate. On the other hand, the 1:3S and 2:2S are generally considered a rejection rule since these are associated with <0.5% false alarm rate. The other QC rules, such as 4:1S and $10\bar{x}$ rules may be considered if systematic error is suspected. It is useful to periodically review the QC data and QC rules to ensure optimal error detection.

8. Do you customize the quality control interpretative rules for different assays?

A. No, we use the same rules for every assay
B. Yes, we customize the rules according to the analytical performance of the assay

Table 4: Results for the QC interpretative rules used in clinical laboratories in Nepal.

QC interpretative rules	Number	Percentage of laboratories
1:2S	20	46.6
2:2S	24	55.8
1:3S	23	53.5
4:1S	7	16.3
10$\bar{x}$	17	39.5

Results
70% of the participating laboratories use the same interpretative rules for all the assays while the other tailor the QC rules according to the number of test request for the analyte.

Comments
Ideally, QC interpretative rules should be tailored such that true errors are detected with minimal false rejections. Most of the laboratories use the same rules for all the assays which may be due to lack of familiarity with QC rule customization or for operational convenience by using standardized QC rules within the laboratory.

Recommendation
When QC rules are tailored according to the clinical requirement, risk tolerance and analytical performance of a laboratory method, it can optimize error detection while reducing false alarm rates. At the same time, the use of tailored QC rule for each assay may introduce significant operational complexity since it may require different frequency of QC testing, different troubleshooting protocol and different QC interpretative rules. Therefore, there is a need of increased resource requirements, the need for advanced data management systems, and the necessity for additional staff training. Phased implementation, leveraging automated systems, and seeking expert consultation would help. Care should be exercised to balance all the above factors when determining the QC policy for the laboratory.

9. Do you use other methods for monitoring the performance of your assay?

A. Yes
B. No

Results
All the participating laboratories only use QC for monitoring the performance of the assays.

Comment
Internal QC remains the only means of monitoring the performance of the assays in the laboratory in Nepal. Patient-based quality (PBQC) is not practiced.

Recommendation
The use of PBQC is a valuable tool for monitoring the performance of the analytical performance of the assay. However, it requires suitable software (instrument, middleware or laboratory information system) to perform this monitoring in real time. In the absence of such advanced laboratory software, common statistical software such as Microsoft Excel may be used to analyze the patient data in a retrospective manner. The use of patient result for monitoring assay may represent a cost-effective alternative for laboratories in Nepal.

Section 2. Method Evaluation

10. Does your laboratory perform method evaluation for a new assay?

A. Yes, before starting clinical service
B. Yes, after starting clinical service
C. No, we do not perform method valuation

Results
Around 88% of laboratories perform method evaluation for a new assay before committing to clinical service. Approximately 10% of laboratories participated in survey do not perform any pre-implementation method evaluation.

Comment
Method evaluation is important for objectively assessing the performance of the laboratory method against manufacturer claims. Data obtained from method evaluation can inform other aspects of laboratory practice (e.g., QC policy). Pre-implementation method evaluation also provides the laboratory with the opportunity to resolve any installation or commissioning issues that may compromise the analytical performance of the laboratory method.

Recommendation
It is necessary to perform method evaluation before committing a new laboratory method to clinical service to ensure it meets the clinical requirement and manufacturer's claim. Method evaluation should be performed with thoughtful planning and execution to ensure laboratory obtains the most useful data for a given amount of resource. Financial constraints in Nepal often necessitates scaled down method evaluation protocols.

11. Which of the following components are routinely evaluated for a new assay in your laboratory?

A. Precision
B. Bias/ accuracy
C. Linearity
D. Method comparison (either with the 'old' assay or a reference assay)
E. Analytical measurement range/ dilution factor
F. Carry-over contamination
G. Assay interference

Results

A majority of laboratories (60%) verify precision, bias and linearity. A quarter of laboratories verify precision and bias. Only 5% of laboratories verify all the components listed in the question.

Comments

When performing method evaluation, the majority of laboratories adopt guidelines that are at least in part developed internally rather than just following international guidelines. There may be financial reason for using the local guidelines, which are often simplified. The lack of local regulatory requirements may contribute to the lower number of analytical components being verified by the participating laboratories. Verifying all the listed performance component can be cost prohibitive to the local laboratories.

Recommendation

There are many components to method evaluation, and each requires dedicated consideration for the experimental design, acceptance criteria and statistical analysis. The component and approach of method evaluation may be guided by clinical requirements, local resources, and local regulatory requirements. The local national regulatory body may provide guidance in this aspect of laboratory practice. At minimum, a laboratory should consider verifying the precision, bias/ accuracy, and linearity of a new laboratory method.

Table 6: Results for the method comparison components used in clinical laboratories in Nepal.

Components evaluated for a new assay	Number	Percentage of laboratories
Precision	41	95.3
Bias/ accuracy	30	69.8
Linearity	34	79.1
Method comparison	17	39.5
Analytical measurement range	7	16.3
Carry-over contamination	5	11.6
Assay interference	4	9.3

12. What material is routinely used for method evaluation in your laboratory?

A. Quality control material from reagent manufacturer
B. Quality control material (third-party) different from reagent manufacturer
C. Leftover patient samples
D. Others

Results

A third (32%) of laboratories use quality control material from reagent manufacturer for method evaluation while a quarter of laboratories use third party QC materials. Only one laboratory uses patient sample for the verification.

Comments

Most of the laboratories use QC material for method evaluation as it is generally accessible, easy to use, and overcomes the challenge of preparing and storing a large quantity of patient samples.

Recommendation

It is ideal to perform method evaluation using leftover patient samples since it avoids potential non-commutability that may be present in QC materials. However, the need to prepare and store these samples in sufficient volume for the method evaluation experiments and in a manner that retains its integrity can be challenging. Moreover, the use of patient samples requires the establishment of target values and uncertainty that may add to the costs. Using QC material for method evaluation is a pragmatic alternative but laboratories should be mindful of potential non-commutability, lack of sample at specific/ desired concentration. Proficiency testing materials can be an alternative.

Table 7: Results for the material used for method evaluation in clinical laboratories in Nepal.

Material used for method evaluation	Number	Percentage of laboratories
Quality control material from reagent manufacturer	29	67.4
Quality control material (third-party)	26	60.5
Leftover patient samples	8	18.6

Discussion

This pilot study surveys the laboratories in Kathmandu, Nepal, on their quality control and method evaluation practices. In this survey, the participating laboratories reported QC practice including the number of levels of material used, frequency of analysis, type and source of material and acceptance criteria. Variability in findings may be in part due to the difference in perceived importance for different considerations for QC practice. Similarly, the method evaluation practice in Nepal also varies among laboratories. The subscription to accreditation may encourage more standardized practice and set minimum requirements. However, only a few laboratories in Nepal are accredited to the ISO15189 standards, which may explain the heterogeneity in practice. Since accreditation may be considered costly, local regulatory/ professional body may consider incorporating some of the accreditation requirements and provide more specific guidance in these areas, taking into account local context and resource availability. The present survey lacks comparative analysis with the international standards. Future follow up studies will include benchmarking against quality control practices and methodologies from clinical laboratories in other countries, particularly those with well-established standards and practices. The interplay between internal QC and external quality assurance (EQA) programs is essential for ensuring the highest standards of quality in clinical laboratories. Internal QC practices are crucial for the daily monitoring and immediate validation of laboratory results, allowing for the detection and correction of errors in real-time. Conversely, EQA programs provide an external benchmark, enabling laboratories to assess their performance against national or international standards and identify areas for improvement. Recognizing the importance of internal QC and EQA programs, further surveys or studies should also focus on EQA programs. The QC practice of a laboratory is influenced by the knowledge, attitude, and practice behavior of its laboratory personnel. A recent study on knowledge of QC practice among laboratory personnel in a medical college in eastern Nepal revealed that only 25% had adequate knowledge [3]. The results of this survey corroborate with the previous survey and provide further evidence that there is a general need to improve the training and education of laboratory personnel in Nepal. The education efforts will help raise the laboratory practice of Nepalese laboratories and improve harmonization of QC and method evaluation practices. Another limiting factor for laboratory management in Nepal is financial constraints. Lack of QC (number of sample and frequency) will mean reduced power of detecting error and increasing the risk of undetected error. This might affect patient care if clinically important error goes undetected. Also, the lack of appropriate sufficient method evaluation may allow method with suboptimal performance to go into routine practice. This may then manifest as poor QC performance, or worse still, if goes undetected, may affect patient results. Ideally, adequate budget should be allowed for appropriate QC testing, participation in external quality assurance programs, pre-implementation method evaluation, laboratory staff training, fee for auditing and accreditation bodies etc. However, the competing financial priorities in a resource constraint setting may mean that some of these considerations are relegated or neglected. There are Nepalese national regulatory policies for total quality management in laboratory. Nonetheless, the implementation of these requirements has been haphazard due to a combination of factors including inadequate knowledge, inadequate guidance, insufficient resources, and poor enforcement [2]. Laboratories may design method evaluation protocols that uses minimal sample size (depending on local resources)/ protocols with suitable statistics to perform method evaluation in resource limited setting [4,5,6]. At minimum, laboratories are advised to evaluate analytical precision, accuracy and linearity. Other specific difficulties encountered by the clinical laboratories in Nepal are shortage of skilled manpower [7], regulatory guidance [8], infrastructure and technological limitation [9], and logistics and supply chain problem [10]. These difficulties can be addressed by policy intervention, capacity building and international collaborations. A major limitation of this study is the inclusion of relatively low number of laboratories that is geographically focused in the capital city of Kathmandu, Nepal as well as the lack of response from government laboratories. However, it should be noted that only the clinical laboratories in Kathmandu were selected in this study due to its representative urban healthcare infrastructure and higher accessibility to diverse laboratory settings. Although this study is based on small sample size, it is still the most comprehensive survey of Nepal to date. Care should be exercise when interpreting the results of this study as it may not be generalizable to other parts of the country that may have different local context (e.g., remote regions). We emphasize that, there is a need of conducting similar studies in diverse geographic locations across Nepal to obtain a more comprehensive understanding of clinical laboratory practices nationwide.

Declaration of Conflict of interests

The authors of this article declare that there is no conflict of

interest with regard to the content of this manuscript.

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