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Successful Use of Near Point-of-Care Early Infant Diagnosis in NAMPHIA to Improve Turnaround Times in a National Household Survey

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Abstract

Background: In the Population-based HIV Impact Assessment (PHIA) surveys, early infant diagnosis (EID) was provided to infants <18 months without a prior diagnosis. For the Namibia PHIA (NAMPHIA), the GeneXpert platform was assessed for the feasibility of near POC EID testing compared to the Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) platform and to implement quality assurance measures for rapid turnaround time to improve EID results reporting.

Methods: NAMPHIA participants were screened for HIV exposure using Determine HIV-1/2 rapid test; samples reactive on Determine received EID testing on the GeneXpert instrument and Xpert® HIV-1 Qual assay using whole blood. Results were confirmed at the Namibia Institute of Pathology using dried blood spots on the Roche CAP/CTM platform per national guidelines.

Results: Of the 762 screened infants, 61 (8.0%) were Determine-reactive and considered HIV-exposed. Of the 61 exposed infants, 2 were found to be HIV-infected while 59 were negative on both GeneXpert and Roche platforms, achieving 100% concordance. Average turnaround time was 3.4 days for the Xpert HIV-1 Qual assay, and average time from collection to testing was 1.0 days for GeneXpert compared to 10.7 days for Roche. No samples failed using GeneXpert while 1 failed using Roche and was repeated.

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Conclusion: Quality POC EID testing is feasible in a national survey through extensive training and external quality assurance measures. The use of decentralized POC EID for national testing would provide rapid diagnosis and improve turnaround times which may prevent loss-to-follow-up, ensure linkage to care and improve clinical outcomes for infants.

Keywords

HIV-1; early infant diagnosis; point-of-care; GeneXpert; population-based surveys; turnaround times

INTRODUCTION

Of the 38 million people living with HIV in 2019, 1.8 million were children (aged 0 – 14 years).[1] Access to early infant diagnosis (EID) and treatment leads to an increase in survival of HIV-infected children.[2] HIV remains a leading cause of adult morbidity and mortality in Namibia, which continues to have one of the highest HIV prevalence rates in the world at 12.6% [95% CI: 11.7-13.5].[3] There had been no national-level, population-based studies that have included pediatric HIV prevalence in Namibia before the 2017 Namibia Population-based HIV Impact Assessment (NAMPHIA) survey. NAMPHIA addressed this gap by estimating the national HIV prevalence in children 0-14 years using early infant diagnosis (EID) testing for all HIV-exposed infants.

National HIV Guidelines in Namibia recommend a nucleic acid test (NAT) for all higher risk infants defined as: born to women with HIV infection who have received less than 4 weeks of ART at the time of delivery; or born to women with HIV infection with viral load (VL) >40 copies/mL in the 3 months prior to delivery or VL unknown; or born to women with HIV infection diagnosed during labour and delivery, post-partum or in the breastfeeding period.[4] The national EID testing guidelines are based on collection of dried blood spot (DBS) samples at health facilities and sending the samples for molecular testing to a centralized laboratory, the Namibia Institute of Pathology (NIP), in Windhoek, Namibia. This protocol requires an efficient sample collection, processing and transportation network to the central laboratory, maintenance and calibration of laboratory equipment, skilled personnel, and data-reporting infrastructure.[5,6] Longer travel distances to NIP, sample batching at the collection facility due to transport constraints, and batch testing on larger conventional molecular instruments can contribute to delays. While the actual molecular testing may only take a few hours, the time for sample collection, storage, transportation, processing, and return-of-results to the health care facility can result in turnaround times (TATs) that are long and unpredictable.[7-11] These delays can increase mortality rates in untreated HIV-infected infants, reduce the effectiveness of or delay antiretroviral treatment (ART), and lead to poor linkage to care.[2,12,13] The 2009 Children and AIDS: Fourth Stocktaking Report showed that almost 50% of infants tested for HIV never received their test results.[14] The World Health Organization (WHO) has encouraged the study of point-of-care (POC). HIV testing platforms and has recommended that ART be initiated in infants with an initial positive virological test result.[15-19]

Near POC NATs are performed closer to the patients and sample collection, at regional or district laboratories rather than a central laboratory. This has the potential to shorten TATs and lessen loss-to-follow-up as it reduces the number of steps needed for centralized testing. The Cepheid Xpert HIV-1 Qual assay received WHO-Prequalification for EID in June 2016 and is a qualitative *in vitro* diagnostic nucleic acid test performed on GeneXpert systems. This platform has shown good sensitivity (98.67%) and specificity (100%) among adults and older children, as well as infants in Elizabeth Glazer Pediatric AIDS Foundation (EGPAF)/ Clinton Health Access Initiative (CHAI)-supported routine EID testing in 14 countries; however, the utility of this test has not been evaluated in a national household survey in Sub-Saharan Africa.[20-26] For NAMPHIA, the GeneXpert platform was used to assess the feasibility of near POC EID testing compared to the Roche COBAS AmpliPrep/COBAS TaqMan (CAP/CTM) testing at the central laboratory.

Due to the decentralized nature of testing, the use of near POC testing requires enhanced quality assurance measures for the increased number of instruments, appropriately trained staff, and the variable communication and data transport conditions.[27-29] Several guidelines with requirements for POC testing emphasize the need for quality management.[30-32] None of the studies have described the difficulties of managing quality assurance for POC testing and the logistics of instrument preparation, sample collection, training, and results reporting in HIV programs or national population-based household surveys. To determine the feasibility and effectiveness, we evaluated the use of the Cepheid Xpert HIV-1 Qual assay in parallel with the Roche CAP/CTM HIV Qualitative Test and a near POC quality management system to diagnose infant HIV infection.

METHODS

Study Design

The overall PHIA study design, consent and assent processes and laboratory methods have been described elsewhere[33]. Briefly, for the 2017 NAMPHIA survey, children in half the surveyed households were eligible for participation, with the consent of their parent or guardian. Participants less than 18 months of age had either a heel stick (<6 months) or a finger stick (6 to <18 months) to collect approximately 1 mL whole blood using an ethylenediaminetetraacetic acid- (EDTA-) coated microtainer (BD, Franklin Lakes, NJ) in the household. Determine HIV-1/2 rapid tests (RT) were then used to screen for HIV exposure using the whole blood sample. Determine screening for exposure was performed in the household on all participating infants, regardless of the mother's HIV status, before further EID testing; parents of infants who screened positive were counselled about the additional testing that would be required and the infants refered to care. The microtainers were transported to a satellite laboratory for immediate testing of Determine-reactive specimens on the GeneXpert instrument using the Xpert HIV-1 Qual assay (Cepheid, Sunnyvale, CA) and processing of all specimens into DBS samples (4-5 spots/card). DBS samples from HIV-exposed to infants were sent to NIP for testing on the Roche CAP/CTM platform using the COBAS® AmpliPrep/COBAS TaqMan HIV-1 Qualitative Test v2.0 (Roche Diagnostics, Mannheim, Germany) as per routine EID testing. All assays were performed according to the manufacturers' instructions.[34,35]

Assay Validation, Instrument Verification and Quality Management

Before implementing the Xpert HIV-1 Qual assay in Namibia for the first time, the assay was validated centrally at NIP using a 32-sample dried tube specimen (DTS) validation panel provided by CDC Atlanta, as described elsewhere.[36-38] The validation panel results were approved by the NIP Quality Management team. Next, the 18 GeneXpert instruments at the satellite laboratories throughout Namibia, which were already in use for tuberculosis and other testing, had to be verified for the Xpert HIV-1 Qual assay. The Xpert HIV-1 Qual assay definition file software was first loaded onto each instrument, followed by running a 16-sample DTS verification panel, prepared at CDC Atlanta containing 12 positive and 4 negative samples, on each instrument using the Xpert HIV-1 Qual assay according to the manufacturer's instructions. Since each satellite laboratory was activated at different times during the survey and at varying times post-verification, an 8-member activation DTS panel was run immediately prior to NAMPHIA sample testing to ensure the instruments were functioning properly and staff remained competent in testing. For quality monitoring throughout the survey, external quality controls (QC) were performed with each sample tested in each satellite laboratory on the GeneXpert instrument using DTS positive and negative controls. For the Roche assay, manufacturer controls and two CDC-provided DBS controls (positive and negative) were included in each run. Results were interpreted according to the manufacturer, NIP and NAMPHIA standard operating procedures (SOPs).

Staff Training

A University of California San Francisco (UCSF) NAMPHIA survey senior laboratory advisor was assigned to ensure adherence to the survey protocol and to review EID results. Fourteen satellite and 4 central NIP medical laboratorians received training on the Xpert HIV-1 Qual assay provided by CDC Atlanta trainers. The multi-day training used both didactic lectures and hands-on training on topics including sample testing, performing QC, maintaining instrument and software, and troubleshooting. Staff competency was assessed by completion of a blinded 3 sample DTS training panel..

Data Management and Return of Results

PHIA data management and return of result processes have been previously described.[39] For NAMPHIA, GeneXpert results were uploaded to the NAMPHIA data server that was operated by survey partner Westat under the supervision of ICAP New York and UCSF. The sample and QC results were reviewed for accuracy and approved by the UCSF senior laboratory advisor and NIP. After approval, all patient reports were printed at the satellite laboratory and returned directly to the family of the infant immediately. The GeneXpert results were confirmed by testing at the central laboratory using the Roche CAP/CTM instrument and if discrepancies were found, repeat testing was planned. Roche results were reviewed according to the NIP SOP and then also uploaded to the NAMPHIA data server. CDC Atlanta subject matter experts reviewed GeneXpert and Roche results for quality and to provide technical assistance before inclusion with survey results and analysis. The TAT metric was determined as the number of days from specimen collection to return of GeneXpert results to the infant's family. The time from specimen collection to testing was also calculated for both platforms.

RESULTS

To determine the feasibility and impact of near POC EID testing, we developed a system of quality assurance methods to ensure quality results throughout the survey (Table 1). Biosafety and management considerations were part of survey planning and development. Given that the Roche CAP/CTM HIV-1 Qualitative Test v2.0 was the only validated assay for EID testing in Namibia, the Xpert HIV-1 Qual assay had to be validated and approved for EID testing prior to survey start (see Table, Supplemental Digital Content 1, Xpert HIV-1 Qual assay validation results at NIP). The Xpert HIV-1 Qual assay passed validation using a panel with a wide range of viral loads (10^3-10^5 copies/mL) which confirmed that the Xpert HIV-1 Qual assay could reliably detect HIV-1 among HIV-exposed participants. Once approved, the GeneXpert instruments at the selected 18 satellite laboratories (see Figure, Supplemental Digital Content 2, map of the NAMPHIA laboratories locations) had to be verified prior to running survey samples. All 18 instruments passed the verification and were approved for survey use. A maximum of five satellite labs was operational at one time during the survey. All staff achieved competency after training, and competency was recorded (see Table, Supplemental Digital Content 3, staff competency results). External quality assurance materials were used throughout the survey to ensure quality testing with each survey sample. Continuous quality monitoring was achieved with multiple levels of results review to ensure quality testing and accuracy of results at all testing laboratories.

A total of 762 screened infants were included in the survey over a 6-month period. Of these, 61 infants were were reactive by the Determine HIV-1/2 rapid test (Figure 1). Of the 61 infants, 27 were males and 34 were females with the mean age of 4.9 months (Range: 0.0-15.0 months). Samples from these 61 HIV-exposed infants were tested immediately upon arrival at the satellite laboratories using the GeneXpert instrument, and 2 infants (3.3%) were found to be HIV-positive on the Xpert HIV-1 Qual assay. There were no survey specimens or external QC that failed during GeneXpert testing. The testing at the central laboratory on the Roche CAP/CTM platform using DBS samples confirmed the 2 HIV-positive and 59 HIV-negative GeneXpert results, resulting in 100% concordance between the two assays with no false positive results found. There was one specimen that failed during Roche CAP/CTM testing, resulting in a failure code of QS_INVALID, an instrument or software malfunction; the specimen was repeated and passed. All Roche external controls passed during testing.

Since the Roche testing confirmed the GeneXpert results with no discrepancies, they were not returned and only used to validate the results. Thus, to understand the potential difference in TAT, the time from sample collection to testing for both platforms was compared. The average time to test a sample on GeneXpert was 1.0 days (Range: 0.0-18.0 days), while it took an average of 10.7 days (Range: 4.0-30 days) on the Roche platform. Reducing TATs for EID results was the primary objective for using near POC testing in NAMPHIA. One major deviation from NAMPHIA participants ≥18 months involved returning laboratory results (in this case EID) directly to the family of the infant rather than to a health facility, to ensure results were received and linkage to care was provided quickly for the HIV-positive infants. All GeneXpert results were returned with a 100% completion

rate. The average TAT to return results from sample collection to the family using the GeneXpert was 3.4 days (Range: 0.0-24 days).

DISCUSSION

The implementation of routine GeneXpert POC EID testing in low- and middle-income countries is becoming more common given the widespread availability of the platform at decentralized laboratories for other testing purposes, such as tuberculosis.[20-24,40,41] This is the first study to implement near POC EID testing and return of results (ROR) of those POC results in a large, nationally representative household study that measures key HIV indicators, such as HIV prevalence, incidence and VL suppression levels. The main objective of using POC EID testing for NAMPHIA was to reduce the TAT and return HIV results as quickly as possible, allowing infants infected with HIV to be linked to care quickly.

To demonstrate near POC testing could reduce TAT for EID results, the time between sample collection and testing for GeneXpert was compared to central EID testing. The average TAT was 1.0 day for GeneXpert testing at the satellite laboratories and approximately 10.7 days for Roche testing at NIP. As noted above, one sample took 18 days from sample collection to testing and an additional 6 days to return the result to the family. This was due to the necessary reconciliation of a discrepent recording of the infant's HIV exposure status in the household, which led to a delay in testing, and the ROR required additional logistical planning as the field team had left the area. This emphasizes the need for high quality of data compilation in all areas which can indirectly impact return of results. In terms of ROR, it took an average of 3.4 days to return results directly to the infant's family when returning GeneXpert results compared to previously reported TAT of 11 days for centralized testing in Namibia.[7] Bringing EID testing closer to the collection site was a major contributor in the reduction in TAT. This also allowed for the use of whole blood which was loaded directly onto the Xpert testing cartridge without the need for further processing. The use of the Roche assay required DBS samples which added at least 12-24 hours to spot, dry and package, plus sample transport time to the central laboratory, before testing could begin. Our 100% ROR completion rate suggests the use of decentralized EID testing in both survey settings and in a national HIV EID program can markedly improve TATs and increase ROR compared to the TATs greater than 30 days and 45% loss to follow up before ROR seen across Sub-Saharan Africa.[14] This could result in faster linkage to care and treatment, and improved outcomes for HIV-infected infants.[42-44]

Introducing a new assay to the country required extensive legwork to validate the assay at the central laboratory, train staff and verify all instruments at the satellite laboratories prior to survey sample testing. Each of these steps, along with multiple levels of data review and approval, confirmatory testing on the Roche platform, and QA/QC measures for each run on the GeneXpert, ensured that accurate results were returned to study participants. The misdiagnosis of HIV infection status by false-positives could have major implications for infants, their families and their communities because of the burden of an unnecessary ART regimen and undue stress and stigma. False-positives can cause severe legal and financial

problems for the HIV program because of the financial commitment to needless life-long treatment and stresses the importance of high quality testing.[45,46]

NAMPHIA was the first nationally-representative household-based survey where near POC EID testing was used and results returned directly to the participant's family. In extrapolating feasibility to the national EID testing program, one of the study limitiations was the sample size where only 61 infants were EID tested with GeneXpert and confirmed by the Roche assay. A larger sample size, including more than 2 HIV-positive samples, may be required by countries to validate the use of the Xpert HIV-1 Qual assay or other POC EID assays on different platforms. Some HIV-exposed infants may have been missed because virologic testing was conducted only among those infants with a reactive rapid test. However, given that only 2 out of 61 (3.3%) HIV-exposed infants were found to be HIV-positive in NAMPHIA it is unlikely that HIV-exposed infants were missed, because with a low overall prevalence of 0.19% (95% CI: 0-0.46) for 0-18 months there is a high negative predictive value.[45-47] These results indicate the success of the PMTCT program in Namibia, and further validate that Namibia has one of the lowest mother-to-child transmission rates according to UNAIDS.[3,47,48]

The implementation of POC testing services for EID in surveys and national testing programs should consider the proper placement of the GeneXpert platforms based on testing volumes, reliable sample and result transport systems, existing laboratory networks and the human resource capacity for optimum patient outcomes and cost effectiveness. NAMPHIA demonstrated that through a combination of training, instrument verification, implementation and monitoring of external quality assurance measures, and supervision, quality point of care testing can consistently be achieved. The use of decentralized POC EID for national testing may be possible and could provide rapid diagnosis and improved turnaround times, which may prevent loss-to-follow-up, ensure linkage to care and improve clinical outcomes for infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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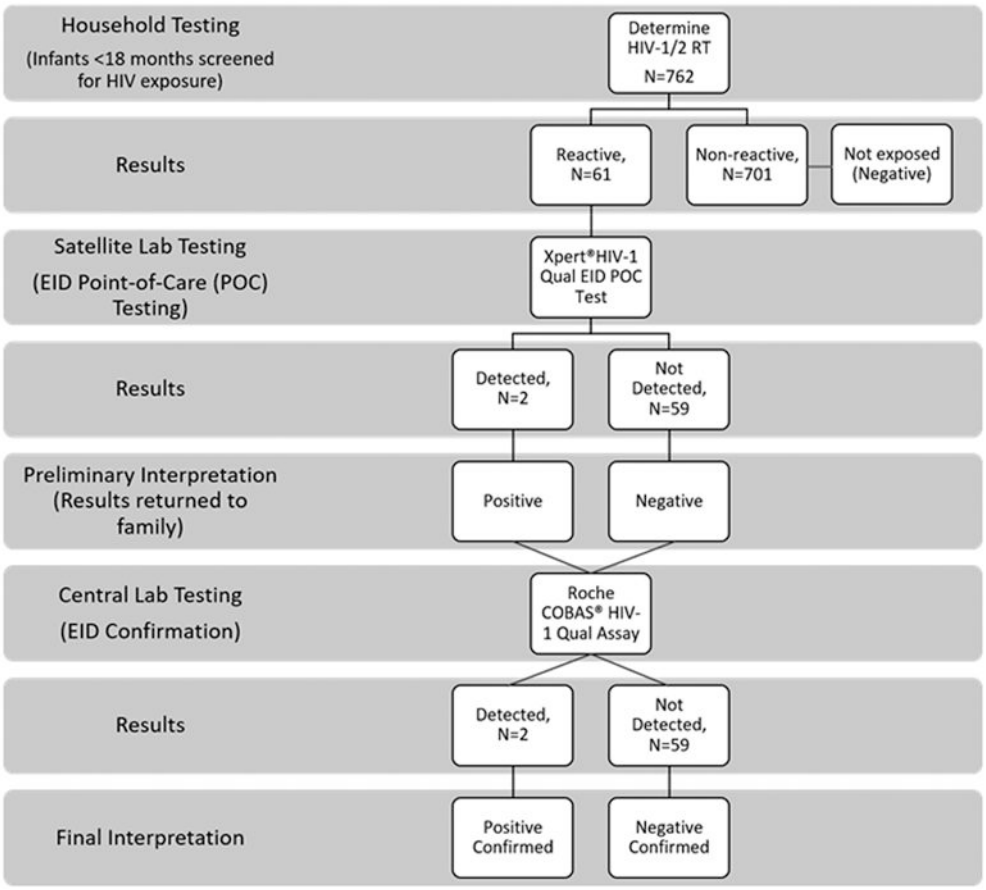

FIGURE 1.
Flowchart of Early Infant Diagnosis (EID) testing process for the NAMPHIA survey.

Table 1.

Description of various quality assurance measures implemented during the NAMPHIA survey for Early Infant Diagnosis (EID) using the point-of-care GeneXpert platform

Quality Assurance Activity	Assessment Metrics	Duration	Frequency
Assessment of Infrastructure and Waste Management	Electrical capacity, water, dust, secure storage, autoclave or incinerator functionality	1 week to 1 month	Once prior to survey start
Instrument Mapping	Number of instruments at site, functionality, available testing capacity, maintenance service contracts	1 week to 1 month	Once prior to survey start
Assay and Instrument Verification	16-sample DTS panel of 3 varying HIV-1 viral load concentrations alternating with an HIV-1 negative sample in quadruplicate	1 week to 1 month	Once prior to survey start
Training and Competency Assessment of Testing Staff	Hands-on training of maintenance, testing procedure, job aids, training panels and DTS competency panels	Up to 1 week per testing site	Prior to survey start and/or when new testers are hired
Instrument Activation Panel	8 DTS samples per instrument	Up to 1 week per testing site	Once immediately before start of survey testing at each site
Development and Verification of Quality Assurance Materials	Creation of DTS samples at CDC Atlanta and verification using the Roche reference method	2 weeks – 1 month	Once prior to survey start
Testing of Quality Assurance Materials	One HIV-1 positive and one HIV-1 negative external validated control	Length of survey	At least once per week or on each day of testing
Review of Quality testing Indicators	Monitoring of Quality Assurance controls, number of failed tests, instrument errors, operator performance, ROR	Length of survey	Continuous, at least bi-weekly