Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications

Presented to the Faculty of Health Sciences, University of Witwatersrand

In Fulfilment of the Requirements for the Degree of Master of Medicine (Virology)

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Declaration by Bhaveshan Reddy

I hereby declare that I have read and am familiar with the current MMED guidelines for submission of a publication in lieu of MMED research report. I have complied with the instructions and stated conditions. The research manuscript, is of my original work and neither is the whole work nor any art of it has been, is being, or is to be submitted for another degree in this or any other university. The manuscript has fulfilled all criteria and has been published in the Southern African Journal of HIV Medicine.

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A special thanks to my family & friends for their support and encouragement. I dedicate this manuscript to all the woman in my life who have inspired me and shaped me into the person I am today.

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Factors influencing the high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and the cost implications

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Background: HIV enzyme-linked immunosorbent assay (ELISA) is one of the most requested test sets within Virology and forms an essential part of patient management. Assessment of the rejection criteria is a key quality indicator, crucial for improving laboratory services and efficiency to ensure accurate and reliable results.

Objectives: The aim of this study was to identify the factors that influence the HIV 1/2 serology rejection rates (RR) at Charlotte Maxeke Johannesburg Academic Hospital and to evaluate the associated costs.

Methods: A retrospective study was conducted (June to December 2019) to identify the RR and rejection criteria of HIV serology samples throughout the total testing process. Descriptive analysis using percentages and frequencies was used to analyse the RR by phase, health establishment, ward and healthcare professional. A cost analysis incorporating minor and major costs was modelled in each phase of testing, and the total cost of rejections was calculated.

Results: A total of 6678 tests were received, and 738 were rejected (RR = 11.1%). The pre-analytical phase contributed significantly to the overall RR, with the requirement of a separate sample (57.44%) the most common reason for rejection. The total cost per rejected test was $2.47, which amounted to a total rejection cost of $197.55, of which $158.18 was caused by the pre-analytical rejection criteria.

Conclusion: High RR of HIV tests were noted, resulting in significant cost wastage. Identification and analysis of rejections must be implemented across all laboratories to improve the efficiency of testing, provide a cost-saving benefit and maintain high laboratory standards.

Keywords: HIV; rejection rates; cost analysis; laboratory; diagnostics.

Introduction

HIV remains a leading cause of increased morbidity and mortality, especially in Southern Africa. Despite active measures to control the course of this disease, over 7 million individuals are living with HIV in South Africa.[1] The Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 goals highlight the role of diagnostic testing as one of the main strategies in controlling this pandemic.[2] Providing accurate and reliable results timeously has proven to have positive outcomes in the management of HIV-infected individuals.[3] In line with the 95-95-95 targets, South Africa adheres to the universal test and treat strategy. As such, the laboratory has a responsibility to provide quality results to promote patient safety. A constant increase in test demand results in increased workload, which leads to inefficiencies within the laboratory and healthcare facility. As a result, laboratory accountability for patient safety has been highlighted in recent studies and should include the monitoring and analysis of key quality indicators such as rejection rates (RR).[4] This can be tailor-made to accommodate different laboratories; however, when doing so, pre-existing limitations such as laboratory design, infrastructure, personnel and operating processes must be considered.

The rejection of a sample has detrimental consequences for the laboratory, health facility and individual tested. This can be reflected in delayed turnaround times, reduced efficiency, poor workflow, cost implications, missed or delayed diagnostic opportunities and loss to follow-up.[5,6] A rejected test caused by laboratory error or an HIV test that is incorrectly requested in a setting such as the early infant diagnosis (EID) programme can be a major pitfall in achieving targets that aim to reduce new paediatric infection rates (0–24 months). Several studies reported that a significant number of rejected tests are not repeated (once-off occurrence) and can account for up

to a 12% increased chance of inappropriate patient care.[7] A projected error rate of this magnitude in the South African context can apply tremendous pressure to the already financially constrained and resource-burdened public health sector, especially in key age categories such as the paediatric population. Recent literature reports several factors contributing to increased RR throughout the total testing process, including haemolysis, the mislabelling of samples and inappropriate sample collection.[8] The total testing process consists of three phases – (1) pre-analytical, (2) analytical and (3) post-analytical – with the majority of rejections occurring in the pre-analytical phase.[9]

With the rise in the burden of diseases and the emergence of novel pathogens, there has been an increased need for diagnostic testing; however, this need has not been met with the necessary financial resources. To support the increase in testing, there is a need to review cost-saving strategies and how they will benefit the laboratory as well as the patient. A costing analysis that used the Markov probability model suggested a total loss of $357.15 per hospital patient.[10] Similarly, a number of studies have estimated pre-analytical RR costs to range between $160.00 and $225.00 per month.[10,11] These substantial costs can have a significant impact on the total hospital budget.

The primary aim of this study was to assess the HIV serology RR and reasons in the Department of Virology, National Health Laboratory Service (NHLS), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The secondary aim was to undertake a costing analysis to illustrate the financial implications of these rejections in a typical South African health laboratory.

Materials and methods

Study setting

This retrospective study was conducted for the period 01 June 2019 to 31 December 2019 in the Department of Virology of the NHLS based at CMJAH (Johannesburg, South Africa). The department provides a dedicated 24-h diagnostic service to CMJAH, a tertiary-level hospital, surrounding primary healthcare (PHC) facilities and both regional and district level hospitals.

Specimen registration

For HIV serology test requests, samples were registered on the laboratory information system (LIS) following standard operating procedures to capture all demographic, clinical and test request details provided on the laboratory request form. The test results are automatically downloaded to the LIS, and all laboratory data are stored in the NHLS corporate data warehouse (CDW).

Test rejections and rejection criteria

All rejection codes and descriptions were defined by the local laboratory and the NHLS expert committees. Electronic gatekeeping of samples was included as a rejection criterion in this study, defined as any HIV serology sample requested before the minimum request interval time had elapsed. The pre-analytical phase included all processes from sample collection to receipt at the CMJAH NHLS receiving office. All processes that pertained to the performance of the test were assigned to the analytical phase, whereas the post-analytical phase involved the analysis, interpretation and authorisation of the test results.

Lookup table

For each rejection, a rejection code is entered into the LIS to indicate to the requesting healthcare practitioner the reason for not performing the test, for example 'specimen insufficient' (SPINS). Because of the vast number of rejection codes reported, a lookup table was developed using Microsoft Excel (Redmond, California, United States) to assign the rejection status (rejected/not rejected) and phase of testing (pre-analytical, analytical or post-analytical). Lookup tables were then used to group assigned codes of large data sets with similar information, avoiding manual coding (Table 1).

Data analysis

An NHLS-specific test code for HIV serology was used to extract data from the CDW for the 6 months (01 June to 31 December 2019). All rejected tests and the reasons for rejection were captured on the LIS and downloaded to the CDW database. The data extract also included the following variables: (1) age, (2) facility name, (3) referring healthcare professional, (4) rejection code, (5) rejection reason description, (6) date of collection, (7) date of rejection, (8) ward code and (9) ward description. Age was stratified into three categories – infants and toddlers (0–24 months), children and adolescents (2–18 years) and adults (> 18 years) – and the total number of rejections per age group was calculated. We used the facility name to assign the health establishment type (PHC facility or hospital). Similarly, we used ward descriptions to assign the following ward types: (1) medical, (2) trauma and casualty, (3) surgical, (4) intensive care unit (ICU), (5) paediatrics, (6) obstetrics and gynaecology and (7) antiretroviral (ARV) clinic. Experts read the ward description and assigned the ward type; for example 'Area 165 Medical Casualty CAS' was assigned as the trauma and casualty ward.

Requisitioner information, which included the healthcare practitioner's name and professional society registration details (South African Nursing Council [SANC] or Health Professions Council of South Africa [HPCSA]), was used to assign the following professional types: (1) nurse, (2) medical

TABLE 1: Example of some rejection codes and rejection reasons used to assign the rejection status and rejection phase values in a lookup table for HIV serology samples.

Rejection code	Rejection reason description	Rejection status	Rejection phase
RSEP	Require separate specimen	Rejected	Pre-analytical
SPINS	Specimen insufficient	Rejected	Pre-analytical
NDLE	Not done: lab error	Rejected	Analytical
ONCOR	Not done: non-reportable result	Rejected	Post-analytical
CEGK	Electronic gatekeeping	Rejected	Pre-analytical

intern (IN) and (3) medical practitioner (MP). For example, requisitioner details that included SANC, IN and MP numbers were assigned as a nurse, intern and medical practitioner, respectively. Data that did not include the rejection reason description could not be categorised and were excluded from this study.

Rejection rate calculations

The RR were calculated using the formula:

$$\left(RR = \frac{\text{Rejections}}{\text{Total test volume}} \times 100\right) \quad \text{[Eqn 1]}$$

and reported as a percentage. The RR were analysed by process phase, health establishment, ward and healthcare professional.

Cost analysis

The cost analysis was performed to determine the cost per rejection for each phase of testing. All costs were obtained in South African rands (ZAR) and converted to United States dollars (USD) using an exchange rate of 14.60/$1.00. The accounting stance was assumed to be the provider of diagnostic services, and costs associated with overheads and laboratory management were excluded. For the pre-analytical phase, data generated from a local study that conducted a top–down costing of historical expenditure data for the 2019–2020 financial period for the CMJAH receiving office were used ($0.77 per registration). A pre-analytical cost per test was calculated using the assumption that on average 3.5 tests are requested per registration.

For the analytical phase (pre-analytical cost + analytical cost), the cost per test associated with the analyser, staffing, reagents and test consumables was determined. These costs were obtained from the Oracle Enterprise Resource Planning (ERP) system of the NHLS (Box 1). The Roche Cobas 8000 modular analyser (module e602; Roche Diagnostics, Basel, Switzerland) was provided through a service placement agreement, and thus the costs associated with the outright purchase, maintenance and servicing of the instrument are included in the reagent cost. All costing data were captured in Microsoft Excel for analysis.

For staffing costs (medical technologist – C2 grade), given the short sample preparation time, the time to perform the test (in minutes) was multiplied by the annual cost per minute, based on the assumption that HIV serology testing is offered on a 365-day running cycle (annual cost / 365). Similarly, for the post-analytical phase, the average time (3 min) for a registrar (D1 grade) to review and authorise the result on the LIS was used. All staff salaries were based on the NHLS cost to company (CTC) salary scales.

BOX 1: Itemised list of resources within the analytical phase of testing.

Itemized list of resources
HIV combi reagent and calibrator
HIV control
Clean cell buffer M 2 × 2 L
ProCell M
Probe clean M
Probe wash M
Assay tip/cup and waste box
Medical technologist (C2) (5 min)

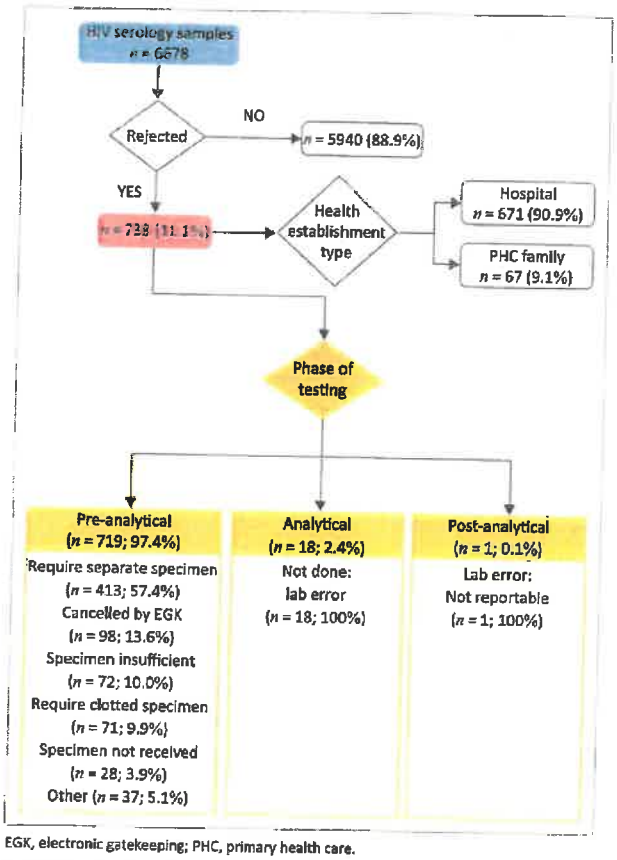
To calculate the total cost of rejection, the cost per test was multiplied by the total number of HIV serology rejections. Corporate warehouse data were provided as a CSV file used for preliminary analysis in Microsoft Excel. Descriptive analysis was conducted using TIBCO Statistica version 13.5.0 analytical software (California, United States).

Ethical considerations

The study was approved by the Human Research Ethics Committee, University of the Witwatersrand (clearance certificate number M201117).

Results

A total of 6678 HIV serology samples were received for the study period, of which 738 samples were rejected (11.1%). Among the rejected group, a mean age of 32 years was reported (standard deviation: 20.57), with the majority attributed to the adult population (560/738; 75.88%). Within



EGK, electronic gatekeeping; PHC, primary health care.

FIGURE 1: Rejection rates and criteria throughout the total testing process for HIV serology samples performed at the Department of Virology, National Health Laboratory Service, Charlotte Maxeke Johannesburg Academic Hospital, South Africa, between 01 June 2019 and 31 December 2019.

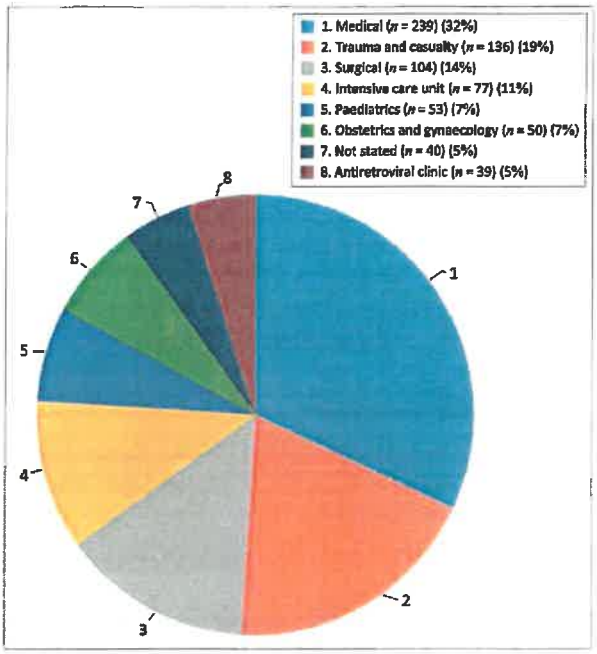


FIGURE 2: Pie chart displaying the percentage of HIV serology sample rejections by ward type at the Department of Virology, Charlotte Maxeke Johannesburg Academic Hospital, South Africa between 01 June 2019 and 31 December 2019. The intensive care unit metric includes both the adult and paediatric age categories.

the age group of 0–24 months, there were 106 rejected samples (14.36%). There were 671 (90.92%) and 67 (9.08%) rejected samples from hospitals and PHC facilities, respectively (Figure 1).

The majority (719/738; 97.4%) of rejections occurred in the pre-analytical phase, where most samples (413/719; 57.4%) were rejected because of the requirement for a separate sample (Figure 1). This was followed by rejections as a result of electronic gatekeeping (13.6%), SPINS (10%), requiring a clotted sample (9.9%) and specimen not received (3.9%). Other (5.1%) reasons for sample rejection in the pre-analytical phase included mislabelling, incomplete healthcare worker or patient information, and unsuitable samples. Eighteen (2.43%) samples were rejected in the analytical phase because of a number of laboratory errors, such as poor sample integrity, and one (0.13%) in the post-analytical phase because of a non-reportable result.

Based on the ward type, the medical unit had the highest number of rejections (239/738; 32%) followed by trauma and casualty (136/738; 19%), surgical (104/738; 14%) and ICU, which accounted for 11% (77/738) (Figure 2). The requirement of a separate sample was the most common reason for rejection across all departments, health facilities and age groups. Within this criteria, hospital samples accounted for 375/413 (90.80%) and clinics for 38/413 (9.20%) rejections. Transport of samples was a rejection criterion associated with clinic samples only (3/67; 4.47%).

Further analysis by health establishment and healthcare profession type revealed that, at hospitals, the majority of

TABLE 2: Number of HIV serology samples rejected, by health establishment and healthcare professional type.

Health establishment type	Healthcare professional type	Number of rejected samples (N =738)	
		n	%
Hospital	Medical practitioner†	543	80.92
	Intern	100	14.90
	Nurse	16	2.38
	Clinical associate	12	1.80
Total	-	671	100.00
Primary health care facility	Nurse	53	79.10
	Medical practitioner	11	16.41
	Intern	3	4.49
Total	-	67	100.00

Note: Data are reported for the Virology Department at the Charlotte Maxeke Johannesburg Academic Hospital, South Africa, between 01 June 2019 and 31 December 2019.

†, 'Medical practitioner' includes community service officer, medical officer, registrar and consultant.

TABLE 3: Itemised cost per sample for each phase of testing for HIV serology rejections.

Item in each phase of testing	Cost per sample (USD)
Pre-analytical	**0.22**
Collection and registration	0.05
Laboratory equipment	0.01
Staff	0.13
Operating costs	0.03
Analytical	**1.83**
HIV reagent pack	1.04
Buffer	0.26
Waste consumables	0.24
Staff	0.29
Post-analytical	**0.42**
Staff	0.42

USD, United States dollars.

TABLE 4: Determining the total cost of rejections for HIV serology testing across the three phases of testing.

Phase of testing	Cost of rejection per sample (USD)	Number of rejections		Total cost of rejections (USD)
		n	%	
Pre-analytical	0.22	719	82.6	158.18
Analytical	2.05	18	17.2	36.90
Post analytical	2.47	1	0.2	2.47
Total	2.47†	738	100.0	197.55

USD, United States dollars.

†, The total cost is calculated incorporating the itemized cost in all three phases of the total testing process (based on a single rejected sample).

rejections were requested by medical practitioners (543/671; 80.92%). In contrast, interns, nurses and clinical associates accounted for the remaining 19%. For PHC facilities, 79.1% of rejections were requested or collected by nursing staff (Table 2).

Table 3 summarises the itemised costs for HIV serology by testing phase. The total cost per sample for the pre-analytical phase was calculated to be $0.22. The bulk of the pre-analytical costs was for staff, at $0.13 per sample. For the analytical phase, a cost per test of $1.83 was reported. The HIV reagent pack contributed $1.04, compared to $0.50 for buffer and waste consumables. The staff cost contributions for the analytical and post-analytical phases were $0.29 and $0.42, respectively (Table 3).

The total cost per sample was calculated to be $2.47 across the three phases of testing. The total cost of rejections was $197.55 (Table 4). The pre-analytical phase contributed 82.6% of the

total cost of rejections ($158.18), followed by the analytical phase, with 17.2% ($36.90). Given the single post-analytical rejection, the total cost for that phase of testing was $2.47.

Discussion

In this study, we assessed the rates, reasons and cost of rejections for HIV serology tests at the Department of Virology at an academic hospital in South Africa over 6 months in 2019. Overall RR of 3.6% were reported for all test requests received during 2019 (CMJAH NHLS statistics, unpublished). This is consistent with other studies that reported similar average RR (0.1% – 3.49%).[12,13] However, the HIV serology RR of 11.1% reported in this study are significantly higher than reported rates and not aligned with the accepted internal test RR of < 5% set for Virology.

In the laboratory setting described, multiple reasons for rejection throughout the total testing process were noted. As reported in other studies, the pre-analytical phase was identified as the main phase of rejection, where 1 in 10 patients had a missed or delayed diagnosis, predominantly as a result of the requirement for a separate sample. This criterion is consistently noted as the most common reason for rejection in the data described here and highlights a gap in training on HIV serology sample collection for healthcare practitioners.

In addition, despite current EID guidelines, which recommend that an HIV DNA polymerase chain reaction (PCR) test be done from birth to 18 months of age, 14% of rejected tests fell within this age group. Our data identified that HIV serology tests are incorrectly requested within this age group, indicating a need for clinical training on guidelines and laboratory requirements for testing. It further underlines the importance of routine monitoring and analysis of the rejection criteria as a key quality indicator for continuous improvement.

This study also illustrates the laboratory's acceptability criteria and how strictly they are adhered to. Within the receiving laboratory, all staff are guided by the standard operating procedures for registration of a sample and the criteria for rejection. A large number of rejection criteria also fall within the clinical domain, over which the laboratory may not necessarily have influence and which requires tighter control with regard to the collection and requisition of samples by clinical departments. Other studies have shown similar findings, in that a large number of errors (pre-analytical) occur outside the laboratory and are caused by actions predominantly by the healthcare workers.[14] This is attributable to frequent staff rotation and substandard training. It is clear from the data of this study which healthcare personnel requested or drew samples that led to rejections and would benefit from additional training. All these aspects are clearly described in the NHLS handbook provided to hospitals and clinics. As such, these errors could have easily been avoided, subsequently eliminating a large percentage of rejections. It is important to note that the rejected tests originate mainly from the medical, trauma and casualty, and surgical wards, where timeous and accurate HIV results are important for clinical management of patients because of the high burden of HIV in South Africa.

In response to these findings, despite the lack of standardised rejection criteria amongst laboratory networks, appropriate corrective and preventative actions can be implemented, monitored and assessed. These include regular staff training and routine competency assessments directed towards key receiving office staff and healthcare workers. These training mechanisms will provide the greatest outcome in terms of RR reduction but should also be extended to all healthcare and laboratory workers. Laboratory manuals targeting key issues such as requesting a separate sample for HIV testing can avoid delays in turnaround time and patient management. Training on the current HIV and EID guidelines, as well as providing itemised rejections for a specific test set by ward, may also aid in the regular monitoring and evaluation of procedures, which will ensure good diagnostic practices.

Reduced RR may lead to improved patient care.[15] The impact of rejecting samples also has financial implications. The current study findings assessed the cost implications of these rejections. For one laboratory, an annual cost of $383.03 was reported.[16] When these data are extrapolated for national HIV serology testing across the NHLS for the 2019–2020 financial period (assuming 11.1% RR), the total cost of rejections amounts to $122 295. This signifies a substantial cost burden to the health system that could be avoided. Furthermore, the cost of rejections must be seen as a contributing loss within the broader healthcare system. Improving the efficiency of testing will have a twofold benefit, firstly providing a significant contribution to healthcare resource savings and secondly improving a key quality indicator that plays a pivotal role in maintaining high laboratory standards.[17,18] As the rejections occurred primarily within the pre-analytical phase in this study, it affirms that measures put in place through detailed rejection criteria by the NHLS also served to reduce the costs associated with performing unnecessary test or tests with compromised quality through the use of shared samples.[19]

The study limitations included a small number of unspecified rejection reasons from the data extract, as well as the rejection reasons being grouped into similar categories. This may have resulted in non-specific rejection codes being used that therefore did not necessarily accurately describe the rejection. The data from this study only take into consideration HIV laboratory-based testing and exclude a large volume of point-of-care testing performed at other health establishments. However, because of the availability of such data, this study recognises an opportunity to improve the analysis of RR if the data are managed properly and categorised in a more user-friendly manner. This will allow for laboratories to monitor their data over shorter time intervals and will lead to the timely identification of problem areas. This will encourage proactive measures to be implemented in order to reduce the overall number of rejections.

Conclusion

There are substantial data to suggest that inappropriate test use, rejections and repeat testing contribute to increased laboratory expenditure and unfavourable patient outcomes. Identification of the key RR is an additional tool to monitor laboratory

efficiency, improve service delivery and identify areas in the testing process that need intervention through corrective actions. Limiting rejections in the laboratory will save significant costs and time and improve the clinical utility of diagnostic tests, which will benefit the laboratory, patients and the healthcare system.

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Competing interests

The authors acknowledge no financial or personal relationships that may have inappropriately influenced them during the write-up of this article.

Authors' contributions

B.R. and Z.M. conceptualised the study. B.R. executed the research and data analysis. The first draft was reviewed by Z.M. N.C. provided input into the cost model and addition of key resources. Z.M, N.C and F.T reviewed the subsequent drafts, provided critical revision and feedback, and contributed to the overall standard of work.

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Data availability

The raw data were generated by the National Health Laboratory Services Corporate Data Warehouse. Derived data supporting the findings of this study are available from the corresponding author, B.R., upon suitable and fair request.

Disclaimer

The views expressed in this article belong to the authors and do not represent an official position of the associated institutions.

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Annexures

Annexure A

- Approved protocol

Annexure B

- Ethics clearance certificate

Annexure C

- Additional documents

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Dear Mr Bhaveshan Reddy

Master of Medicine in the Specialty of Virology: Approval of Title

We have pleasure in advising that your proposal entitled *Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

1922 2022

Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications

SUBMITTED TO THE UNIVERSITY OF WITSWATERSRAND,

Faculty of Health Sciences

In fulfilment of the requirements for the degree

Master of Medicine (MMed) Virology

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Co-supervisor: Dr F TREURNICHT- PhD

Date: 21/07/2020

1. INTRODUCTION

HIV is an epidemic associated with a high rate of morbidity and mortality especially in Sub-Saharan Africa and remains a serious global health challenge. Worldwide, over 36.7 million people live with HIV/AIDS and there are currently over 7 million people that are infected with HIV in South Africa (1). In the fight against HIV, the UNAIDS 90-90-90 treatment goals demonstrate how diagnostic testing forms a key step in managing HIV holistically. This strategy aligns well with South Africa's policy given the current national estimates of 20% to 30% of undiagnosed HIV infection (2). In line with the 90-90-90 targets, South Africa has adhered to the Universal Test and Treat Strategy with diagnostic testing again forming an essential link in the chain of management. With the implementation of these strategies and with accurate and reliable results being released from laboratories this has been shown to have direct effects in drastically reducing the mortality in Southern Africa and support in the fight against HIV (3).

The current South African HIV testing policy algorithm uses two HIV1/2 testing technologies: a serological based test for children older than 18 months and adults, while Polymerase Chain Reaction (PCR) should be used for children less than 18 months. One serological test is run as a screening test and if reactive, a different serological test is then run to confirm the result. If the screening test is non-reactive a negative result should be reported but the possibility of recent exposure must be considered.

These two testing methods are based on the Enzyme Linked Immunosorbent Assay (ELISA) and PCR a form of Nucleic Acid Amplification Technique (NAAT).

The Roche Cobas HIV Combi PT and the Abbott Architect HIV Ag/Ab combo are the two testing platforms for screening and confirmation used respectively at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The Cobas is an electrochemiluminescence immunoassay, while the Architect is a chemiluminesense immunoassay. Both are 4th generation ELISA in vitro qualitative assays which detect HIV1/2 antibodies as well as the P24 antigen (4). This has the added advantage of shortening the diagnostic window period and improves early detection of HIV. The performance characteristics of both testing platforms share a sensitivity of >99% (95% confidence interval) and specificity of >99%. This contributes to improved precision and accuracy of the test.

The National Health laboratory Service (NHLS) is a parastatal organization that serves up to 80% of the South African population. All laboratories in South Africa look to uphold the high standards set by South African National Accreditation System (SANAS) and International Organization of Standardization (ISO). These organizations are also responsible for continuously improving the quality of services that positively impacts on patient care (5). Criteria set out by these respective bodies state that sample testing is one arm in good management of a patient. The ISO defines laboratory error as "failure of a planned action to be completed as intended, or use of a wrong plan to achieve an aim, occurring at any part of the laboratory cycle, from ordering examinations to reporting results and appropriately interpreting and reacting to them" (6). Audits form part of this criteria and are a continuous process to ensure quality improvements within the lab and are measured against standards set by these local and international committees (7).

Patient care and safety has become increasingly more important in laboratory medicine and is not only confined to the clinical team assessing and managing the patient (8). A great deal of attention has been placed around quality assurance of laboratories and its effects on patient safety. One of the key contributing factors towards monitoring quality within a laboratory is rejection of samples (9). All laboratories are continuously striving to improve their rejection rates and in doing so are able to maintain their high levels of service and quality within the laboratory and towards the patient (10).

The total testing process is critical in identifying the reasons of rejection which includes the pre-analytical, analytical and post-analytical phases (11). Recent literature has shown that there are a number of factors contributing to the large rejection rates, many of which are reversible (12). A large percentage of rejections are attributed to the pre-analytical and analytical phase of testing. However, the majority occur within the pre-analytical phase and this accounts for up to 70% of laboratory errors (13). The rejection of unsuitable samples has a detrimental effect on both the patient and the laboratory. This results in delayed turnaround time, reduced productivity, poor workflow, costing and patient outcomes (14). Early awareness and detection of these factors can have a beneficial outcome to both the patient and the laboratory (15).

The pre-analytical phase of a diagnostic test refers to all processes essential to receive the requested sample from the patient to the actual analytical assay (16).
The laboratory has no direct control of this process. Some of the pre-analytical factors that can affect results include the following (17):

- Request form and patient information (labelling errors, incorrect information on request form and no health care worker credentials)

- Sample collection (inappropriate sample, insufficient volume, inappropriate sample container, specimen container empty)
- Sample transport (storage conditions i.e. temperature, sample lost or not received by laboratory)
- Others: Laboratory error, separate specimen required and no patient consent.

The most prevalent and repeated errors include haemolysis, clotting, insufficient blood volume, wrong sample tube and misidentification (18). These errors can account for a 6.4%-12% chance of inappropriate care (19). An error rate of this scale applied in a setting such as South Africa can apply tremendous pressure to an otherwise already financially constrained and resourced burdened public health sector (20). This can be further supported by studies that have achieved similar rejection rates. The main reasons for rejection were inappropriate clotting (30%) and inadequate sample volume (22%) (21). Only 51.7 % of their rejected samples were repeated and of those repeated samples, 5.1 % had results within critical values. Examination of patient folders showed that in 40 % of cases the rejection of samples had a direct impact on patient care (16). Projections have been made that show rejection rates will result in additional financial costs, poor patient outcomes and preventable repeat blood tests (22). Thus, identifying key reversible factors influencing high rejection rates in the laboratory will impact directly on healthcare costs and patient care (23, 24). This highlights the fact that a laboratory audit is an extremely valuable tool used in identifying errors within the laboratory (23).

Once identified, corrective actions can be implemented to ensure that a high standard of quality is maintained in accordance to the respective accreditation bodies. These

actions must be robust and incorporate factors within the total testing process that includes proper phlebotomy technique, correct transport and timely processing of samples to ensure not only good specimen integrity but also accuracy of test results (25).

International studies have estimated average costs of pre-analytical error in North American and European institutions. These costs ranged between R 2475- R3435 per month on average and 0.23% - 1.2% of total hospital operating costs (22). The impact of improved testing of HIV 1/2 serology will therefore have major benefits in terms of supporting clinicians in faster decision making and treatment and in doing so will have improved clinical outcomes (26). There will also be a cost saving benefit, as to run one sample requires many costly steps that is not always known to other health care workers who request these tests on a daily basis (27).

A multitude of reversible factors that directly affects patient care from initial assessment will be highlighted and once identified can create awareness to both the laboratory and clinical staff in order to reduce protracted hospital stays and persistent long term downstream effects (28). This has a major impact on the total operating costs within the health care budget that may not always be recognized and an opportunity to place these funds in an area of need to improve quality within the laboratory (13). Therefore, it must be understood that the real cost is not only financial but related to improved patient safety, efficiency, accurate and reliable results.

2. AIM

To identify factors that influence the HIV 1/2 serology rejection rates at Charlotte Maxeke Johannesburg Academic Hospital and cost analysis associated with it.

3. STUDY OBJECTIVES

- To identify reasons of rejection in HIV 1/2 serology tests conducted at CMJAH
- To determine the associated rejection rates
- Cost analysis associated with a rejected test

4. METHODS

4.1 Study design

This will be a retrospective audit study.

4.2 Study setting

This study will be conducted in the Virology laboratory of the National Health Laboratory Service (NHLS) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The Virology laboratory provides a service not only to CMJAH but also receives samples from other surrounding clinics and district level hospitals.

4.3 Study population

The study population will include all routine HIV 1/2 serology samples (adults and children) received, sent and rejected at CMJAH over the audit period. This will also include samples received by other referral clinics and hospitals.

4.3.1 Inclusion Criteria & Exclusion criteria

The study will include the following routine blood samples. Children >18 months and adults, drawn from any site on the body i.e. arm, leg etc, arterial and venous blood , from any department including wards and clinic, drawn by any member of the health care team. The following samples will be excluded from the study. Specimens that are

not analyzed at CMJAH, urine, stool, sputum, pleural fluid and ascitic fluid, any health care worker or staff member associated with the NHLS and /or University of Witwatersrand.

4.4 Sampling method

Routine daily samples that were received from CMJAH and surrounding clinics and hospitals. Samples will be audited over a 6 month period commencing from 1st June 2019- 31st December 2019.

4.5 Sample size determination

To determine an accurate sample size the confidence levels and margins of error should be used. Confidence level is an indicator of accuracy, whereas the margin of error is a range determined by your confidence level. A standard survey will usually have a confidence level of 95% and margin of error of 5% (29).

To determine an appropriate sample size that would enable an accurate assessment of rejection rates, the following formula was used (30):

$Z_{\alpha/2}^2 P(1-P)/d2 =$ **Sample size (n) = 1.96 x 1.96 x 0.5 (1-0.5) / 0.05x0.05**

n = 384

Sample size estimates for hypothesis testing are often based on achieving 80% or 90% power. The calculation used to determine the power is as follows:

$$p^* = p - 1.282 \sqrt{p(1-p)/n}$$

$$p^* = p - 1.282 \sqrt{0.9(1-0.9)/384}$$

$$= 0.88$$

Therefore, the power of the test is calculated to be 88 %. Although formal power calculations have been made, it should be noted that the sample size will be based on retrospective analysis of the database and inclusion criteria.

4.6 Data Collection

HIV 1/2 serology results will be extracted from the National Health Laboratory Service's Corporate Data Warehouse (NHLS CDW). This warehouse collects and stores results electronically which is then available upon request. Results will be extracted over the stipulated audit period and will include demographic data such as age and gender. Additional variables to be collected and analysed include the date period, total number of tests performed, test-set (HIV serology), reason for rejection, health establishment, department, as well as sample requested by and sample taken by. These variables will allow for analysis of centres who have different health care personnel and departments who are responsible for collection and requisition of HIV specimens. Rejection criteria to be assessed will be categorized in pre-analytical, analytical and post-analytical phases of testing.

Pre- Analytical			
Specimen not received	Unsuitable: Require blood specimen	Not tested: no HCW name/number	Unsuitable: clotted
Cancelled by doctor	Unsuitable: Require clotted specimen	Not tested: no patient ID	**Analytical**
Cancelled by gatekeeping	Unsuitable: Require separate specimen	Not tested: no patient number	Not tested: lab error
Not tested: no patient name/surname	Unsuitable: Specimen container empty	Unsuitable: Specimen not received	**Post - Analytical**
Not tested: info does not match	Unsuitable: Specimen insufficient poor quality specimen	Unsuitable: haemolysed	Lab error (non-reportable)

- The data collection tool will be a data capture sheet (see Appendix 1).

4.7 Data Analysis

Data collection and entry will be conducted by the researcher and reviewed by the supervisor for accuracy and completeness. A descriptive analysis using percentages and frequencies will be used to determine the overall rejection rate and rate of rejection for each stage of testing (pre-analytical, analytical and post-analytical). The Z-proportion test will be used to compare the differences in the percentages of rejection rates between the three testing phases. This will also be used to identify the most frequent reason(s) which led to overall rejection in HIV 1/2 serology tests and the most frequent reason(s) which led to rejection for each stage of testing. A look up table using Microsoft Excel™ will categorize data in: (a) location, e.g. healthcare facility/laboratory (b) reason for rejection, e.g. specimen unsuitable for analysis (c) sub-reason, e.g. sample haemolysed and (d) phase of testing, e.g. pre-analytical/analytical. Cross tabulations will be done between the rejection outcome and location, sub-reason and testing phase. The association of these factors with the rejection outcome will be assessed using the Chi-square test for independence. To quantify the associations, the odds ratios will be calculated together with their corresponding confidence intervals. For all tests, the level of significance will be set at 5%, and a p-value< 0.05 will represent statistical significance. All data analysis will be performed using STATISTICA™ analytical software.

4.8 Cost Analysis

A cost model reflecting laboratory losses based on rejection criteria and its correlation to the phase of testing will be done. This will incorporate both, major and minor laboratory costs which includes consumables used for testing such as blood collection tubes, request forms, syringes, cotton swabs and transport. Other expenditures such as

data capturing costs and loss in revenue with regards to down-time required to process repeat tests will also be modelled. These costs will be tabulated using Microsoft Excel™ and the cost per unit for each item will be determined by accessing the Oracle procurement purchase order. Costing of analytical factors such as reagents, test kits as well as other analytical resources will be taken into consideration and will provide a more accurate representation of the total cost of a repeated test. The cost model will be done per test and then calculated per month for the stipulated audit period. This will provide an estimated total laboratory cost for losses incurred by rejected tests.

5. ETHICS

Permission will be obtained from the data warehouse of the NHLS in order to obtain the number of samples received and criteria for rejection. No personal identifiers will be presented during this study. The data will only be extracted once the study has gained ethics approval from the Faculty of Health Science Ethics Committee at the University of Witwatersrand.

6. LIMITATIONS

The study is limited by pre-collected data that may be incomplete and not include all parameters that need to be identified according to the objectives outlined. This study is also limited to CMJAH and its referral centers and only includes routine samples.

7. FUNDING

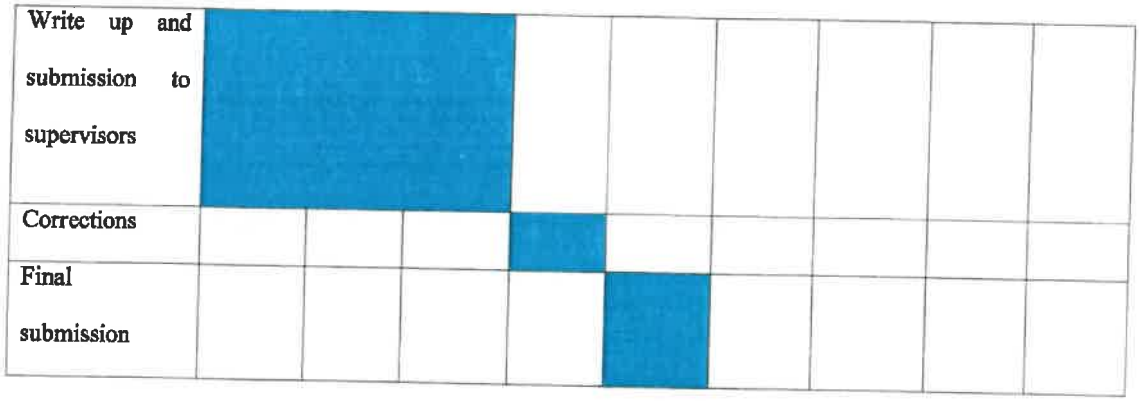
This study will not require additional funding as it will be a retrospective analysis of data from samples sent for routine testing. Other costs outlined in the table below are essential items that will be used during the collection and analysis of the data. Application of funding

will be made through the Universities academic research funding portfolio or the Virology academic research budget.

ITEM	COST (RAND)
Stationary	600
Biostatistician	1000
Communication	500
TOTAL	2100

8. TIMING

OUTLINE	MAR 2020	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV
Concept sheet & Literature review									
Protocol preparation									
Protocol submission & Ethics application									
Data collection									
Data analysis									
	DEC	JAN 2021	FEB	MAR	APR	MAY	JUN	JUL	AUG



9. DISSEMINATION AND IMPLEMENTATION OF FINDINGS

Access to this data will allow for effective interpretation in answering the main objectives. We will be able to depict rejection rates at CMJAH and specific referral centres and assess which phase of the total testing process is affected the most. We will also identify key rejection criteria and formulate a cost model which will determine the total cost of rejections. This will be conducted per test and then extrapolated as a monthly average during the audit period.

Once the study is concluded, the results of the study will be made available to the Department of Virology at CMJAH and the NHLS Virology Expert Committee. Key stakeholders will be better placed to identify significant rejection rate criteria and implement awareness and adjustment strategies in order to improve and strengthen the laboratory component in managing HIV more efficiently.

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APPENDIX 1

DATA COLLECTION SHEET

HIV1/2 SEROLOGY REJECTION CRITERIA

CHARLOTTE MAXEKE ACADEMIC JOHANNESBURG HOSPITAL

NHLS- VIROLOGY LABORATORY

DATE	SAMPLE NO.	TEST REQUESTED	HEALTH FACILITY	DEPARTMENT	AGE	GENDER

REJECTION CRITERIA	Pre- Analytical	
	Specimen not received ☐	Require blood specimen ☐
	Cancelled by doctor ☐	Require clotted specimen ☐
	Cancelled by gatekeeping ☐	Require separate specimen ☐
	Not done: no patient name/surname ☐	Specimen container empty ☐
	Info does not match ☐	Specimen insufficient ☐
	Not tested: no HCW name/number ☐	Specimen not received ☐
	Not tested: no patient ID ☐	Unsuitable: clotted ☐
	Not tested: no patient number ☐	Unsuitable: haemolysed ☐
	Not tested: no patient consent ☐	Duplicate registration (non-reportable) ☐
	Not tested: poor quality specimen ☐	
	Analytical	
	Not tested: lab error ☐	
	Post - Analytical	
	Lab error (non-reportable) ☐	

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr B Reddy

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201117

NAME: (Principal Investigator) Dr B Reddy

DEPARTMENT: School of Pathology
Department of Virology
Medical School
University

PROJECT TITLE: Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications

DATE CONSIDERED: 2020/11/27

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Drs Z Makatini and F Treurnicht

APPROVED BY: CB Penny
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2020/12/15

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in November and therefore reports and re-certification will be due in the month of November each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

11/01/2021
Date

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs

TO:	Dr B Reddy School of Pathology Department of Virology Medical School University E-mail: reddybavheshan@gmail.com
CC:	Supervisor: Drs Z Makatini and F Treumicht <Zinhle.Makatini@nhls.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2020/12/15
REF:	R14/49
PROTOCOL NO:	**M201117** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, **Bhaveshan Reddy** student number [**0603664G**], declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research Report.

Signature of Student: Bhaveshan Reddy.....**Date 11/4/2022**

Name of Primary Supervisor **Dr Zinhle Makatini**

.....

Signature of Primary Supervisor **Date** 11/4/2022

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications

Journal name, year, volume and page numbers: Southern African Journal Of HIV Medicine, Vol 23 No 1(2022).....

Authors	Name	Signature	Date
1st author	Bhaveshan Reddy		11/04/2022
2nd author	Naseem Cassim		11/4/22
3rd author	Florette Treurnicht		11/4/22
4th author	Zinhle Makatini		11/4/2022

Comments by primary supervisor:

.....

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Article 2: Title: .....

Journal name, year, volume and page numbers: .....

Authors	Name	Signature	Date
1st author			
2nd author			
3rd author			
4th author			
5th author			
6th author			

Comments by primary supervisor:

.....

.....

Article 3: Title: .....

Journal name, year, volume and page numbers: .....

Authors	Name	Signature	Date
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3rd author			
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5th author			
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Comments by primary supervisor:

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SAJHIVMED External Review Decision 1326 - Accepted for publication

6 messages

aosis@sajhivmed.org.za <aosis@sajhivmed.org.za> Fri, Nov 12, 2021 at 10:47 AM
Reply-To: "Dr David C. Spencer" <editor@sajhivmed.org.za>
To: Dr Bhaveshan Reddy <reddybhaveshan@gmail.com>
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****

Dear Dr Reddy

Thank you for this submission. I think that your article has something to say to the community of health care providers and am happy that you followed your reviewers suggestions. These have enhanced the final read of your manuscript. Congratulations, your paper will be going forward for publication. Sincerely, Dave Spencer Editor-in-Chief.

The journal has a double-blinded peer review process and your manuscript was assessed by two expert independent reviewers. Read our peer review process https://aosis.co.za/policies#peer_review.

Thank you for your revised manuscript. We have reached a decision regarding your submission. I am pleased to inform you that your manuscript has now been accepted for publication.

The Editorial Office will contact you by 19 November 2021 to finalise your manuscript for the Finalisation and Publication Office. If you need any assistance, kindly contact the Editorial Office at submissions@sajhivmed.org.za with any questions or concerns.

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Naseem Cassim <naseem.cassim@wits.ac.za> Fri, Nov 12, 2021 at 10:54 AM
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Original Research

Factors influencing the high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and the cost implications

Bhaveshan Reddy, Naseem Cassim, Florette Treurnicht, Zinhle Makatini

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Abstract

Background: HIV enzyme-linked immunosorbent assay (ELISA) is one of the most requested test sets within Virology and forms an essential part of patient management. Assessment of the rejection criteria is a key quality indicator, crucial for improving laboratory services and efficiency to ensure accurate and reliable results.

Objectives: The aim of this study was to identify the factors that influence the HIV 1/2 serology rejection rates (RR) at Charlotte Maxeke Johannesburg Academic Hospital and to evaluate the associated costs.

Methods: A retrospective study was conducted (June to December 2019) to identify the RR and rejection criteria of HIV serology samples throughout the total testing process. Descriptive analysis using percentages and frequencies was used to analyse the RR by phase, health establishment, ward and healthcare professional. A cost analysis incorporating minor and major costs was modelled in each phase of testing, and the total cost of rejections was calculated.

Results: A total of 6678 tests were received, and 738 were rejected (RR = 11.1%). The pre-analytical phase contributed significantly to the overall RR, with the requirement of a separate sample (57.44%) the most common reason for rejection. The total cost per rejected test was $2.47, which amounted to a total rejection cost of $197.55, of which $158.18 was caused by the pre-analytical rejection criteria.

Conclusion: High RR of HIV tests were noted, resulting in significant cost wastage. Identification and analysis of rejections must be implemented across all laboratories to improve the efficiency of testing, provide a cost-saving benefit and maintain high laboratory standards.

Keywords

HIV; rejection rates; cost analysis; laboratory; diagnostics

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11 April 2022

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Dear Sir/ Madam/ Prof/ Dr

Re: Dr Bhaveshan Reddy submission of MMED (Virology) by publication

This is to confirm that I, Bhaveshan Reddy, have successfully published the following article titled: **Factors influencing high rejection rates of HIV 1/2 serology samples at Charlotte Maxeke Johannesburg Academic Hospital and cost implications.**

This article has been accepted by a DoHET accredited journal: Southern African Journal of HIV medicine. This is to confirm that the first author is Dr Bhaveshan Reddy and this to confirm that the documents herewith in are to accordance of the format for the submission of a publication in lieu of a research report for the MMED qualification. The supervisors and co-authors have read and are in agreement with the submission of the MMED manuscript.

Please see attached requested documents.

Dr Bhaveshan Reddy
1st Author

Dr Zinhle Makatini
Main Supervisor

Dr Florette Treurnicht
Co-Supervisor and HoD

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Date: ___11/04/2022_____

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