Title: The potential for quality assurance systems to save costs and lives: the case of early infant diagnosis of HIV.

Abbreviated title: The potential costs and impact of averting misdiagnosis in point of care testing

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Key messages:

- Although point-of-care HIV testing is critical for expanding access to infant HIV diagnosis, misdiagnoses and associated excess costs can be substantial, and stock-outs and screening interruptions lead to substantial missed cases.
- The study examines the cost-effectiveness of quality assurance systems for early infant diagnosis in five African countries with varying health systems and HIV prevalence rates.
- Our study helps to inform countries, programmes and key stakeholders on the cost of quality monitoring systems and highlights the value of implementing sustainable programs to ensure accurate and uninterrupted diagnostic testing.

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ABSTRACT

OBJECTIVES: Scaling up of point-of-care testing (POCT) for early infant diagnosis of HIV (EID) could reduce the large gap in infant testing. However, suboptimal POCT EID could have limited impact and potentially high avoidable costs. This study models the cost–effectiveness of a quality assurance system to address testing performance and screening interruptions, due to e.g. supply stockouts, in Kenya, Senegal, South Africa, Uganda, Zimbabwe, with varying HIV epidemics and different health systems.

METHODS: We modelled a quality assurance system raised EID quality from suboptimal levels: i.e. from misdiagnosis rates of 5%, 10% and 20% and EID testing interruptions in months, to uninterrupted optimal performance (98.5% sensitivity, 99.9% specificity). For each country, we estimated the 1-year impact and cost-effectiveness (US$/DALY averted) of improved scenarios in averting missed HIV infections and unneeded HIV treatment costs for false positive diagnoses.

RESULTS: The modelled 1-year costs of a national POCT quality assurance system range from US$69,359 in South Africa to US$334,341 in Zimbabwe. At the country-level, quality assurance systems could potentially avert between 36 and 711 missed infections (i.e. false negatives) per year and unneeded treatment costs between US$5,808 and US$739,030.

CONCLUSIONS: The model estimates adding effective quality assurance systems is cost-saving in four of the five countries within the first year. Starting EQA requires an initial investment but will provide a positive return on investment within five years by averting the costs of misdiagnoses and would be even more efficient if implemented across multiple applications of POCT.

Introduction

Point-of-care testing (POCT) is critical for expanding access to diagnosis in low- and middle-income countries (LMIC). In the case of early infant diagnosis of HIV (EID), POCT can be performed by lay providers, primary care nurses or non-healthcare professionals in decentralised and remote locations(1, 2). POCT allows infants to be tested and receive their results during the same visit, thus can be linked to care more quickly and effectively to antiretroviral treatment (ART), potentially reducing loss-to-follow-up (LtFU) (3, 4). There is increasing evidence of the cost-effectiveness EID: for example, EID with immediate ART for Thailand(5), and POCT for EID for Zimbabwe(6) although it is not clear if quality assurance has been incorporated into these EID programs.

Innovation in rapid HIV virologic POCT has the potential to reduce the 'gap' in EID (infants born to HIV-positive women and tested for HIV-infection as a percentage of all infants born to HIV-positive women), which ranges from 13%-58% across Kenya, Senegal, South Africa, Uganda and Zimbabwe(7, 8). Although decentralised EID using dried bloodspot specimens is widely available in Africa, return of results can be slow, from weeks to months(9), and cause delays in initiating ART and ultimately to high rates of loss-to-follow up(10). For EID, this is particularly detrimental: HIV progression is rapid in undiagnosed infants(11); 30% will die by one year of age and 50% by two(12). In contrast, diagnosis at six-weeks of age with immediate ART initiation for HIV-positive infants leads to reductions in mortality and HIV progression(13).

However, the rapid expansion of POCT is also sometimes associated with suboptimal screening programme performance. This can be caused by poor performance of the

diagnostic itself, the person implementing the test or screening interruptions due to instrument down-time and stock outs(14). In a review of HIV testing quality among adults, more than a third reported user errors and poor management systems, resulting in misdiagnoses(15). To our knowledge, there are no data on misdiagnosis in infants. Misdiagnosis of HIV among infants carries significant consequences. False positive results lead to stigmatisation and infants being incorrectly treated with ART, potentially for life. The consequences of unnecessary ART treatment include drug toxicity, burden of care on patients and wasted resources. Conversely, false negatives, including infants who are not screened at all, lead to missed diagnoses and potential death among HIV infected infants. Given the remote settings in which POCTs are frequently used with limited access to confirmatory testing, it is even more critical to ensure correct results by monitoring testing quality through an external quality assurance (EQA) system. EQA adds an objective external measure to quality assurance systems. The system also focuses on opportunities for improvement by identifying problems throughout the testing system and providing corrective action.

While POCT brings great opportunities for reaching those with limited access, decentralisation also brings challenges of supply chain management, where the lack of a single testing component can interrupt testing for significant periods. A good quality assurance system, which may extend to connectivity (i.e. connecting diagnostic platforms with a central database), would enable testing interruptions to be identified in real time and supply issues to be rapidly corrected. Even without connectivity, the increased supervision provided through the quality assurance system may support health workers to better recognise the adverse health impact of treatment interruptions, thus improve their supply chain management.

Quality assurance systems, including EQA, with consequent corrective action is critical if decentralized testing is to be adopted(16). EQA programmes typically include external proficiency testing programs (where providers' proficiency is evaluated on a panel of four to six samples with known results), visits from external experts or retesting of a subset of specimens in a laboratory(17). However, at present there is no regional provision of quality assurance systems for HIV EID POCT, nor are there established norms for the size of proficiency panels or cut-offs to trigger corrective actions. This is critical because, for example, on a panel of five samples, one incorrect result can be considered to translate in clinical practice into a 20% misdiagnosis rate. While generally, quality assurance systems are considered important, the question of affordability is not resolved. Eaton showed that high costs of ART among adults with false positive HIV diagnoses quickly outweighs the cost of confirmatory testing prior to ART initiation(18). Dunning also explored the cost-effectiveness of confirmatory testing at ART initiation to reduce false positive infants on ART and showed how this varied by HIV prevalence(19). While confirmatory testing can reduce inappropriate ART initiation, it does not address missed cases due to screening interruptions or poor quality.

The aim of this study was to model the incremental costs and cost-effectiveness of adding a quality assurance system, including EQA, onto EID POCT programmes in five African nations with varying HIV epidemics and responses. To the best of our knowledge, this is the first study to address the potential cost-effectiveness of improving diagnostic quality. We examined the impact on hypothesised rates of misdiagnoses in scenarios where HIV POCT was widely used for EID, but had no quality assurance system. We contrasted this with the implementation of a quality assurance system that is hypothesised to maintain high sensitivity and specificity of POCT EID, i.e. be as good as during a field based evaluation in

Mozambique (1). Although supply chain management is not within the conventional remit of EQA, in many countries, health care workers are often tasked with request supplies and initiate testing(20). Where these falter, the health consequences to infants are often unseen. To demonstrate the impact of not screening, we also modelled the impact of screening interruptions, where these may be alleviated within the quality assurance system's supervisory activities, i.e. checking for interruptions in screening in the patient registers and inventory management (20).

Methods

This analysis estimates the costs of introducing national quality assurance system, with EQA, and models the incremental benefit of the quality assurance system in terms of averted DALYs and treatment costs to generate the incremental cost-effectiveness ratios (ICER) and thresholds for cost saving and cost-effectiveness.

Quality assurance system and corrective action scenarios

Two three-day consultations/workshops with key stakeholders, including members of national reference laboratories, QA manager and clinicians, were held aimed at strengthening quality-assurance systems in Africa, including POCT for EID. In breakout groups, participants prepared qualitative descriptions of the specific processes they wanted to cost, thinking about the resources needed at each step. Training was provided on how to collect and analyse cost data. Following the consultation, participants costed a quality assurance system that provided blinded proficiency testing panels, scored reports, and corrective action that would correct to any supply chain problems. For other components, participants

modelled the system and associated costs as suitable in their situations. Because neither POCT EID nor a quality assurance system were available at the time of the consultations, costs were modelled from existing data sources, primarily point-of-care platforms for CD4 quantification, in each respective country. The differences between the quality assurance system, including EQA and corrective action, across countries were reflected in the variations across their costs. The number of POCT sites modelled to receive the quality assurance system varied from 36 in Senegal to 360 in Zimbabwe (Table 1), with the total annual EID tests performed estimated to range from 1,800 in South Africa to 50,000 in Uganda. Though countries planned varying frequency of quality assurance system monitoring rounds, for the purpose of this paper these rounds have been standardised to two annually. The approaches to modelling corrective action also varied according to additional supervisory visits (1-2), instrument maintenance (0-1), machine replacement (0-1), refresher trainings (0-1), as well as variations in prices. After these costs were collected, participants were led through the cost analysis and modelling with support from an experienced economist (STR).

Cost estimations

Costs were estimated from a provider's perspective over a one-year period. All costs are presented in 2016 US dollars (US$). Data were collated between March and May 2016 across Kenya, Senegal, South Africa, Uganda and Zimbabwe. The ingredients-based costing categorised cost inputs as: one-off start-up (mainly training), capital (equipment and vehicles), recurrent (supplies, transport and staff) at both reference laboratory and clinic level and by quality assurance system activity. Standardised cost assumptions across countries were the diagnostic platform costs US$20,000, a diagnostic cartridge costs US$20 (one needed per EID test), and single three-member panel is needed for checking testing

performance at each site per quality assurance monitoring round (US$10 each). A 10% wastage rate was applied to the supplies used.

The Model

An excel spreadsheet model was developed as a transparent approach for countries to explore the potential impact of a quality assurance system in terms of improved identification of HIV infected infants (i.e. reducing false negatives) and reduction in costs associated with not treating HIV negative infants (i.e. reducing false positives). This model is available upon request. Table 2 presents eight key country specific inputs needed, each of which can be varied as appropriate to test alternative assumptions. The model assumes that not all infants born to HIV-infected mothers would have access to EID; they need to be born to mothers who access antenatal care (ANC). Within the model, a choice can be made to model coverage of POCT EID to: only be introduced where there is a gap in EID coverage, i.e. infants born to HIV-infected mothers who attended ANC and had no EID ("the gap"), or to replace current EID, i.e. the current feasible coverage. This paper focusses on the using EID to close the gap only. Infant linkage to ART was assumed not to be affected by EID method, however the model can accommodate changes to linkage for decentralised POCT as compared to centralised laboratory testing and is explored in the univariate sensitivity analysis. Costs of incorrectly treating HIV-negative infants can be captured over a 2, 5, 10 and 20 year period. Further details of the model are provided in Supplement 1.

The model was customised with country-specific costs and epidemiological data (Table 2) and allowed estimation of the benefit of introducing a quality assurance system under a number of common challenges in HIV testing programmes. For example, what is the cost-

effectiveness of the quality assurance system under misdiagnoses rates of 5%, 10%, 20%, or if programmes faced testing interruptions. Screening interruptions are modelled by in terms of a proportionate (months of screening interruptions/12 months) reduction in numbers of incorrectly treated infants and increase numbers of missed cases. This reduces the costs of excess treatment but increases DALYs lost by not identifying and treating HIV+ infants.

Sensitivity analysis

The model has a number of parameters that can be varied to explore their impact: treatment cost timeframe, duration of infant screening interruptions and discount rate. In the univariate sensitivity analyses, we varied the discount rate, numbers of years of treatment averted, duration of testing interruption and proportion of infants accessing ART and loss to follow-up (LtFU) on ART (on costs only). In the probabilistic sensitivity analyses, a Monte-Carlo simulation generated an incremental cost-effectiveness ratio (ICER) using a combination of values for: years of treatment averted (mean 10; range 2-20 years), variation in the costs of quality assurance system scale up (-25%/+100%), infant treatment costs (+/- 33%), discount rate (0%-10%). This process was repeated 1,000 times. Beta distributions were used for discount rates, and gamma distributions were used for infant treatment and quality assurance system cost.

Results

Costs

Capital costs captured a range of costs, including vehicles used for sample transportation, EID platforms, other equipment involved (e.g. pipettes for aliquoting), and the space used for

storage of supplies and equipment. Recurrent costs reflected both the scale of the quality assurance system (i.e. number of POCT sites receiving the quality assurance system monitoring visits) and the existing health infrastructure; South Africa, for example, has a postal system allowing samples to be sent in the mail, which is less costly than transporting in programme vehicles, as was planned in other countries. On average the cost per site per quality assurance system monitoring round ranged from US$345 in South Africa to US$1,095 in Senegal. These estimates account for differences in existing infant testing services and the assumption that POCT EID would only be introduced to fill the testing gap. South Africa currently has a high EID coverage, thus could have a relatively smaller POCT EID programme, while coverage of EID in Senegal is currently very low, requiring a far larger scale up of POCT EID to address the testing gap.

Effectiveness

Figure 1 compares the effectiveness of implementing a quality assurance system in each setting, where we compare an EID programme with no quality assurance system, assuming no quality assurance system results using a conservative misdiagnosis rate of 5%. In the 5% misdiagnosis base-case scenario, between 53 to 757 HIV infected infants would be missed for treatment each year (represented by the size of the outer circles in figure 1.1), and 6 to 942 infants could be incorrectly put on treatment depending on the country (represented by the size of the outer circles in figure 1.2). With our assumptions on sensitivity and specificity of POCT EID in the presence of EQA, misdiagnosis rates would decrease by 68% to 95%. However, even with a very strong quality assurance system, low levels of unavoidable misdiagnosis remain, with between 15 and 45 missed HIV+ infants and 2 to 47 infants

incorrectly put on treatment (represented by the size of the inner black dots in figures 1.1 and 1.2).

Cost-Effectiveness

Table 3 summarizes the cost and effectiveness of a quality assurance system for each country, where a quality assurance system is compared with a variety of base-case scenarios (5%, 10%, 20% misdiagnosis and one month testing interruption, i.e. missing the opportunity to test eligible infants). In all countries and scenarios, introducing a quality assurance system, even if solely servicing the EID programme, would likely be highly cost-effective or cost saving, ranging from $107 per DALY averted (5% misdiagnosis in Senegal) to a savings to the health system of over US$2.7 million in the 20% misdiagnosis scenario in Uganda.

A robust quality assurance system should also identify testing interruptions by assisting test providers to better manage their supply chain. If testing is not offered when the infant presents at the clinic the first time, be it for vaccination or other reasons, access to the infant is assumed lost. This is addressed in the model by translating testing interruptions into missed cases (last column in Table 3). This could avert between 1,686 and 21,095 DALYs in Senegal and Kenya, respectively.

Threshold analysis

For each country, a threshold reduction in misdiagnosis rate was estimated, above which quality improvements driven by an effective quality assurance system would result in the

programme saving costs. The decrease in misdiagnosis rate, regardless of the absolute misdiagnosis rates in countries, was 3.10% for Kenya, 0.91% for South Africa, 39.1% for Senegal, 1.38% for Uganda and 2.39% for Zimbabwe.

The model estimated the highest quality assurance system costs that would fully cover its own costs through saving excess treatment costs (i.e. the cost of treating false positives in settings without a quality assurance system minus the cost of treating false positives with a quality assurance system). This analysis can also be seen as evaluating space for error, specifically underestimation, of the cost of the QAS. At a 5% misdiagnosis rate, this was US$316,559 for Kenya, US$353,251 for South Africa, US$3,949 for Senegal, US$702,078 for Uganda, and US$656,845 for Zimbabwe. This equates to more than 152% of the modelled quality assurance system costs in Kenya, 4% of the costs in Senegal, 509% of the cost in South Africa, 345% of the costs in Uganda, and 196% of the costs in Zimbabwe, i.e. in most countries the estimated programme costs were well below the cost-saving threshold. This does not include benefits in terms of lives saved by correctly identifying HIV infected infants who would otherwise be missed.

Sensitivity analyses

Table 4 presents the univariate sensitivity analysis. The quality assurance system programmes were cost saving over a range of assumptions in the discount rate, numbers of years of treatment averted, duration of testing interruption, and proportion of infants accessing ART and LfFU. With the exception of Senegal, quality assurance system for EID remains cost-saving in all countries. The cost effectiveness planes for the five African nations are presented in Supplement 2, showing that the vast majority of runs in the sensitivity analysis fall in the south east quadrant, establishing that a quality assurance system, even if solely

covering the EID testing programme, is highly likely to be cost-saving, with the quality assurance system highly cost effective in Senegal.

Discussion

This paper illustrates the potential cost-effectiveness of introducing quality assurance systems alongside EID POCT roll out in five African nations to address the current screening gaps for EID while ensuring quality testing outside of the laboratory. We estimate the annual false negatives and false positives that could be avoided if a quality assurance system were included in each country. This translates directly into lives saved (by avoiding false negatives) and money saved (by avoiding ART costs of infants without HIV). Though each EQA round could cost between US$400 to US$1,500 per site, this investment is likely to avert between 36 and 711 missed HIV cases among infants, and even with modest rates of misdiagnoses (5%) could save up to 500,000 USD in averted health care costs attributable to treating uninfected infants. While it was not cost-saving in Senegal because of the low prevalence of HIV (with an HIV prevalence of 0.4%, only few cases of HIV in infants would be diagnosed and misdiagnosed, even in the absence of EQA), EQA was highly cost-effective. In the four countries it was cost-saving, even over the short timeframe of five years.

We also explore the impact of one symptom of health system that represent a number of operational challenges: screening interruptions. This can be due to higher level inventory distribution, clinic level stock management or health worker time constraints; there are a vast range of reasons the screening may not happen. While POCT aims to alleviate some health system constraints, the quality of the performance POCT services may still rely on these very

same health system constraints (21). A strong quality assurance system cannot be narrowly focussed on EQA but must include supportive supervision to identify and address challenges faced by health workers throughout the health system.

Limitations

This study has some limitations. First, there is scarcity of published data across settings for POCT for EID on the observed rates of misdiagnoses and the share of false positives and false negatives. To mitigate this, we modelled a range of misdiagnoses rates, with conservative rates as our central estimate, relative to a lower rate that would be achieved using EQA proficiency panels. There is however clear need for better information on misdiagnosis rates of POCT for EID in clinical settings and for POCT for other diseases. Moreover, the impact of identifying a problem is dependent on being able to correct it. Though costs of some corrective actions have been included (e.g. retraining of staff), other problems may be beyond the control of the quality assurance team. We assumed that six-monthly quality assurance activities would be sufficient to restore and sustain diagnostic accuracy, however future models may consider a waning effect on quality in-between EQA visits. Second, this analysis only accounts for the excess treatment cost associated with a false positive result, ignoring the costs of other HIV care and social consequences of a positive HIV test, such as long term effects of social stigma and possibly lower levels of investment in these infants(22). Third, though LtFU is commonly estimated around 20% per year, we explored this impact only in the sensitivity analysis for reducing treatment costs, because estimating the health impacts of LtFU at different ages is beyond the scope of this simple model. Additionally, we applied a simplified model of the consequences of a false negative HIV result, with some assumed to immediately re-join the treatment cascade and achieve

normal life expectancy and no disability, with others being lost for good, resulting in AIDS and early death. Though the prior is likely more optimistic than reality and the latter may be more pessimistic, this was chosen as a balance between simplicity and realism in the absence of observed data. Fourth, this analysis assumes all HIV transmission occurs prior to testing, which will depend on when current EID is being performed. Guidelines suggest EID at six-weeks, this analysis may then over-estimate the impact of POCT EID in identifying late infections(23). However, no consistent dataset was available to estimate only intrauterine, intrapartum and very early infections, though it is suggested to represent 80% of infant infections(23). This model aimed to be transparent while informative, and we have tested the impact of our assumptions in the PSA, which showed the results are robust to most assumptions(23).

Quality assurance system in practice: capitalising on economies of scope

This analysis applies the full costs of the quality assurance systems to a narrow intervention of EID testing. It is clear that a quality assurance system can achieve large economies of scope, where relatively small additional costs would be incurred to broaden the quality assurance system to address quality issues across the range of HIV testing, such as viral loads, adult HIV testing, as well as tuberculosis and malaria POCT programmes. This would greatly reduce single programme costs. Due to this narrow focus, this analysis has applied a very high cost-effectiveness bar for a quality assurance system. This is particularly relevant in low HIV prevalence setting such as Senegal, where there are relatively few infants needing testing for HIV, but a high incidence of malaria between .5% and 20% across the country's regions (24). Were the quality assurance system to span the full HIV testing programme and beyond (e.g. malaria), its cost-effectiveness would likely become cost-saving. Other higher prevalence countries would experience even greater cost-savings. While this analysis shows

that even a very narrow quality assurance system is highly cost-effective, in practice we recommend broader quality assurance systems.

Conclusion

This study demonstrates the impact and cost effectiveness of averting screening interruptions and improving quality of POCT testing for EID. If the quality assurance system reduces misdiagnosis from as low as 5%, it has potential to save lives and costs in most settings. The quality assurance system will be most cost saving in countries with high HIV prevalence or where current infant testing gaps are large. Implementing broader quality assurance systems across multiple POC diagnostics in lower prevalence settings will reduce single programme costs even further. Most importantly, when introducing POCT, ongoing support for their use is critical to ensure they fulfil their great potential for alleviating testing bottlenecks.

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513

Table 1 Total and average annual quality assurance system costs in 2016 USD

	Kenya		Senegal		South Africa		Uganda		Zimbabwe	
Cost Category	*USD*	*%*	*USD*	*%*	*USD*	*%*	*USD*	*%*	*USD*	*%*
Quality assurance system (QAS)										
Annualised Start-up Costs										
Central training	$5,130	2%	$12,320	12%	$12,230	18%	$23,541	12%	$22,304	7%
Personnel	$2,476	1%	$3,653	4%	$5,444	8%	$41,569	20%	$11,032	3%
TOTAL START-UP COSTS	***$7,606***	***4%***	***$15,973***	***16%***	***$17,674***	***25%***	***$65,110***	***32%***	***$33,336***	***10%***
Annualised Capital Costs										
Building and Storage	$484	0%	$533	1%	$279	0%	$333	0%	$3,609	1%
Equipment	$6,509	3%	$1,977	2%	$4,901	7%	$5,412	3%	$2,282	1%
Vehicles	$2,425	1%	$949	1%	$-	0%	$1,082	1%	$6,468	2%
TOTAL CAPITAL COSTS	***$9,418***	***5%***	***$3,459***	***3%***	***$5,180***	***7%***	***$6,827***	***3%***	***$12,359***	***4%***
Recurrent Costs										
Personnel	$91,458	44%	$22,481	22%	$16,215	23%	$66,900	33%	$95,691	29%
Supplies	$17,056	8%	$9,526	9%	$20,835	30%	$15,796	8%	$89,244	27%
Recurrent Vehicle and Transport	$34,016	16%	$18,869	18%	$-	0%	$12,264	6%	$2,884	1%
Building Operation and Maintenance	$37,522	18%	$160	0%	$2,166	3%	$2,544	1%	$40,204	12%
TOTAL RECURRENT COSTS	***$180,052***	***86%***	***$51,036***	***50%***	***$39,216***	***57%***	***$97,504***	***48%***	***$228,023***	***68%***
Corrective Action Costs	$11,457	5%	$32,385	31%	$7,288	11%	$33,888	17%	$60,623	18%
TOTAL ANNUAL COSTS	***$208,533***	***100%***	***$102,853***	***100%***	***$69,358***	***100%***	***$203,329***	***100%***	***$334,341***	***100%***
QAS costs in perspective										
Estimated number of EID tests	36,000		1,800		23,760		50,000		30,000	
Incremental $ of QAS / EID test	$5.79		$57.14		$2.92		$4.07		$11.14	
As percent of $20 EID test	28%		272%		14%		19%		53%	
Number of POCT sites	90		36		90		100		360	
$/ POCT site	$2,317		$2,857		$771		$2,033		$929	
Number EQA rounds/year	2		2		2		2		2	
Cost per POCT site/QA round	$1,159		$1,429		$385		$1,017		$464	

516 **Table 2** Country level inputs and intermediate estimates

Input	Kenya	Senegal	South Africa	Uganda	Zimbabwe	Source or formula
1. Pregnancies among HIV-infected women	69,000	2,300	250,000	95,000	63,000	(25)
2. Antenatal care coverage	96%	96%	97%	93%	94%	(8)
3. Accessible infants needing testing	63,030	1,924	213,620	102,630	64,653	=[r1]*(100%-[r2])
4. EID testing coverage	51%	23%	87%	48%	65%	(25)
5. EID testing gap for POCT	49%	77%	13%	52%	35%	=1-[r4]
6. Potential infants reached by POCT	20,780	1,618	28,609	50,324	33,584	=[r5]*[r3]
7. Access to treatment - Infant	41%	26%	49%	37%	38%	(25)
8. Access to treatment – HIV-infected pregnant women	76%	55%	95%	95%	93%	(25)
9. Perinatal HIV transmission rate:						(26); Average (risk_start ART during pregnancy, risk_ART start just before pregnancy)
9a. HIV-infected pregnant woman on ART	19.1%					
9b. HIV-infected pregnant woman not on ART	4.8%					
10. Perinatal HIV transmission rate among HIV+ mothers	17%	20%	4%	8%	12%	=[r8*r9a]+[(1-r8)*9b]
Annual paediatric HIV treatment cost (includes provision)	$329	$519	$898	$447	$898	Kenya (27), Senegal*, South Africa (28) Uganda (29), Zimbabwe [(30, 31) in (6)]
8. Life expectancy at age 2 (in years) **	64.7	68.5	63.8	62.3	62.6	(32)
9. Life expectancy at age 21 (in years)	48.6	51.1	46.3	38.5	46.8	(32)
Gross domestic product per capita (USD)	$1,358	$1,067	$6,482	$727	$965	(33)
Years of treatment costs averted	2, 5, 10, 20	2, 5, 10, 20	2, 5, 10, 20	2, 5, 10, 20	2, 5, 10, 20	

517 *[r] refers to input rows. For a full explanation of methods for estimating years of life lost and DALYs, see "The model" section, within "Methods". * personal*
518 *communication Moussa Sarr. **Life expectancy is for infants without HIV and used as a proxy for life years lost among infants living with HIV in the absence of ART.*

519 **Table 3** The potential costs, effectiveness and cost-effectiveness of implementing a quality
520 assurance system (QAS) in five African countries, compared to varying rates of misdiagnosis
521 (5%, 10%, 20%), and with 1-month of testing interruption. Negative costs signify cost savings.

		Programme scenarios without QAS			
	A programme with QAS	Misdiagnosis 5%	Misdiagnosis 10%	Misdiagnosis 20%	1-month testing interruption & 5% misdiagnosis
Kenya					
Cost of QAS ($)	US$208,532				
Cost of treating false positive infants ($)	$20,206	$336,765	$673,531	$1,616,117	$308,702
DALYs lost by missing HIV positive infants	1,141	19,016	38,031	61,811	22,582
Incremental cost S ($)		$-108,028	$-444,793	$-1,387,379	$-79,964
Incremental DALYs averted		17,875	36,890	60,670	21,441
ICER ($/DALY averted)		Cost saving	Cost saving	Cost saving	Cost saving
South Africa					
Cost of QAS ($)	US$69,359				
Cost of treating false positive infants ($)	$29,885	$383,136	$766,272	$1,532,544	$351,208
DALYs lost by missing HIV positive infants	369	4,728	9,455	18,910	5,553
Incremental cost S ($)		$-283,893	$-667,029	$-1,433,301	$-251,965
Incremental DALYs averted		4,359	9,086	18,542	5,184
ICER ($/DALY averted)		Cost saving	Cost saving	Cost saving	Cost saving
Senegal					
Cost of QAS ($)	US$102,853				
Cost of treating false positive infants ($)	$1,859	$5,808	$11,616	$23,232	$5,324
DALYs lost by missing HIV positive infants	436	1,362	2,723	5,446	1,636
Incremental cost S ($)		$98,904	$93,096	$81,480	$99,388
Incremental DALYs averted		926	2,287	5,011	1,200
ICER ($/DALY averted)		$107	$41	$16	$83
Uganda					
Cost of QAS ($)	US$203,330				
Cost of treating false positive infants ($)	$739,030	$739,030	$739,030	$739,030	$677,444
DALYs lost by missing HIV positive infants	764	19,701	30,553	61,107	23,890
Incremental cost S ($)		$-498,748	$-1,237,778	$-2,715,837	$-437,162
Incremental DALYs averted		18,937	29,790	60,343	23,126
ICER ($/DALY averted)		Cost saving	Cost saving	Cost saving	Cost saving
Zimbabwe					
Cost of QAS ($)	US$334,342				
Cost of treating false positive infants ($)	$44,014	$700,859	$1,401,719	$2,803,437	$642,454
DALYs lost by missing HIV positive infants	445	7,092	14,185	28,370	8,558
Incremental cost S ($)		$-322,503	$-1,023,363	$-2,425,082	$-264,099
Incremental DALYs averted		6,647	13,739	27,924	8,113
ICER ($/DALY averted)		Cost saving	Cost saving	Cost saving	Cost saving

522

Table 4 Univariate sensitivity analyses of incremental cost-effectiveness ratio ($ per disability life years averted) using base case (i.e. 5% misdiagnosis), in five African nations (in 2016 USD).

		Kenya	South Africa	Senegal	Uganda	Zimbabwe
Base case*		CS	CS	$107	CS	CS
Discount rate	1%	CS	CS	$56	CS	CS
	5%	CS	CS	$184	CS	CS
Number of years of treatment averted	5 year	CS	CS	$102	CS	CS
	10 years	CS	CS	$94	CS	CS
	20 years	CS	CS	$80	CS	CS
Testing interruption duration per year	1 month	CS	CS	$83	CS	CS
	6 months	CS	CS	$40	CS	CS
Infant access to treatment	50%	$3	CS	$109	CS	$1
	75%	CS	CS	$108	CS	CS
Loss to follow up in ART	20%	CS	CS	$108	CS	CS

*Green box = cost-saving (CS), Orange box = ICER within 1 times GDP, * Base case: 3% discount rate, 2 years of treatment averted, 0 months of testing interruption, infant access to treatment variable depending on the country – see Table 1, no loss to follow up on ART.*

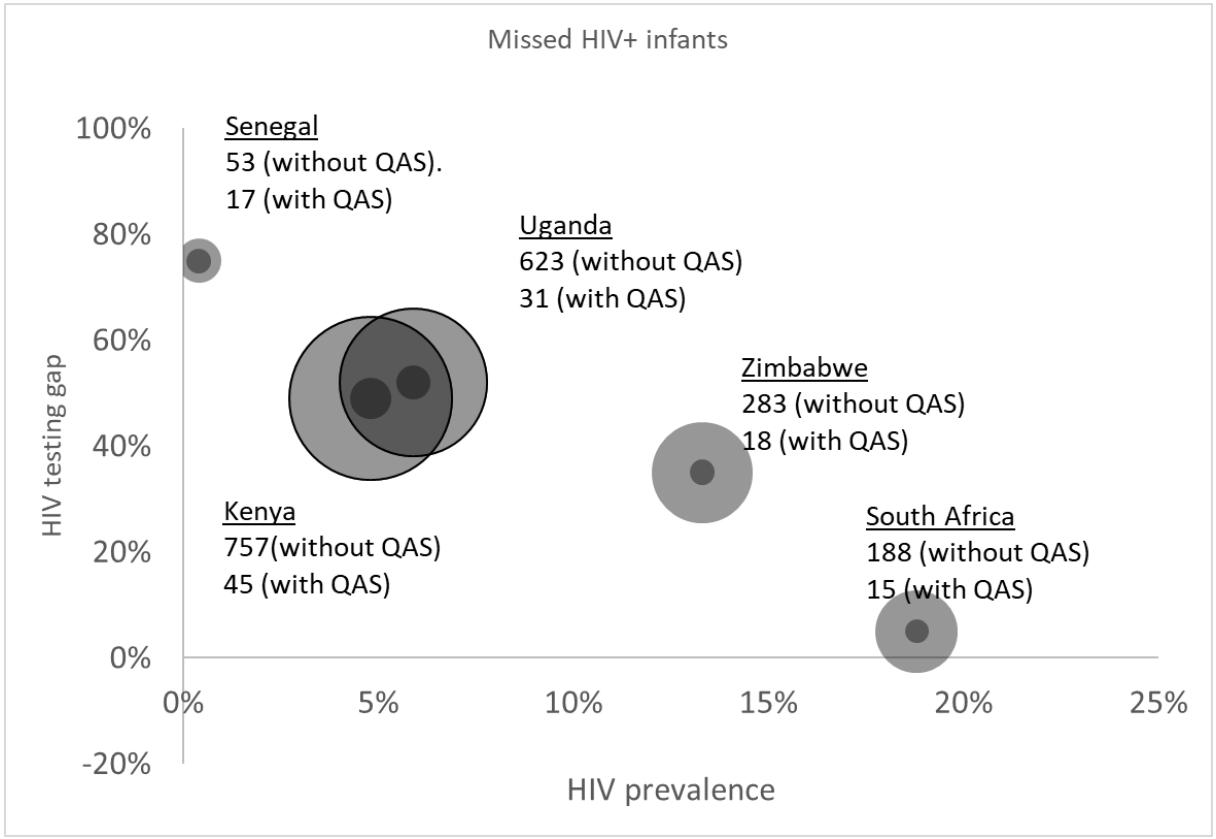


Figure 1.1 Numbers of false negative EID results in a year in five African nations by HIV prevalence and the size of the gap in testing coverage. Senegal has a very low HIV prevalence, but very large gap in screening for EID, while South Africa has a high HIV prevalence and small number of infants born to HIV infected mothers who do not get tested. The size of outer grey circles represent the number of HIV + infants that would not be identified in the absence of a quality assurance system, and the small inner black circles represent what may be achievable by introducing a quality assurance system.

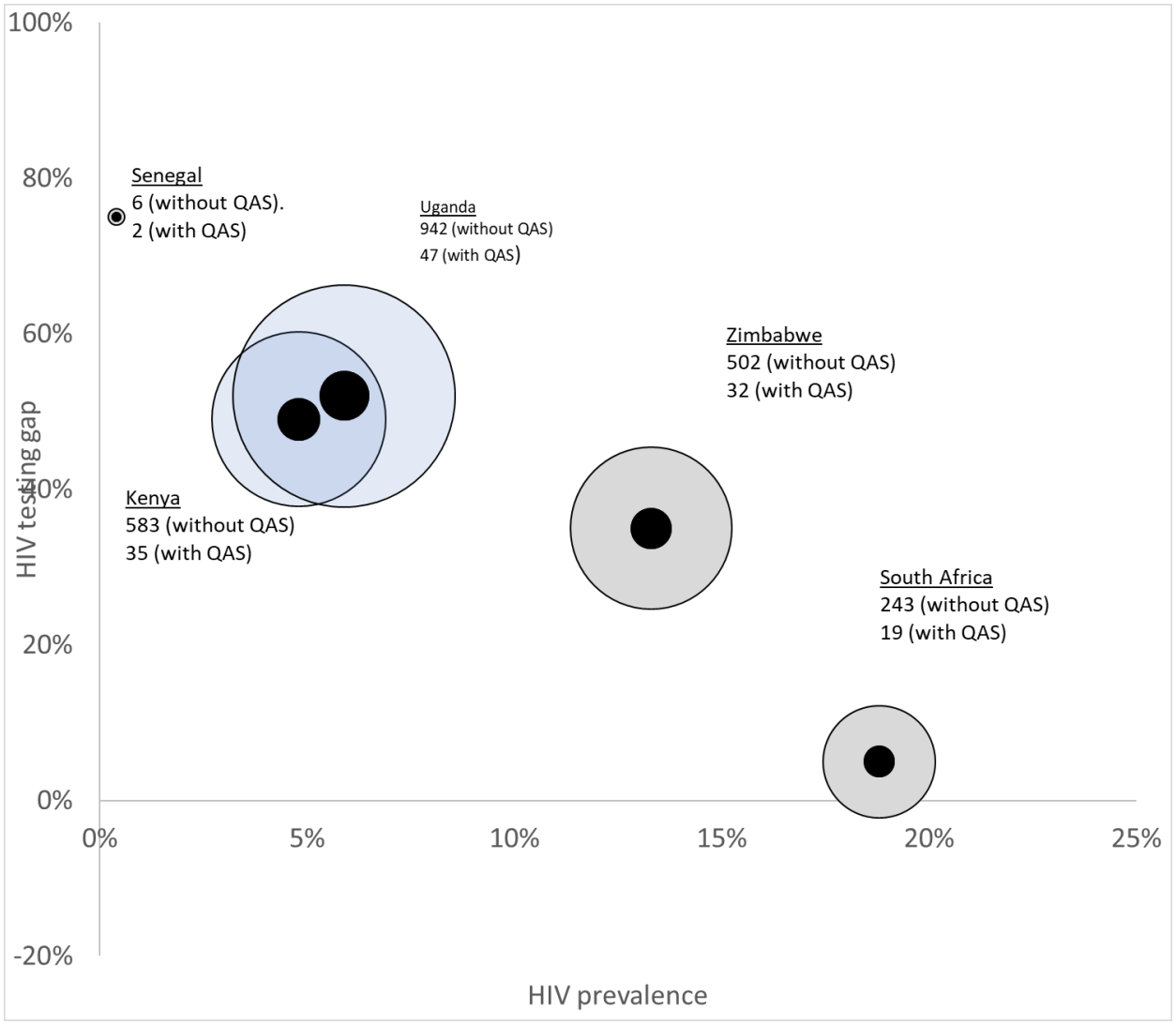


Figure 1.2 Comparison of the numbers of false positive results in a year in five African nations with a quality assurance system (QAS) (black circles) compared with no QAS (grey circle)

Supplement 1 – Further details of the model.

We assumed that even in the best-case scenario at clinic level with quality assurance system in place, some misdiagnosis would persist, due to the innate sensitivity and specificity of the test. This was estimated using a sensitivity of 98.5% and specificity of 99.9%,(1) assumed to be the best realistic estimate. Misdiagnosis rates are assumed, with worst case scenario set to be the minimum level of misdiagnosis that could be identified by a five-member panel as commonly used for proficiency testing among providers. Identifying one incorrect result, implies a 20% (1/5) misdiagnosis and would be the minimum level that would trigger corrective action. A field-evaluation of POC for EID in South Africa found an error rate of 9%,(34) thus we explore a 10% misdiagnosis. A 5% misdiagnosis was also explored, roughly corresponding to the 95% confidence interval of clinic POC for EID as presented by Jani, et al. and is used as the central estimate.(1) False positive and negative rates were calculated using Bayes' Rule to solve conditional probabilities (Supplement 1).(35)

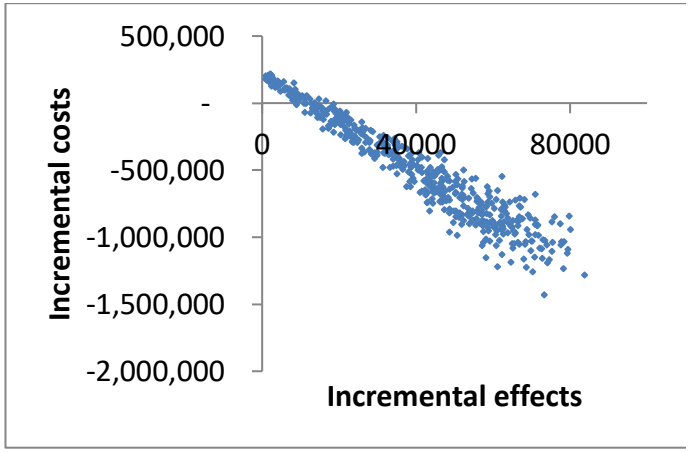
To calculate the costs of a false positive result, we estimated the cost of providing ART for an infant who is not HIV-infected in each respective country and multiplied this by the national rate of access to paediatric ART, ranging from 26% in Senegal to 49% in South Africa. To calculate the health impact of a false negative result in terms of DALYs lost, we separated those with and without access to treatment. For infants with access to treatment we assume normal life expectancy.(36) For untreated infants, we estimated that 50% of infants would die by age two, and 100% would die by age 21, and used the WHO country life tables to estimate the potential years of life left at the time of death.(11, 32, 37) We applied disability weights following Solomon.(38)

The model was designed to undertake threshold analyses in two dimensions: 1) Above which misdiagnosis rate will each quality assurance system be cost-saving *i.e.* where the averted treatment costs are greater than the quality assurance system costs, and so any DALYs averted occur at no additional cost; and 2) How cheap must the quality assurance system be to be cost-saving? It is important to note that at higher quality assurance system costs or lower rates of misdiagnosis, the quality assurance system can still be cost-effective to introduce and needs to be compared against the cost-effectiveness of competing programmes or country-specific cost-effectiveness thresholds. We use one-times the gross domestic product (GDP) per capita,(32) albeit under increasing criticism for being too high.(39) Treatment costs averted can be chosen as 2, 5, 10 and 20, with 2 being the used as the default.

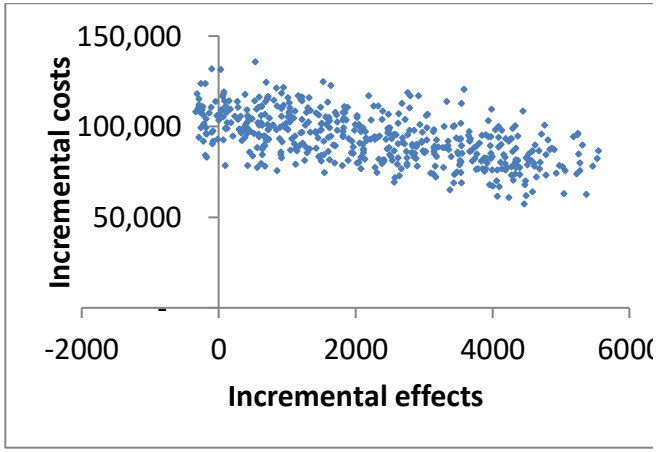
The participating countries represent very different epidemic settings with annual pregnancies in HIV infected women ranging from 2,000 in Senegal to 220,000 in South Africa. All countries have high rates of antenatal care coverage (93-96%) but vary widely in their coverage of infant testing (12%-87%). Our model evaluates the incremental cost-effectiveness within the context of scaling up POCT EID to address this 'testing gap'.

Supplement 2: Sensitivity analysis*: cost effectiveness planes.

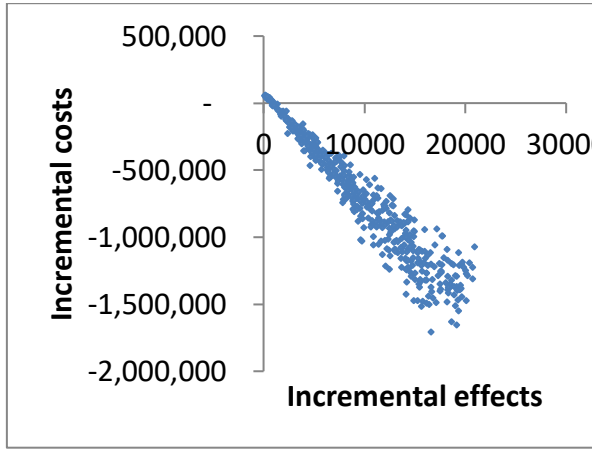
Kenya



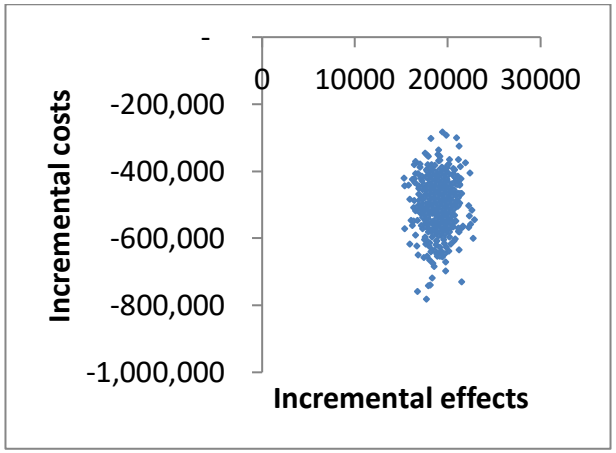
Senegal



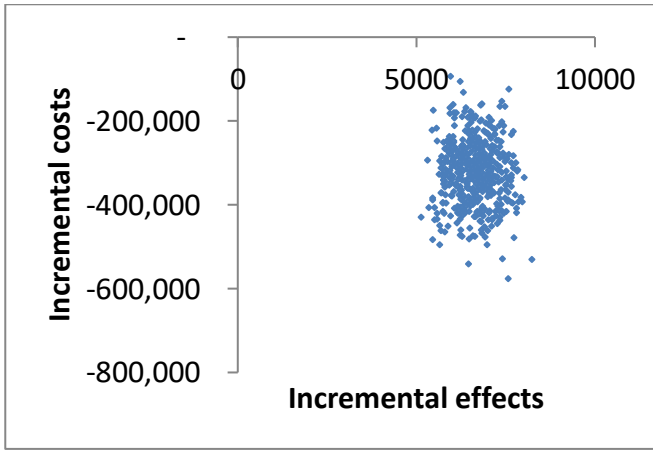
South Africa



Uganda



Zimbabwe



* Parameter uncertainty is evaluated for years of treatment costs averted, cost of quality assurance scale up, infant treatment cost, and discount rate.