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Impact of SMS/GPRS printers in reducing time to early infant diagnosis compared to routine result reporting: a systematic review and meta-analysis

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Running title: Reduced test delivery time with SMS/GPRS printers

AUTHOR CONTRUBUTIONS

Conceived and designed: LV JM NF TP. Performed the experiments: LV CB LH. Analyzed the experiments: LV JM CB BU AG NF TP. Wrote the manuscript: LV JM CB MP BU AG LH NF TP.

CONFLICT OF INTEREST DECLARATION

The authors have declared that no competing interests exist.

ABSTRACT

Background: Despite significant gains made towards improving access, early infant diagnosis (EID) testing programs suffer from long test turnaround times that result in substantial loss to follow-up and mortality associated with delays in antiretroviral therapy initiation. These delays in treatment initiation are particularly impactful due to significant HIV-related infant mortality observed by 2-3 months of age. Short message service (SMS) and general packet radio service (GPRS) printers allow test results to be transmitted immediately to health care facilities upon completion of testing in the laboratory.

Methods: We conducted a systematic review and meta-analysis to assess the benefit of using SMS/GPRS printers to increase the efficiency of EID test result delivery compared with traditional courier paper-based results delivery methods.

Results: We identified 11 studies contributing data for over 16,000 patients from East and Southern Africa. The test turnaround time from specimen collection to result received at the health care facility with courier paper-based methods was 68.0 days (n=6,835), while the test turnaround time with SMS/GPRS printers was 51.1 days (n=6,711), resulting in a 2.5 week (25%) reduction in turnaround time.

Conclusions: Courier paper-based EID test result delivery methods are estimated to add 2.5 weeks to EID test turnaround times in low resource settings and increase the risk that infants

receive test results during or after the early peak of infant mortality. SMS/GPRS result delivery to health care facility printers significantly reduced test turnaround time and may reduce this risk. SMS/GPRS printers should be considered for expedited delivery of EID and other centralized laboratory test results.

Keywords: EID, early infant diagnosis, SMS printer, GPRS printer

INTRODUCTION

Globally approximately 50% of HIV-exposed infants receive an HIV test within the first two months of life (1). Furthermore, of those found HIV-infected only 30% are on antiretroviral therapy (1). Morbidity and mortality are high in untreated HIV-infected infants and early initiation of antiretroviral therapy is strongly recommended by the World Health Organization (WHO) and national guidelines to reduce mortality (2). The peak of mortality for HIV-infected infants is at 2-3 months of age (3), and approximately 50% of HIV-infected infants die before two years of age (4). The turnaround time of HIV testing for early infant diagnosis (EID), however, is often several weeks or months.

HIV diagnosis of infants under 18 months of age is conducted using molecular diagnostic technologies rather than serological methods, due to the potential presence and persistence of maternal anti-HIV antibodies (5). Virological testing for early infant diagnosis (EID) is, therefore, generally performed at central laboratories. However, test volumes are distributed across hundreds or thousands of health care facilities in most countries and many patients do not have easy access to laboratories. With current technologies, very few infants have on-site, same-day access to this critical test. Test specimens and the subsequent test results are typically transported over long distances and this can introduce long testing and result reporting delays, especially for patients in rural and remote areas.

Traditional specimen referral networks link health care facilities lacking on-site testing throughout the national network with centralized laboratories. The specimen type used for EID, dried blood spots, are stable for relatively long periods at ambient temperatures and thus can be stored or transported up to weeks before laboratory processing (6). Many specimen referral networks, however, are inefficient and unreliable because they are often informal, fragmented, and non-standardized. The same specimen referral networks are also used to deliver test results to health care facilities. This often results in long turnaround times. Solutions and interventions to reduce long turnaround times, particularly for EID, are needed to ensure more efficient and reliable testing services to this vulnerable population.

While courier paper-based result delivery methods contribute a significant proportion to the overall test turnaround times and delays, additional challenges exist. There are several phases in the testing cascade: specimen collection, specimen storage at facilities, specimen transportation to laboratories, specimen processing, testing, result delivery to facilities, and result delivery to clinician/patient. Each phase contributes to the overall delay in testing. In order to optimize conventional laboratory-based testing, each phase must be improved. Short message service (SMS) and general packet radio service (GPRS) printer systems are a relatively easy to implement technological tool that can support more efficient result delivery while the overall health system is enhanced.

SMS/GPRS printer systems to return test results from central laboratories to district hospitals or health centers have been developed and implemented in several countries. SMS/GPRS printers are devices designed to reduce turnaround time for delivering laboratory test results in order to improve patient care and outcomes. Upon completion of testing, the laboratory can send the test result through an SMS or GPRS network system directly to a small printer at the health care facility for immediate retrieval. Understanding the impact of SMS/GPRS printers in returning results quicker will provide important information on this

innovative technology, its possible role in initiating infants on antiretroviral therapy earlier, and ultimately guide investment to strengthen EID programs in countries.

Several studies have been published assessing the impact of SMS/GPRS printers to return EID test results (7–17). We undertook this systematic review in order to comprehensively assess the impact of using SMS/GPRS printers in EID test result delivery compared to the traditional courier paper-based system, particularly focusing on test turnaround times. The results of this review were used to inform the revision of the WHO Consolidated ARV Guidelines released in early 2016.

METHODS

Search strategy and study selection

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18), and followed a study protocol. PubMed and EMBASE databases were searched from 1 January 2005 to 1 March 2015 to identify peer-reviewed original research. Search terms were developed using the PICO question format (population, intervention, comparator, outcome) as follows: HIV-exposed infants (population), SMS/GPRS printers (intervention), conventional paper-based results (comparator), and outcomes (time to receipt of result and retention along the testing and treatment cascade). Conference abstracts within the search dates from the Conference on Retroviruses and Opportunistic Infections (CROI), International Conference on AIDS and STIs in Africa (ICASA), International AIDS Society (IAS), and AIDS Conference and bibliographies were also screened and reviewed for possible inclusion. Two independent reviewers screened all titles and abstracts for eligibility. Studies were included if they compared the impact of SMS/GPRS printers to traditional courier paper-based reporting and pertained to EID testing for infants under 18 months of age. The majority of early infant diagnosis testing was conducted at the traditional WHO-recommended six weeks of age. Data were extracted from each included study

including the sample size, test setting, study dates, outcomes, etc. Studies were assessed for quality, bias, and applicability following QUADAS-2 guidelines (19). The overall quality of the evidence was assessed using the GRADE approach (20). Heterogeneity was assessed by visual inspection of forest plots.

Data analysis

Because almost all studies provided only a point estimate, weighted and unweighted averages, as indicated, were used to determine the overall summary estimates of turnaround times. Two researchers independently performed the statistical analysis to ensure accuracy. Graphic representations were completed in GraphPad Prism v6.0 (La Jolla, California, USA) and analyses were completed in Microsoft Excel (Redmond, Washington, USA).

RESULTS

Study characteristics and assessment

From a total of 3,127 articles screened 11 studies met the inclusion criteria and were included in the review (Figure 1 and Table 1) (7–17). Over 16,000 patients were included in the analysis and the median sample size per study was 1,415 patients. Studies were performed in East and Southern Africa, spanning eight countries. All studies were observational in design and conducted between 2008 and 2015.

Overall, the quality of the evidence contributing to this review was rated as low due to the lack of randomized controlled trials. Most studies reviewed and analyzed programmatic implementation data; therefore, limited bias or patient exclusion was expected. Some studies used a pre-post analysis while others compared different groups of facilities with and without SMS/GPRS printers. Some temporal or facility bias could have been introduced and there were some concerns about applicability: all studies were carried out in Africa in routine clinical settings making the results potentially less applicable and generalizable to other regions.

Timeliness of testing and antiretroviral therapy initiation

Courier paper-based results were returned with a mean weighted turnaround time of 68.0 days between specimen collection and results received at the health care facility (n=6,835) (Figure 2a). In contrast, using SMS/GPRS printers to expedite result delivery from the laboratory to the health care facility reduced the overall mean weighted test turnaround time from specimen collection to result received to 51.1 days (n=6,711) (Figure 2b). There was, however, some observed heterogeneity between the point estimates. The mean and median within-study differences observed for the turnaround time of results between SMS/GPRS printers and traditional courier paper-based results were 23 and 24 days, respectively, with a difference range of 9 – 33 days.

Two studies provided additional sub-analyses. One study showed a significant reduction in the test turnaround from the laboratory to caregiver receipt when SMS/GPRS printers were utilized instead of paper-based methods (25.9 days versus 11.2 days) (Figure 3a) (7). Furthermore, there were no clear differences between turnaround times in two different settings: urban and rural hospitals. A second study found a significant reduction in the time from laboratory testing to antiretroviral therapy initiation when SMS/GPRS printers were used (52.31 days versus 37.5 days) (Figure 3b) (11)

DISCUSSION

Traditional specimen transportation and courier paper-based result delivery networks are often associated with long test turnaround times. This review found that sending test results immediately from laboratories to SMS/GPRS printers at health care facilities can reduce the turnaround time between result generation at the laboratory and result receipt at the hospital or health center. We found that SMS/GPRS printers reduced the overall test turnaround time from specimen collection to results received in the health care facility by 17 days. SMS/GPRS printers are fairly easy to use and require minimal skills to operate, while significantly reducing the test turnaround time.

Mortality of untreated, HIV-positive infants peaks at 8-12 weeks of age [4]. Testing infants at six weeks of age would result in the courier paper-based result being returned to the health care facility by an average age of approximately 13 weeks after which time the caregiver must return to receive the result, a further delay (Figure 4a). SMS/GPRS printers allow for the result to be returned to the health care facility by approximately 10 weeks of age (Figure 4b). While SMS/GPRS printers will not prevent all of the mortality observed for untreated HIV-infected infants, they have the potential to reduce the overall test turnaround times which is critical to supporting early ART initiation in HIV-infected infants and this may reduce infant mortality. Furthermore, several countries are considering testing infants at birth. The role of SMS/GPRS printers at birth testing should be investigated to understand if they would support faster report transmission to avert the peak in mortality for HIV-infected infants.

While this review focused on returning results specifically for conventional EID testing, the use of electronic communication could be effective for all tests for which specimen referral to centralized laboratories for testing is required: chemistry, hematology, tuberculosis, opportunistic infection screening, HIV viral load, and hepatitis C diagnosis are regularly transported and tested at supporting laboratories. The use of SMS/GPRS printers implemented initially for returning EID test results could be expanded to include all diagnostic tests requiring laboratory referral in order to improve care and expedite clinical decision-making.

There are several limitations to the evidence base included in this review. First, most studies were retrospective, non-randomized designs, and none reported patient important clinical endpoints such as antiretroviral therapy initiation rates or mortality; both of these limitations have been identified as common limitations of studies of diagnostic tests (21, 22). Second, while substantial data were available, several studies (60-70%) failed to report 95% confidence intervals or ranges; therefore, overall confidence intervals or levels of significance could not be calculated. Furthermore, there was heterogeneity between results and many studies were small, reducing the confidence in the overall result; however, heterogeneity is

expected in implementation studies yet despite this, and the small sample size of many studies, an indicative trend and thus clear conclusions towards reduced turnaround time was observed across studies. The data was skewed by the largest data set, which also had the longest turnaround times for both groups. Additionally, there were little or no data focusing on cost-effectiveness, acceptability, or linkage to care, including the timeliness of result retrieval by caregivers. Understanding the impact of SMS/GPRS printers on retention along the testing and treatment cascade and likelihood to initiate antiretroviral therapy would be beneficial.

SMS/GPRS printers are one of many recent innovations to support improved health care in resource-limited settings (23). Additional, more sophisticated result transmission technologies are under development or currently exist using mobile applications and including bidirectional communication. Furthermore, several point of care testing technologies have entered the market or are in the development pipeline. Most of these technologies can transmit testing data to a central database to allow for remote yet rapid monitoring, more efficient problem resolution, and improved testing quality (24, 25). Additionally, rapid diagnostic test readers can support the real-time testing procedure and interpretation of results as well as transmit testing data similar to point of care technologies (26, 27). Linking laboratory information management systems with electronic patient management records, when and where they exist, can allow for easier and faster test result retrieval. Finally, direct communication with patients via secure text messaging services has been considered in several settings to further expedite test result delivery (28, 29).

Though SMS/GPRS printers can reduce test turnaround times, ongoing challenges exist with any technology, including device malfunction, transmission interruption, remote troubleshooting difficulties, stock-out of printer paper, etc. Monitoring the functionality of these technologies is critical to a successful system. In addition to SMS/GPRS printers, significant improvements can be incorporated into the overall system. Challenges experienced in the laboratory, such as reagent stock-outs, equipment breakdowns, and volumes exceeding capacity, can further delay testing and receipt of result. Nevertheless, an important reduction in

test turnaround time could be significantly impactful given the high early mortality rates observed for untreated HIV-infected infants. This review informed the 2016 WHO recommendation that electronic communication (including SMS/GPRS printers) can be considered to transfer test results and reduce delays in acting on results of early infant diagnosis and other essential laboratory tests (30).

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FIGURES LEGENDS

Figure 1. PRISMA diagram of search outcome and included studies.

Figure 2. Forest plots for mean weighted turnaround times in days from specimen collection to results receipt for (a) conventional paper-based; (b) SMS/GPRS-based. Finocchario *et al.* included data from urban and rural hospitals.

Figure 3. Reduction in turnaround time from (a) laboratory testing to caregiver result receipt in urban and rural hospitals in Zambia [6]; (b) laboratory testing to antiretroviral therapy initiation in Rwanda [10].

Figure 4. Testing and result delivery timing with paper-based results receipt (a) compared to SMS/GPRS-based results receipt (b). This figure has been taken and adapted from Bourne *et al.* (3).

Table 1.

#	Author	Journal	Source Database	Year	Countries of study	Type of study	Years of study	Site type	# of participants
1	Allmayer	unpublished	none	2015	Kenya	retrospective	2013-2014	MOH facilities	6,764
2	Deo	unpublished	none	2015	Mozambique	retrospective	2008-2010	MOH facilities	1,679
3	Finocchario	AIDS	EMBASE	2014	Kenya	retrospective	2010-2012	Urban, rural hospitals	643
4	Jian	PLoS One	none	2012	Swaziland	prospective	post-2010	6 facilities	1,041
5	Kiyaga	PLoS One	EMBASE	2013	Uganda	retrospective	2012	19 MOH facilities	876
6	Lumano	Clinical Chemistry and Laboratory Medicine	EMBASE	2014	Zambia	retrospective	2010	21 MOH facilities	1,876
7	Seidenberg	Bull WHO	EMBASE	2012	Zambia	prospective	2010-2011	10 MOH facilities	1,415
8	Hungu	EID Meeting	Reference	pre-2010	Kenya, Nigeria	retrospective	pre-2010	MOH facilities	300+
9	Ginwalla	EID Meeting	Reference	pre-2010	Zambia	retrospective	2008-2010	MOH facilities	unknown
10	Umutoni	EID Meeting	Reference	pre-2010	Rwanda	retrospective	2010	270 MOH facilities	1,531
11	Ethiopia	presentation	CHAI	2012	Ethiopia	retrospective	2011-2012	30 MOH facilities	unknown

EID Meeting: Improving PMTCT and Pediatric HIV Programs Conference; 2010 May 13-15; Arusha, Tanzania

Figure 1.

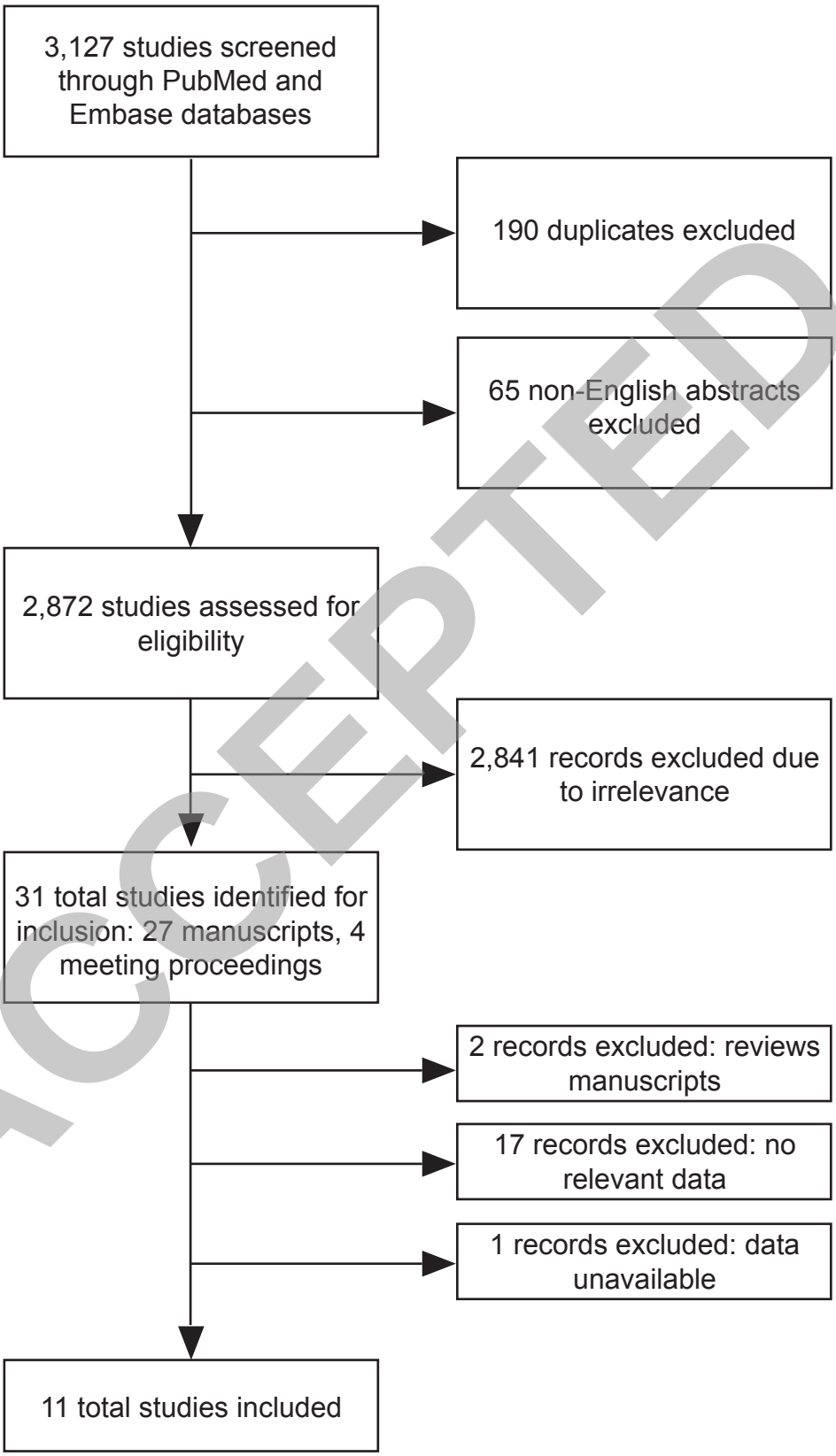
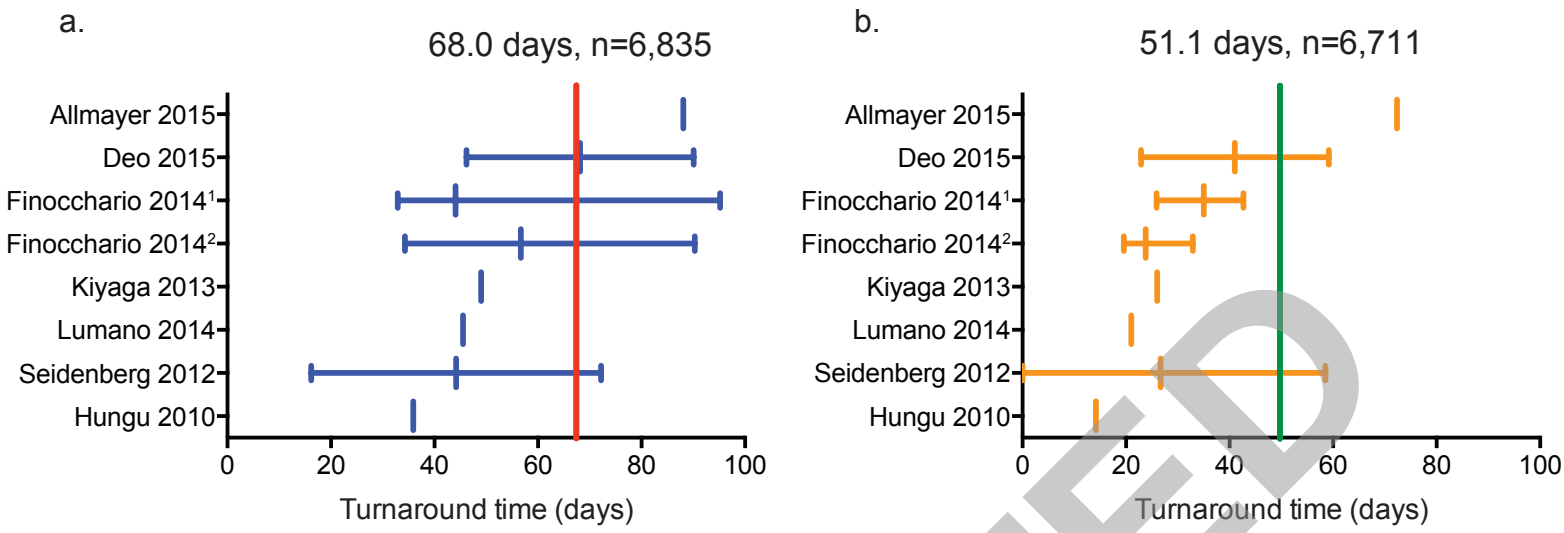


Figure 2.



[1]: Substudy in urban hospitals
[2]: Substudy in rural hospitals

Figure 3.

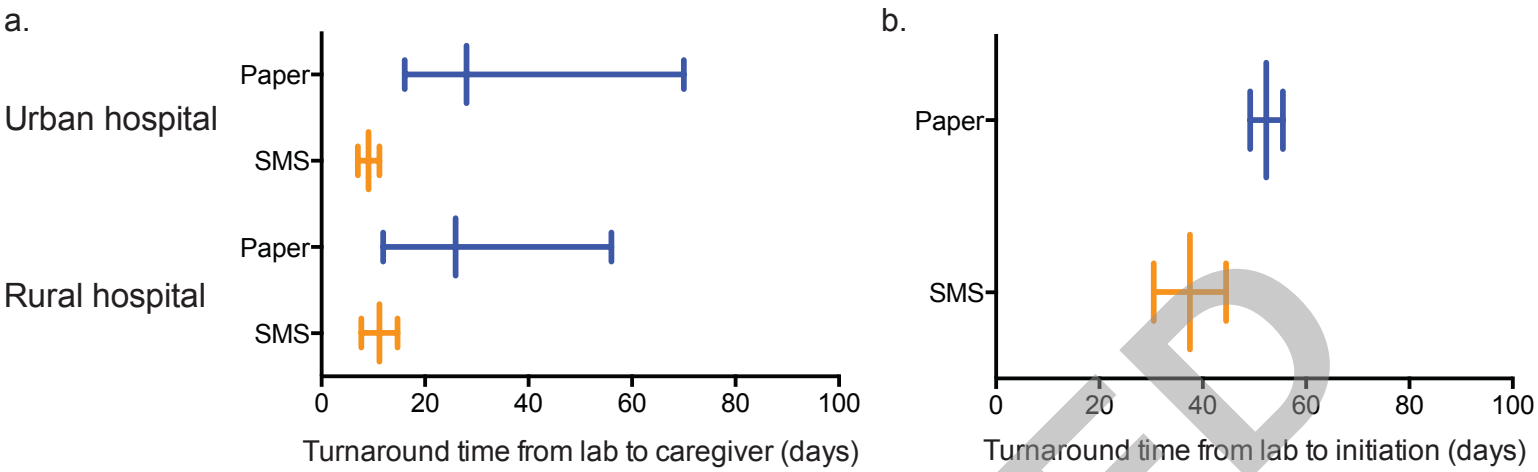
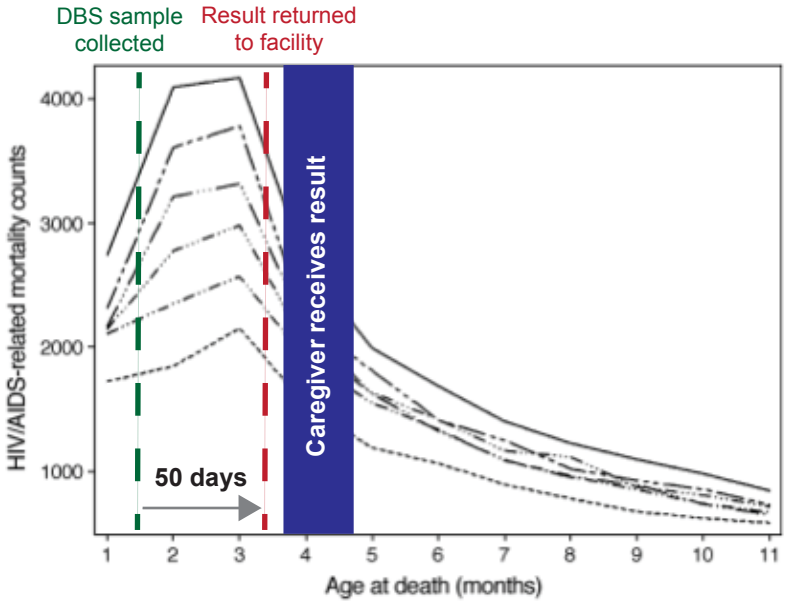


Figure 4

a.



b.