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July 2017

Impact Evaluation Report 63

HIV and AIDS

3ie International Initiative for Impact Evaluation

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About this report

3ie accepted the final version of the report, *Integration of EPI and paediatric HIV services for improved ART initiation in Zimbabwe,* as partial fulfilment of requirements under grant TW7.08, issued under the HIV self-testing thematic window. The content has been copy-edited and formatted for publication by 3ie. All the content is the sole responsibility of the authors and does not represent the opinions of 3ie, its donors or its board of commissioners. Any errors and omissions are also the sole responsibility of the authors. All affiliations of the authors listed in the title page are those that were in effect at the time the report was accepted. Comments or queries should be directed to the corresponding author, Marta Prescott, mprescott@clintonhealthaccess.org. This trial was registered in the Pan African Clinical Trial Registry (PACTR201507001178614).

The study carried out through the integration of HIV services thematic window, which was funded by the Bill & Melinda Gates Foundation.

Suggested citation: Prescott, M, Boeke, C, Gotora, T, Mafaune, HW, Motsi, W, Graves, J, Mangwiro, A and McCarthy, E, 2017. *Integration of EPI and paediatric HIV services for improved ART initiation in Zimbabwe*, 3ie Impact Evaluation Report 63. New Delhi: International Initiative for Impact Evaluation (3ie)

Executive editors: Beryl Leach and Emmanuel Jimenez
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Acknowledgements

We would like to thank Brett Keller for his role in the development and beginning phases of this evaluation. We would like to acknowledge and appreciate the dedicated work of the data collectors, field staff and facility staff.

Summary

Testing HIV-exposed infants for HIV by 6–8 weeks of age is critical to preventing early morbidity and mortality among those who are HIV positive. Zimbabwe's paediatric HIV treatment guidelines recommend testing for HIV-exposed infants at or before six weeks, yet practical implementation of these guidelines varies. Many demand- and supply-side gaps in service delivery lead to infants either not receiving the HIV test at all or receiving it well beyond the recommended six weeks of age. When HIV-positive infants remain undiagnosed, they lose the opportunity to access antiretroviral therapy.

Meanwhile, Zimbabwe's Expanded Programme on Immunisation (EPI) consistently demonstrates high coverage rates of childhood vaccinations, particularly for the first and second doses of the pentavalent vaccine, which are scheduled for 6 weeks of age (pentavalent 1) and 10 weeks (pentavalent 2). Given that most Zimbabwean infants interact with a health facility to receive these vaccines, an opportunity exists to integrate and leverage the EPI service to identify HIV exposure status and swiftly link infants to appropriate HIV services.

The Clinton Health Access Initiative designed an intervention in collaboration with Zimbabwe's Ministry of Health and Child Care that integrated referral for early infant diagnosis into health facility-based EPI services. Standard EPI visits at 6 and 10 weeks of age were used as entry points for referral to early infant testing and receipt of results. In addition to implementing an entry point referral system, the intervention included support to the HIV testing service and paediatric treatment programme.

This impact evaluation assessed whether integration of early infant diagnosis into health facility-based EPI services improved coverage of HIV testing among HIV-exposed infants, and HIV treatment initiation among HIV-positive children.

Evaluation design

To assess the impact of integrating early infant diagnosis and EPI, we used a cluster-randomised controlled trial study design of 29 facilities across seven provinces of Zimbabwe (14 in the control arm and 15 in the intervention arm). The intervention was implemented in September 2015 and ran for seven months. The baseline assessment for the pre-intervention period occurred in July and August 2015; endline data collection for the study period occurred in May 2016. Data was collected from medical registers and the Logistics Management Information System database. Additional data was collected through interviews with healthcare workers and patient caregivers.

To compare the control and intervention arms, we used unweighted t-tests for the initial analyses, comparing outcomes throughout the study period. As a secondary analysis, we used unweighted t-tests to examine the change in study outcomes from a pre-intervention period to the study period (a difference-in-difference analysis). For qualitative data, codes for analysis were developed based on topics discussed during interviews. Programme costs were tracked throughout the study and used to calculate the cost per HIV-positive test by 16 weeks and the cost per treatment initiation by 20 weeks.

Results

We observed no significant difference between the intervention arm and the control arm during the study period in the HIV testing by 16 weeks, receipt of results by 20 weeks or treatment initiation by 20 weeks.

Overall, most caregivers appeared to be satisfied with the care they received (92% in intervention facilities and 87% in control facilities; p=0.2). Key issues noted by some caregivers included long wait times and inadequate human resource capacity. All nurses interviewed at intervention facilities indicated that they had successfully implemented EPI and paediatric HIV services. However, some caregivers reported frustrations, including delayed turnaround of results and lengthy wait times as under-resourced health facility staff struggled to integrate services in a timely manner. Despite the integration challenges noted, healthcare workers were overwhelmingly positive about the approach and felt that integration could be successful with increased staff support.

The total cost of the intervention was US$44,104. This figure excludes US$19,000 spent on personnel costs and US$17,500 spent on administrative costs. Given that we did not see an impact on additional HIV-positive infants identified in the intervention arm compared to the control arm, the costs per additional HIV-identified infant and per HIV-positive infant treated as a result of the intervention would be high.

Overall, this randomised controlled trial exploring the integration of EPI and early infant diagnosis services in Zimbabwe clinics from October 2015 to April 2016 did not result in a statistically significant impact on early infant diagnosis of HIV or any discernible impact on early antiretroviral therapy initiation for HIV-positive infants. The strengths of this impact evaluation included its randomised design to minimise confounding, clustering by health facility to minimise spillover effects, relatively long time frame (seven months), triangulation of data across several sources, and sensitivity analyses accounting for various analytical factors.

With respect to the limitations of this study, although considerable effort was made to ensure high-quality data capture, data collection was challenging due the method of record-keeping at sites. Identifying the total population of infants exposed to HIV was a particular challenge, given the many potential entry points to the health facility.

This study did not conclusively determine that integrating EPI and early infant diagnosis will not have an impact on early infant testing and treatment initiation in any setting. Rather, we explain the limitations and challenges that future implementers should consider as they plan a similar intervention.

Specifically, future interventions would benefit from (i) incorporating more intensive training to gain buy-in from health facility staff, (ii) focusing on facilities with adequate staffing, (iii) solving the laboratory challenges that result in delays, and (iv) targeting areas with a high prevalence of HIV-positive infants. Implementation may help to identify more HIV-positive mothers, leading to better coverage for prevention of mother-to-child transmission and preventing some infants from becoming HIV positive but we were not able to evaluate this potential area of impact in the present study.

Given the challenges noted and the relatively small number of HIV-positive infants in Zimbabwe because of a highly successful prevention of mother-to-child transmission programme, we conclude that early infant diagnosis and EPI integration as implemented through this study may not have the desired impact in Zimbabwe at this time. However, future studies that address the challenges noted above could more accurately reflect the potential impact of this integrated approach on paediatric testing and treatment initiation. In addition, the provision of point-of-care testing for early infant diagnosis will remove many of the challenges associated with laboratory testing and sample transport. Therefore, it should be examined as a potentially important strategy to increase the effectiveness of an integrated programme.

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Abbreviations and acronyms

ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
CHAI	Clinton Health Access Initiative
DBS	Dried blood spot
EID	Early infant diagnosis
EPI	Expanded Programme on Immunisation
FHS	Family Health Services
HTS	HIV testing services
MOHCC	Ministry of Health and Child Care
NGO	Non-governmental organisation
PCR	Polymerase chain reaction
PNC	Postnatal care
PMTCT	Prevention of mother-to-child transmission (of HIV)
SD	Standard deviation
SOC	Standard of care
SMS	Short message service (text message)
WHO	World Health Organization

1. Introduction

The World Health Organization (WHO) recommends testing HIV-exposed infants as early as possible to prevent early morbidity and mortality among HIV-positive infants. It further recommends a virological test for HIV-exposed infants at 4–6 weeks of age, or as soon as possible thereafter (WHO 2016). Unfortunately, mortality remains high among HIV-infected infants, with many dying before their diagnosis or being diagnosed late, after they are three months old (Innes et al. 2014). Integrating early infant diagnosis (EID) of HIV and immunisation services is one way to increase the number of infants tested early for HIV and swiftly initiated into treatment.

Zimbabwe's paediatric HIV treatment guidelines recommend HIV testing for HIV-exposed infants at or before six weeks of age (National Medicine and Therapeutics Policy Advisory Committee 2013). While all health facilities are expected to invite HIV-positive mothers to return to the clinic to test their infants at six weeks old as part of prevention of mother-to-child transmission (PMTCT) services, the implementation of these guidelines varies in practice. Many demand and supply gaps in the 'PMTCT cascade' (steps in the care delivery pathway from a woman first receiving an HIV test to her child receiving testing and treatment services) result in children not receiving these HIV services (Newell et al. 2004).

Integrating HIV testing and infant immunisation capitalises on and leverages the successful operation of an existing high-coverage service in Zimbabwe – the Expanded Programme on Immunisation (EPI). National programme data shows a moderate increase in the proportion of HIV-positive children aged 0–14 years on HIV treatment in 2014 (38%) and 2015 (44%) (Zimbabwe Ministry of Health and Child Care 2015a), compared with more than 85% coverage for most routine immunisations (Zimbabwe National Statistics Agency and ICF International 2015). This is a high priority for Zimbabwe's Ministry of Health and Child Care (MOHCC). While study results from Zambia have shown integrating EID and immunisation does not have a deleterious effect on immunisation rates (Wang et al. 2015), few studies have rigorously assessed the impact of EID-EPI integration on the extent of linkages to HIV treatment initiation once a child is diagnosed as HIV positive.

Our aims were to design an intervention, in collaboration with the MOHCC, that integrated referral for EID into health facility-based EPI services, and to provide a detailed picture of the feasibility, benefits and challenges of this service integration.

The study objectives were as follows:

- To evaluate the impact of integrating infant HIV testing and treatment referral into routine EPI services on:
  - infant HIV testing by 16 weeks of age;
  - infants receiving their HIV results by 20 weeks of age;
  - the initiation of antiretroviral therapy (ART) for those who test HIV positive by 20 weeks of age;
  - the turnaround time between testing and receiving HIV results for infants under two years old;
  - the volume of EPI services;

- To describe the process failures or successes in testing and sample transport logistics at health facilities integrating infant HIV testing and treatment referral into routine EPI services;
- To describe caregiver and staff attitudes towards the integration of infant HIV testing and treatment referral and routine EPI services;
- To evaluate the cost-effectiveness, per additional ART initiation by the age of 20 weeks, of integrating infant HIV testing and treatment referral into routine EPI services; and
- To evaluate the cost-effectiveness, per additional HIV test for infants younger than 16 weeks, of integrating infant HIV testing and treatment referral into routine EPI services.

2. Background and intervention implementation

The MOHCC in Zimbabwe has primary responsibility for undertaking initiatives to respond to the country's HIV epidemic. For the last two decades, the country has consistently adopted HIV treatment guidelines proposed by WHO to support the implementation of successive versions of the Zimbabwe National HIV and AIDS Strategic Plan (2006–2010; 2011–2015; 2015–2018). Zimbabwe has a generalised HIV epidemic, although HIV prevalence has declined significantly in recent years. In the last decade, adult HIV prevalence has halved, from 26.5% to 14.3%, and new HIV infections have declined by more than 50% in adults and 75% in children (Government of Zimbabwe 2015). Still, prevalence remains unacceptably high.

As of 2015, 1,495 sites were offering lifelong ART for PMTCT – referred to as 'Option B+'. In the same year, 425,188 women registered for their first antenatal care (ANC) visit. MOHCC PMTCT programme data from 2015 shows that 30,058 of these women booked for their first ANC check-up with a known HIV-positive result (MOHCC 2015b). Of the 395,130 women with an unknown or negative HIV status, 390,563 (99%) were tested for HIV and received results via ANC check-ups.

Through Option B+, the national programme has seen estimated 6–8-week mother-to-child HIV transmission rates decline from the 8.8% reported in 2011 to 3.6% in 2014 (MOHCC 2012). Despite these successes, there are points of high attrition in the PMTCT cascade that reduce the identification of HIV-exposed infants, leaving them vulnerable to HIV transmission during breastfeeding and to HIV-related mortality.

The EID programme is the most direct entry point for paediatric HIV testing and counselling. Under EID, dried blood spot (DBS) samples taken from HIV-exposed infants are sent for DNA polymerase chain reaction (PCR) testing at one of three national laboratories. Almost half of the samples in 2015 were drawn from infants older than six weeks, highlighting the need to strengthen earlier testing of HIV-exposed infants. Additionally, challenges with long turnaround times between sample collection, sample testing and delivering results to caregivers worsen health and survival outcomes as they delay treatment initiation.

In 2015, the National Microbiology Reference Laboratory, responsible for the implementation of DBS sample collection and testing in Zimbabwe, reported that although the turnaround time for laboratory testing was typically less than seven days,

delays in transporting samples from the testing sites and challenges with the electronic transmission of results back to the sites increased nationwide turnaround time to more than 4–6 weeks (MOHCC 2015b). Such delays ultimately affect the timely initiation of treatment for children who are diagnosed as HIV positive, putting them at risk and decreasing their chances of survival.

EID services offered to infants presenting at health facilities at six weeks of age intersect with immunisation services provided to the same age group through the high-coverage EPI. Therefore, an opportunity exists to integrate EPI and EID services for children already visiting a health facility for vaccinations. In Zimbabwe, the essential package of maternal, newborn and child health services – including immunisation, growth monitoring, ANC and postnatal care (PNC) – is provided in primary healthcare clinics in rural and urban centres. Higher-level facilities (district, provincial and central) also provide primary healthcare services, but they mainly serve as referral centres for specialised chronic care services beyond the scope of primary healthcare clinics. In 2004, the MOHCC started providing paediatric HIV treatment and care services in a handful of primary healthcare facilities.

Through the years, the number of primary care facilities offering paediatric HIV treatment and care services has steadily increased. As of 2015, 1,849 public health facilities offered paediatric HIV services nationwide, with 1,341 health facilities (72.5%) offering both EPI and paediatric HIV and ART services, 131 (7.1%) facilities provided only EPI services; 16 (0.9%) provided only EID services and 361 (19.5%) offered neither service.

Zimbabwe is moving steadily towards accreditation of all health facilities to offer paediatric HIV care and treatment services. With the support of implementing partners, the country has intensified training nurses and nurse mentors in integrated HIV management, including EID and ART initiation, which are areas of weakness in the PMTCT programme (MOHCC 2015b).

Zimbabwe has adopted new HIV treatment guidelines that expand treatment eligibility to all HIV-positive children under five years old and to all HIV-positive pregnant women for life. Programmatically, the MOHCC has sought to implement innovative mechanisms to ensure that those in need of treatment receive it.

The country has adopted the Double Dividend approach, which provides a framework for pursuing the goals of eliminating paediatric HIV and AIDS and improving child survival in tandem, reflecting the national commitment to scaling up the testing and treatment of paediatric patients. Enhancing the delivery of immunisations and HIV services is noted in the Double Dividend policy document as a useful integrated approach to service delivery that may help achieve the Double Dividend goals (Zimbabwe MOHCC 2015c, 2014a). However, there is insufficient evidence to support strong advocacy for a nationwide policy of integrating EID into EPI.

2.1 Integrating EID and health facility-based EPI

The link between paediatric HIV treatment for HIV-positive infants and improved survival (our long-term goal) has been well documented (MOHCC 2014b). Challenges remain in retaining mother-infant pairs in the PMTCT cascade. Despite progress over the years,

many countries still fall short of their paediatric treatment coverage goals; work remains to improve the way paediatric HIV services are operationalised (Stringer et al. 2008).

This evaluation focuses on the Zimbabwean PMTCT cascade at the time of EID. We evaluated whether, by reaching more infants who were already receiving immunisation services at six weeks old, more of them exposed to HIV would be identified and tested for HIV. And, by reaching the infant again when returning for 10-week immunisation services, we evaluated whether more children would receive their HIV test results and initiate treatment. At the same time, we assessed EPI volumes to ensure that they remained steady and were not negatively influenced by the addition of HIV testing services (HTS) to the EPI visits.

2.1.1 Control arm

Health facilities in the control arm performed standard of care (SOC) practices for health facility-based EPI and EID services. For SOC, EID and EPI services were separate stations with no active referral system between them. For EID, a DBS sample was drawn from HIV-exposed infants (via heel prick) during a scheduled visit and the sample was sent to the reference laboratories for DNA PCR testing. Caregivers were notified of their infant's HIV results when the results were returned to the health facility (6–10 weeks, depending on laboratory demands). Separate from these services, the SOC for the pentavalent vaccine, which vaccinates against hepatitis B, *Haemophilus influenzae* type B, diphtheria, tetanus and pertussis, involves three doses of the vaccine occurring at 6, 10 and 14 weeks of age.

2.1.2 Intervention arm

For service integration, the standard EPI visits were used as important touchpoints for active referral to EID testing and receipt of results. For the referral system, EPI workers were trained to identify HIV-exposed infants and refer them to the EID stations. At the EID stations, EID workers were trained to support the turnaround of results, such that they would be ready by the next EPI visit. The service integration stages were as follows:

- *Dose one of pentavalent vaccine at six weeks of age:* The EPI healthcare worker was trained to ascertain an infant's HIV status using the child health card, where the mother's status is indicated. If a mother had an unknown or negative HIV status that was more than three months old, the mother and infant were referred to the health facility's appropriate HIV testing location – the Family Health Services (FHS) clinic, the HTS delivery point or the ANC clinic – where the mother was counselled and offered a rapid HIV test. A mother testing positive for HIV was then referred for treatment (in the same facility) to improve her health and prevent the ongoing risk of transmitting HIV to her HIV-negative child via breastfeeding. If the EPI healthcare worker ascertained from the child health card that the mother was HIV positive or the infant presented with symptoms of infection, both mother and child were also referred for EID testing services at the appropriate location within the health facility. At the designated testing location, HIV-exposed children received the DNA PCR test as outlined above at the HTS. The results were scheduled for collection at FHS/HTS/ANC four weeks later, to coincide with the next round of pentavalent immunisations. When the child was brought to the health facility by a caregiver other than the mother, the presence of the guardian or caregiver at the next appointed immunisation date was

requested, in keeping with guidelines requiring parent or caregiver consent for children younger than 16 years.

- *Dose two of pentavalent vaccine at 10 weeks of age:* On the same day as the second pentavalent vaccine dose, the child went to FHS/HTS/ANC to receive the result of the DNA PCR test. If the child tested positive for HIV, the child and mother were immediately referred to ART services (in the same health facility). In cases when results were not available by the 10-week visit for pentavalent vaccine and the caregiver consented to receive notifications by text message (SMS), caregivers were notified directly by the laboratory to visit the health facility. If the caregiver did not consent to receive SMS notifications from the laboratory or health facility, they were notified by a healthcare worker visit that the results were ready to receive in person at the FHS/HTS/ANC site.

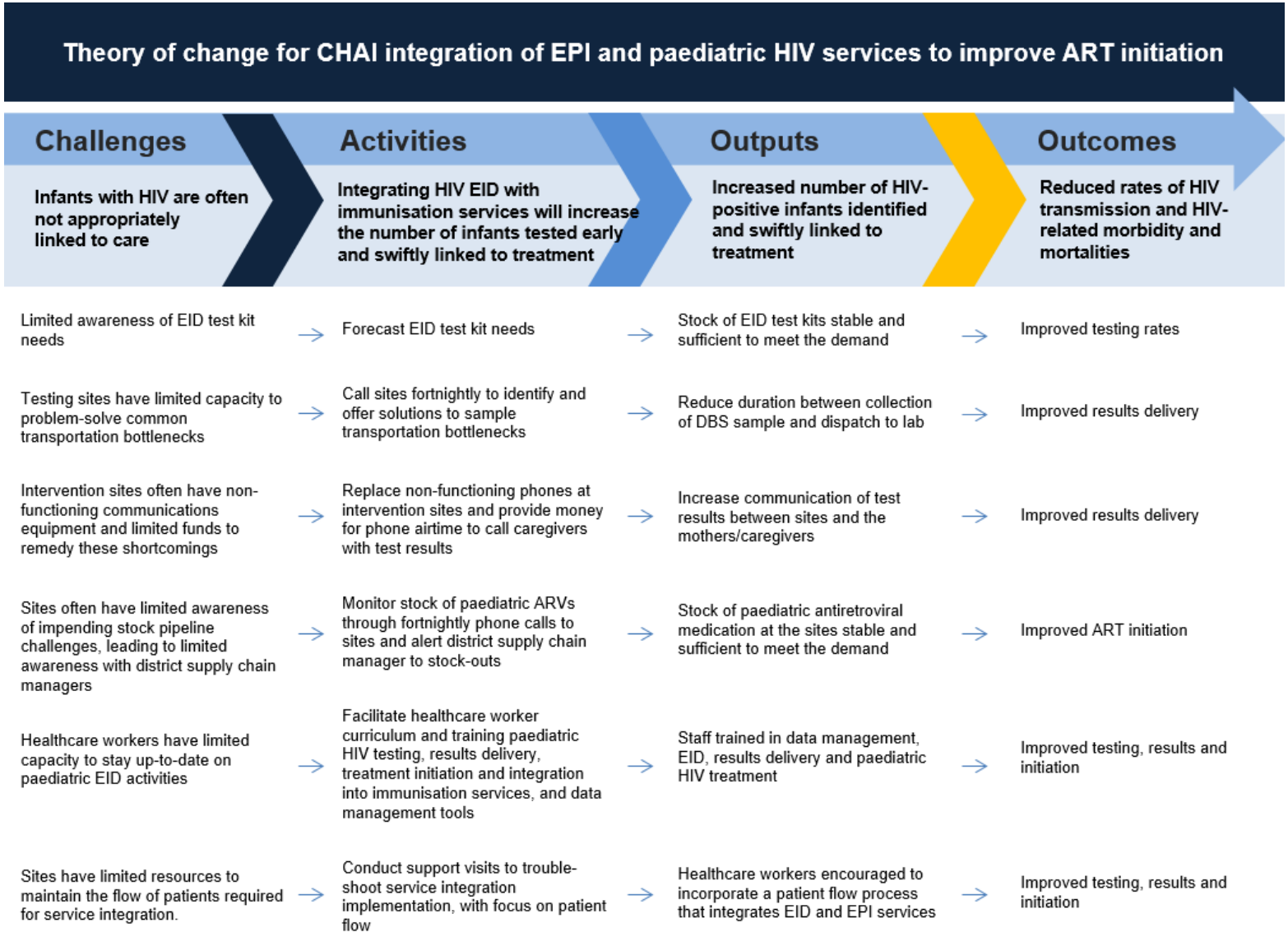
In addition to implementing the touchpoint referral system, the Clinton Health Access Initiative CHAI and MOHCC also supported additional intervention activities. They worked with health facility staff to consider service station layouts between EPI and HTS and helped troubleshoot any patient or workflow issues. CHAI also provided support to help overcome systems-level challenges. For example, to avoid stock-outs of EID test kits, CHAI provided test kit forecasting assistance, and to help prevent bottlenecks in transporting samples, the team made regular calls to the sites to offer solutions and replaced non-functioning phones so that sites could receive test results from the laboratories. The team also helped to ensure that health facility staff were able to connect with caregivers about the availability of EID test results by providing money to cover the cost of phonecalls.

By troubleshooting these challenges on an ongoing basis, enhancing provider knowledge through refresher training and working with staff to restructure patient flow, we expected not only to increase retention rates in the mother and infant HIV service delivery cascade, but also to reach children at a younger age and decrease the time between each step in the cascade.

2.1.3 Theory of change

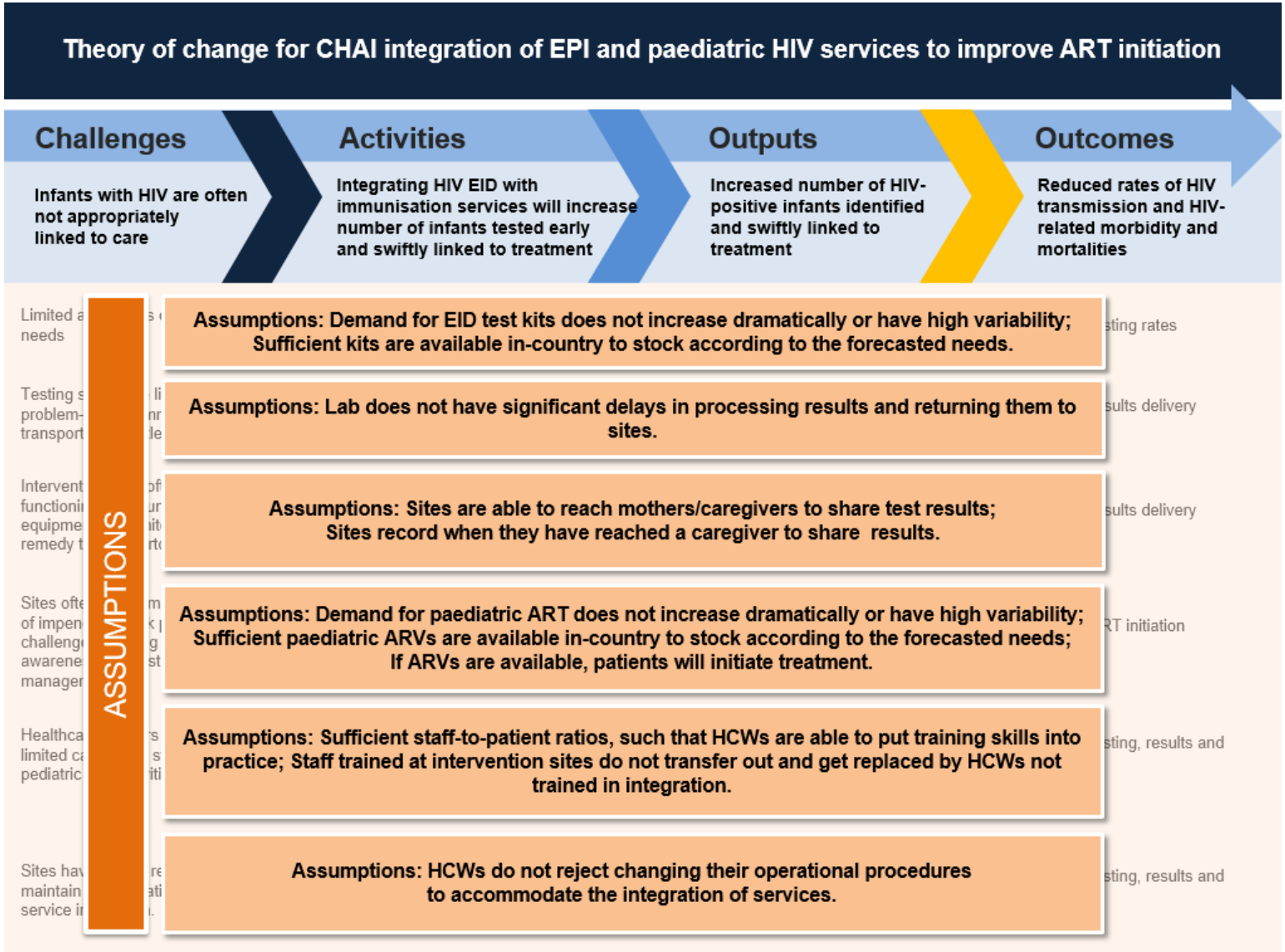
The programme's logical framework is illustrated in Figure 1. This highlights the expected outcomes arising from programme outputs, themselves resulting from intervention activities designed to address key challenges thought to be impeding the success of the paediatric HIV treatment programme. We expected to see a change in outcomes (HIV testing, results delivery and ART initiation) within the timeframe of the study, and designed our protocol accordingly. We expected testing to be completed by 10 weeks of age and ART initiation to be completed by 16 weeks of age.

Figure 1: Logical framework underlying EID and EPI integration theory of change



Assumptions (see Figure 2) were made at each step, as with any evaluation performed outside of a controlled laboratory setting. When we forecasted EID test kit needs with the intervention health facilities, we assumed that the demand would not increase dramatically or have high variability during the study period. We also assumed that sufficient kits would be available in the country to stock according to the forecasted needs. The intervention team made fortnightly calls to identify and offer solutions to sample transportation bottlenecks to reduce the time between the collection of DBS samples and their dispatch to the laboratory. We assumed that the laboratory would not have significant delays in processing the results and returning them to the sites. By replacing non-functioning phones at intervention sites and providing money for phone airtime to call caregivers with test results, we expected to see an increase in the communication of test results between sites and caregivers. For the intervention to function properly, the assumption was that sites would be able to reach caregivers to share test results. To track progress, they would record when a result had been delivered.

Figure 2: Assumptions underlying EID and EPI integration theory of change



To improve ART initiation, the intervention team monitored the stock of paediatric antiretroviral drugs (ARVs) through fortnightly telephone calls to intervention sites and alerted the district supply chain manager about any stock-outs. This was done to ensure that the stocks of paediatric ARVs were stable and sufficient to meet demand. The link between the activity and the output depended on the assumption that the demand for paediatric ART would not increase dramatically or have high variability, and that sufficient paediatric ARVs would be available to meet the forecasted needs. We also assumed that if a sufficient supply existed, so too would sufficient demand – that is, if ARVs were available, patients would initiate treatment.

To improve key points along the cascade – testing, the delivery of test results and initiation or ART – the intervention included refresher training for healthcare workers in paediatric HIV testing, results delivery and treatment initiation, integrating these into immunisation services, and data management tools. Staff being trained in these skills at the intervention sites depended on the assumption that there would be sufficient staff-to-patient ratios for the healthcare workers to have the flexibility, time and motivation to put their training into practice.

To encourage healthcare workers to incorporate a patient flow process integrating EID and EPI services, the intervention team conducted support visits to troubleshoot the implementation of service integration, with a focus on patient flow. The underlying assumption was that healthcare workers would not reject changing their operational procedures to accommodate the integration of services.

2.2 Implementation successes and challenges

Implementation of the intervention commenced with training healthcare workers in EPI and HIV and ART integrated service delivery. SOC training for all study sites included overviews of HIV testing and counselling procedures for mothers and/or caregivers and children, DBS sample collection techniques, ART initiation and patient management, stock management and data collection, and reporting procedures for monitoring and evaluation. The study team routinely checked data quality at both intervention and control sites, and provided refresher training on data management where necessary.

The intervention training, at intervention sites only, focused on integrating EID and EPI services. Through the training the following outputs were achieved:

- SOC refresher training for 53 healthcare workers from intervention and control facilities, including representatives from the provinces and districts of study health facilities;
- Intervention training for 28 representatives from all 15 intervention facilities for 1.5 days, with MOHCC trainers facilitating the training sessions;
- Health facility-specific workflow and client flow procedures designed to enable service integration at intervention facilities; and
- Simplified job aids supporting the protocol for HIV testing and treatment for children during immunisation visits, and age-appropriate references for healthcare workers to use when testing for and diagnosing HIV in infants.

Logistical challenges hindered the completion of the training as proposed in our protocol. First, the training for healthcare workers was delayed due to challenges obtaining

MOHCC staff to facilitate the SOC refresher and intervention training sessions. As a result, the training was conducted two weeks after completing the baseline data collection and analysis. Ideally, training would have begun immediately after the baseline analysis was completed and would have included the EPI refresher sessions. However, there was a strong benefit in having the MOHCC trainers conduct the training sessions, as this ensured standardisation across sites, thereby allowing the results to be more generalisable for potential national scale-up of the intervention.

Second, refresher sessions on EPI, intended to be part of the SOC training for intervention and control sites, were not conducted as planned. This was due to the lack of availability of the national EPI team to conduct the refresher training sessions. The national EPI team had a scheduling conflict, as they were preparing for a national measles-rubella catch-up campaign, conducting supplementary training throughout the country for other healthcare workers.

Third, while all intervention facilities had at least one representative attend the training, we originally planned to have two healthcare workers present to ensure continuity in intervention implementation in the event of the absence of any of the healthcare workers. Unfortunately, this was not possible for all sites.

These challenges necessitated the urgent deployment of the site support team to visit all sites within two weeks of completing the centralised training. The site support team consisted of one PMTCT officer from the MOHCC's AIDS and Tuberculosis Unit, one officer from CHAI and one officer per district from the districts participating in the study. The intervention team carried out three site support visits to each of the 15 intervention sites.

These site support visits had the following goals:

- Observe healthcare workers conducting immunisation sessions and assess how the service integration was being implemented;
- Provide appropriate mentorship where necessary;
- Assess knowledge gaps in the provision of integrated paediatric HIV services and EPI services;
- Review any operational challenges being faced in implementing integrated EPI and paediatric HIV services at each health facility and assist facilities to identify possible solutions, and;
- Carry out data quality monitoring and verification.

At each visit, the site support team documented observations on the implementation by healthcare workers, and related recommendations and lessons learned. Formal reports on these three site support visits were shared as updates with the MOHCC.

Unfortunately, challenges experienced by sites around long turnaround times for EID results critically threatened the success of the intervention. Stock-out of reagents and consumables at the national testing laboratory in Harare in October and November 2015 meant that no testing happened during that period. Even after testing resumed in December 2015, backlogs of samples resulted in protracted delays in delivering samples to sites, seriously jeopardising the four-week turnaround time. Challenges at the national laboratory affected all sites (intervention and control). While this did not directly affect

implementation of the intervention in terms of patient flow, workflow or infant tracking, the intervention was compromised by the laboratory not functioning optimally. In response to this challenge, CHAI's laboratory service team intensified efforts to provide management support to the national testing laboratory and logistics unit, to ensure timely orders and delivery of commodities required for testing and avoid further disruptions to testing. Still, turnaround times were long.

Another factor contributing to delays in testing arose from uncertainty around the continuity of the sample transportation system due to a funding gap (October –December 2015) and general inefficiencies (healthcare workers not sending DBS samples for testing in a timely fashion). With the MOHCC having secured funding for the current sample transportation system, the intervention team attempted to strengthen on-site support mechanisms to ensure that samples were sent to the laboratory in a timely manner and that results were reported back to the sites within four weeks. This was done by (a) assessing site-specific bottlenecks in the sample transport system and providing feedback to MOHCC, and (b) supporting sites with phone airtime to follow up with caregivers, and using the SMS notification platform that alerts clients (upon consent to receive notifications) when EID test results would be available for collection at the site.

3. Impact evaluation methods

3.1 Study design

This impact evaluation was a cluster-randomised controlled trial of an intervention that integrated EID services and health facility-based EPI services in Zimbabwe.

3.1.1 Study outcomes

HIV testing:

- Proportion of known HIV-exposed infants that were tested for HIV by 16 weeks of age.

Receipt of HIV test results:

- Proportion of infants tested for HIV by 16 weeks of age who received test results by 20 weeks of age;
- Turnaround time between testing and receiving HIV results among those who tested by 16 weeks of age.

ART initiation:

- Proportion of HIV-positive infants initiated on ART by 20 weeks of age;
- Turnaround time between HIV results received and ART initiation among those who initiated by 20 weeks of age;
- Age at ART initiation among those who initiated ART by 20 weeks of age.

Immunisation impact and costing:

- Proportion of children receiving pentavalent 1 over the study period;
- Cost per additional HIV test by 16 weeks of age;
- Cost per additional ART initiation by age 20 weeks of age.

3.1.2 Treatment assignment

Health facilities were the unit of randomisation, rather than individuals. Randomisation occurred after the baseline data collection. Twenty-nine facilities (14–15 per arm) were randomised to intervention and control, according to the minimum-maximum t-statistic methodology, to ensure balance on covariates during the pre-intervention period (Essajee et al. 2015) given the small number of study sites. In this method, one of many simulated randomisations is chosen according to pre-specified criteria to ensure maximum balance across a number of observed covariates.

For this study, a series of 1,000 randomisations were performed in Stata, after which a programme was run to regress individual variables against treatment assignment. These individual regression variables included the baseline value of primary and secondary outcomes, an urban/rural dummy, a Harare versus other province dummy, baseline DBS sample turnaround time, proportion of pentavalent 1 immunisations provided via outreach activities versus at the health facility, an index or other measure of stock-outs, and other covariates identified as potential confounders in the baseline analysis. The randomisation method with the minimum maximum t-statistic in these regressions was chosen as the randomisation assignment for this evaluation.

Spillover effects from intervention to control sites were limited by excluding health facilities within 10 kilometres of others in the study. Also, contamination was minimised by excluding health facilities with active relevant research occurring at the site at the onset of this study.

Health facilities and caregivers could not be blinded to the intervention due to the nature of the intervention. The data needed to assess study outcomes is routinely collected at all health facilities with ART services. The SOC training provided at both control and intervention sites covered reporting procedures to ensure that reporting on variables relevant to the study design was consistent across all sites.

3.1.3 Inclusion and exclusion criteria

All public health facilities across Zimbabwe that provided ART and EPI services were eligible for the study, provided they met three criteria:

- They did not have active, relevant research ongoing at the site;
- The site was reasonably accessible for study staff to visit; and
- The site was not within 10 kilometres of another selected site.

Based on MOHCC EPI data (2014b) and ART initiation data from selected months in 2014 after Option B+ was implemented, 52 health facilities were identified as potentially meeting these criteria. Forty-six facilities had sufficient EPI volumes (more than 500) and initiated infants on ART, and six facilities initiated infants on ART and had unknown EPI volumes. During province- and district-level sensitisation, study staff determined whether those facilities met the study criteria. Only 39 sites initially appeared to meet all criteria and had a quantitative baseline data collection. However, during baseline data collection, 10 additional sites were excluded due to not meeting all criteria. Six sites in Bulawayo were excluded because they did not directly initiate children on ART, and other sites were excluded for a combination of reasons – research being conducted at the site (two sites), proximity to other study sites (two sites, one of which also had research taking place on-site) and the lack of an EPI register (one site).

3.1.4 Sampling methodology

All eligible sites were included in the sample, and all infants who were seen in the health facilities and were eligible for the first dose of pentavalent were included. As such, paediatric patients visiting study sites for care between 1 January and 31 July 2015 were included in the pre-intervention period measures if they were no older than 16 weeks as of 1 January 2015. Paediatric patients visiting study sites for care between 1 October 2015 and 30 April 2016 were included in the study period measures if they were no more than 16 weeks of age on 1 October 2015.

3.1.5 Power calculation

To estimate the minimum detectable difference in our study outcomes, we first used estimated power calculation parameters and later updated these estimates based on data collected from the pre-intervention period (the seven-month period prior to study initiation) in control facilities. The updated estimates are shown below. We assumed that both arms of the study would experience a similar minimum of health facility clusters with specific outcomes, average cluster size and rho (σ). Using these parameters, we then estimated the minimum value required in intervention facilities to detect an effect when comparing the intervention to the control group. The calculations used the intraclass correlation coefficient (rho [σ]) rather than kappa because the study outcomes were large proportions (Bruhn and McKenzie 2009). Where possible, rho was estimated using the pre-intervention data from random effects models in Stata. For outcomes with few facilities (n < 8) during the baseline data, the intraclass correlation coefficient was not possible to estimate and a conservative value of 0.20 was used.

The following formula (A) was used for calculations with proportions (Rutterford, Copas and Eldridge 2015), where π_1 is the minimum value required to detect an effect in the intervention facilities:

$$c = 1 + (z_{\alpha/2} + z_{\beta})^2 \frac{[\pi_0(1-\pi_0) + \pi_1(1-\pi_1)] * [1 + (m-1)\rho]}{m(\pi_0 - \pi_1)^2}$$

The following formula (B) was used for calculations with continuous outcomes (Hayes and Moulton 2009), where μ_1 is the minimum value required to detect an effect in the intervention facilities:

$$c = 1 + (z_{\alpha/2} + z_{\beta})^2 \frac{[{\sigma_0}^2 + {\sigma_1}^2] * [1 + (m-1)\rho]}{m(\mu_0 - \mu_1)^2}$$

The following assumptions were included in all calculations:

Parameter	Value
Alpha (α)	0.05
$Z_{\alpha/2}$	1.96
Power (β)	0.8
Z_{β}	0.84

These values, and the final outcome values needed to detect a statistically significant effect of the intervention, are listed in Table 1.

Table 1: Parameters used for power calculations and corresponding estimated minimum detectable value required in intervention facilities to detect an effect

Outcome	Formula	Estimated number of clusters/ health facilities per arm	Mean cluster size	Rho	Estimated value for control health facilities (pre-intervention value)	Value required in intervention health facilities to detect an effect
1: Proportion of known HIV-exposed infants tested for HIV by 16 weeks of age	A	14	77	0.11	0.84	**0.96**
2.a: Proportion of infants tested for HIV by 16 weeks that received their results by 20 weeks of age	A	14	65	0.6	0.42	**0.81**
2.b: Turnaround time between testing for HIV and caregiver's receipt of results	B	11	30	0.28	40 days (SD=11.0)	**33.3 days**
3.a: Proportion of HIV-positive infants that initiate on ART by 20 weeks of age	A	6	5.4	0.18	0.33	**0.80**
3.b: Turnaround time between receiving HIV results and ART initiation	B	4	1.5	0.20	80.3 days (SD=35.0)	**11.0 days**
3.c: Age at ART initiation (days), among those who initiated by 20 weeks of age	B	4	1.5	0.20	97.0 days (SD=24.0)	**49.0 days**
4: Proportion of children receiving pentavalent 1*	B	14	1,112	0.20	0.85	**0.80**

Note: * Calculations assumed a non-inferiority analysis and the boundary was established at 5% difference based on conversations with MOHCC.

The presented calculations are those estimated using pre-intervention data collection after the study outcomes were revised. In the original design, our study outcomes were focused primarily on ART initiation. Upon updating the study power calculations with data from the pre-intervention period, we noted the low power to detect change in ART outcomes, as illustrated in the above calculations. Therefore, we revised our study outcomes to examine not only ART initiation outcomes, but also the effect of the intervention on HIV testing and the receipt of test results, for a more comprehensive picture of the intervention effects throughout the HIV testing cascade.

3.2 Data collection and analysis

The baseline assessment for the pre-intervention period occurred in July and August 2015 and endline data collection for the study period occurred in May 2016.

Data collection for the main study outcomes was based on routinely collected data from medical registers (ANC register, PNC register, HIV-exposed infant register, HIV infant diagnosis laboratory register, HIV testing and counselling register, pre-ART register, opportunistic infection/ART patient care booklet and ART register) and the Logistics Management Information System database. All patients with routine immunisations and/or HIV testing in the appropriate age window at the study health facilities were included in the data collection.

In addition to data collection for the main study outcomes, several other types of data were collected to assess the perspectives of the caregivers and healthcare workers on integrating EID and EPI services. A quantitative questionnaire, administered in interview format by the study data collectors, aimed to assess caregivers' attitudes towards HIV testing and the integration of infant HIV testing and treatment referral and routine EPI services. These quantitative interviews consisted primarily of closed questions with multiple-choice responses. Participants were recruited from the EPI session before or after their EPI visit and were approached after a general introduction from the EPI nurse or person in charge.

The perspectives of healthcare workers concerning the process and challenges of integration were collected through qualitative interviews. For these interviews, the peson in-charge provided the initial information for the health facility and introduced the enumerators to other EPI or nurse staff. One or two staff members per health facility were invited for each interview. Interviews with healthcare workers were audio recorded using Android tablets loaded with SurveyCTO software, and were then fully transcribed. Because some interviews were conducted in the local language (Shona), translation to English was done during the transcription process. No compensation was provided for study participation.

Trained enumerators collected all quantitative data using Android tablets. Study data collection was electronic, wherever possible, to reduce data entry errors and improve data quality. Electronic data collection helped to improve the quality of the data collected, as many fields had built-in quality control (for example, for dates, numbers and multiple-choice options). Range checks and non-response checks were also built into the data collection programme. The data collection tools were designed to cross-reference between registers to minimise the likelihood of errors.

In five control health facilities and seven intervention facilities, we compared the number of HIV-exposed infants gathered from the HIV infant diagnosis register by also collecting information from the ANC and PNC registers and the HIV-exposed infant register.

Daily data quality checks were employed to assess the data as it came in electronically. To this end, the total count of child entries was collected and compared to the field entry, along with the median response of health facility-based entries.

3.2.1 Data cleaning and categorisation

Data for the pre-intervention period (1 January – 31 July 2015) and study period (1 October 2015 – 30 April 2016) was included if it was recorded within the appropriate timeframe. Of those, data was included for each outcome if the dates of DBS sample collection and birth were reported appropriately.

For missing data, no imputation was conducted for the primary analyses. If any date or information that was necessary for the primary outcomes was missing for a patient, that patient was not included in the calculations. The most incomplete indicator was the date of caregiver's collection of the child's HIV test results. During the pre-intervention period, five of the health facilities did not have the caregiver's date of collection recorded during the pre-intervention period. Among the remaining 24 facilities, the enumerator was not required to enter the caregiver's date of collection into the tablet, which resulted in missing data on this variable. During the study period, one health facility did not routinely record the caregiver's results collection date.

Coverage of the pentavalent 1 vaccination was calculated as the total number of vaccinations recorded over the seven-month study period, compared with the reported annual target for pentavalent 1 vaccines from Zimbabwe's National Statistics Agency. Three health facilities were removed in this analysis: one did not have vaccination data available to record, and two did not have reliable estimates for the pentavalent 1 target population.

3.2.2 Data analysis

First, balance in the two arms was assessed using unweighted t-tests for continuous outcomes and chi-square tests for categorical characteristics. These tests and corresponding p-values examined whether there were any general or global differences in the distribution of the selected characteristics between the two arms.

For the HIV testing and treatment cascade outcomes, we used unweighted t-tests to compare outcomes during the study period for primary analysis. We used t-tests of health facility-level summary data, as there were fewer than 20 facilities per arm; facility-level summary analysis is considered the most robust method of analysis for a cluster-randomised controlled trial with fewer than 20 facilities per arm (Hayes and Moulton 2009). The primary t-test was unweighted to allow each health facility to contribute equally. However, comparisons were also performed, to account for varying facility sizes, by running individual-level bi-variable regressions, accounting for facility-level clustering. As a secondary analysis, unweighted t-tests examined the change in the study outcomes from the pre-intervention period to the study period (a difference-in-difference analysis).

To incorporate individual- and health facility-level characteristics into the analysis, generalised estimating equations were used using individual-level data, which were then

clustered within facilities. These population average models allowed us to control for any individual- and facility-level differences found between comparison groups during the pre-intervention period, and thereby reduce the chance of confounding, while accounting for clustering of the individual-level data within facilities. The Stata programme 'xtlogit' with a 'pa' option was used to fit these two-level models.

We conducted a number of sensitivity analyses in addition to those described above. We changed the definition of the intervention window to start later and be shorter, to allow time for the scale-up of the intervention and remove the period when the Harare national laboratory had reagent stock-outs. Similarly, we restricted the analyses to only those health facilities that did not submit samples to the Harare laboratory. To assess the heterogeneity of the impact, we ran models that examined whether there was any effect measure modification based on sex of the child or the presence of non-governmental organisations (NGOs) operating in the area.

For the outcome on immunisation impact and costing, we ran a non-inferiority analysis to demonstrate that the outcomes in the intervention arm were not worse than the outcomes in the control arm, using a non-inferiority margin of 5 per cent. As compared to the aforementioned testing, in which we assessed whether there was a difference in the outcome between the two study arms, the non-inferiority test assessed whether the two arms were equal or the intervention arm is better (whether the intervention arm was non-inferior to the control arm).

For qualitative data, codes for analysis were developed based on topics discussed during the interviews with healthcare workers.

Finally, programme costs were tracked throughout the study and classified as either programmatic (including routine monitoring and evaluation that would be part of programme scale-up) or evaluation costs. Costs were also coded as facility-, district- and national-level costs. All costs were expressed in US dollars. Using the number of additional outcomes in the intervention arm (infants tested, ART initiations) plus costing data, we calculated the cost per HIV-positive test by 16 weeks of age and the cost per ART initiation by 20 weeks of age.

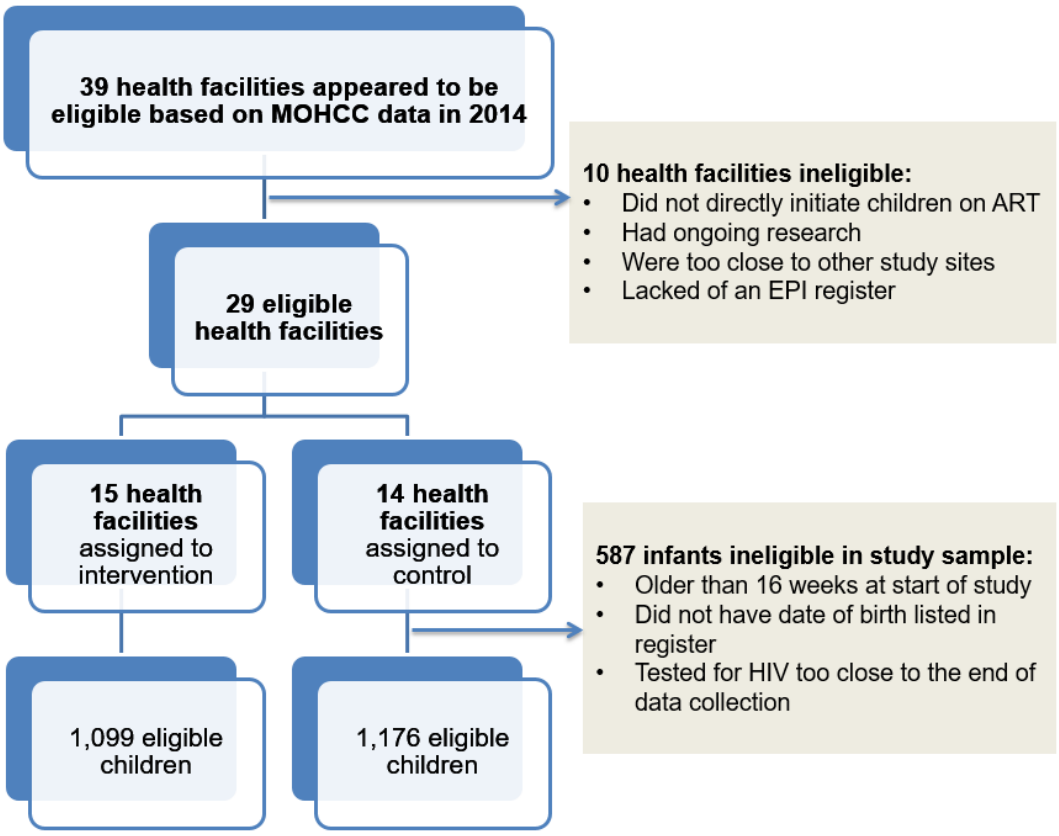
The proposed analysis plan included a number of additional sensitivity analyses to tease apart differences in the data, based on different time windows and subgroups. Because our primary and secondary analyses demonstrated very consistent null associations, we did not perform all originally proposed sensitivity analyses, as we felt that additional analyses might be construed as searching for significant findings rather than accepting a consistent null association.

Data analysis occurred in Stata version 13. For qualitative data, we used Dedoose software to facilitate the organisation and retrieval of data. Statistical significance was defined as $p < 0.05$.

4. Results

Figure 3 describes the final study sample.

Figure 3: Study flow chart



4.1 Balance of characteristics between study arms

Tables 2 and 3 show the relative balance of health facility- and patient-level characteristics between the two arms during the study period. There were 1,176 known exposed infants in control facilities and 1,099 in intervention facilities during the study period. There were no statistically significant differences in the other health facility- or individual-level characteristics. Although not significant, there were slight differences by age and sex. Mean (standard deviation (SD)) age at first test was 8.0 (5.9) weeks in control facilities and 8.8 (6.3) weeks in intervention facilities (p=0.1). Although GPRS printers appeared to be equally available at intervention and control facilities, they were more likely to be in use at control facilities.

There were substantially more missing data points for sex at intervention health facilities than at the control facilities. This difference highlights potential differences in data quality and record-keeping between the two arms. Specifically, the HIV infant diagnosis register did not have a column for sex, and therefore the recording of sex in the comments section depended on the health facility-level policy.

Table 2: Distribution of health facility-level characteristics by treatment arm

	Control arm		Intervention arm		
	N	Health facility average value	N	Health facility average value	p-value*
Total health facilities	14		15		
Number of known HIV-exposed infants per facility (facility mean, SD)	14	84 (38.4)	15	73.3 (64.3)	0.6
Catchment area population size (facility mean, SD)	14	43,512.3 (33,803.7)	15	35,904.7 (33,962.9)	0.6
Target population size for vaccination (facility mean, SD)	14	1,367.5 (1,444.3)	15	1,614.5 (2,169.0)	0.7
Stock-out of paediatric ARV medications in past 7 months					0.4
Often	1	7.1%	1	6.7%	1.0
Rarely	5	35.7%	2	13.3%	0.2
Never	8	57.1%	12	80.0%	0.2
Stock-out of vaccines in past 7 months					0.5
Often	1	7.1%	1	6.7%	1.0
Rarely	5	35.7%	3	20.0%	0.3
Never	7	50.0%	7	46.7%	0.9
Other	1	7.1%	1	26.7%	0.2
Other NGO working within health facility					0.4
Yes	12	85.7%	11	73.3%	-
No	2	14.3%	4	26.7%	-
GPRS printer for lab results					0.1
Yes and in use	2	14.3%	3	20.0%	0.7
Yes but not in use	4	28.6%	0	-	0.03
No	8	57.1%	12	80.0%	0.2
Harare lab					0.5
Yes	10	71.4%	9	60.0%	
No	4	28.6%	6	40.0%	

Note: * P-value was generated as follows: (1) for continuous outcomes, t-tests were used to compare means; (2) for categorical outcomes, chi-square tests were used to compare distributions.

Table 3: Distribution of individual-level characteristics by intervention arm

	Control arm		Intervention arm		
	N	% within arm	n	% within arm	p-value*
Total known exposed infants	1,176	100	1,099	100	
Sex					0.7**
Male	284	24.2	34	3.1	< 0.01
Female	287	24.4	37	3.4	< 0.01
Missing	605	51.5	1,028	93.5	< 0.01
Age (weeks) at first test (mean, SD)	8.0	5.9	8.8	6.3	0.1
Provinces					0.2
Harare	354	30.1	512	46.6	0.5
Manicaland	45	3.8	121	11.0	0.3
Mash Central	478	40.7	221	20.1	0.3
Mash West	107	9.1	0	-	0.3
Masvingo	69	5.9	182	16.6	0.4
Mat South	123	10.5	0	-	0.3
Midlands	0	-	63	5.7	0.3
District					0.4
Harare	354	30.1	512	46.6	0.5
Chipinge	45	3.8	121	11.0	0.3
Bindura	0	-	105	9.6	0.2
Centenary	0	-	60	5.4	0.2
Mazowe	364	31.0	0	-	0.05
Mt Darwin	114	9.7	56	5.1	0.6
Chegutu	107	9.1	0	-	0.4
Masvingo	69	5.9	0	-	0.4
Chiredzi	0	-	142	12.9	0.3
Chivi	0	-	40	3.6	0.3
Beitbrudge	123	10.5	0	-	0.3
Gokwe North	0	-	63	5.7	0.3

Note: * P-values reported from two methods: (1) for categorical outcomes, chi-square tests accounting for clustering at the health facility level; (2) for continuous outcomes, adjusted Wald F-test adjusting for clustering at the health facility level.
**Missing data for sex was excluded from this global p-value calculation.

With respect to the study outcomes during the pre-intervention period (Table 4), there were no significant differences between the arms. With respect to trends, outcome 1, (the proportion of known HIV-exposed infants tested for HIV by 16 weeks of age) was marginally higher in the control facilities (95%) than the intervention facilities (925; p = 0.05). Note that these proportions were quite high in both arms during the pre-intervention period, but cannot be interpreted in an absolute sense, as the study methodology likely underestimated the number of known HIV-exposed infants identified through other entry points.

Additionally, the receipt of HIV test results by 20 weeks of age was equally high in both arms, but this value was only calculated among those with complete data; as mentioned above, the receipt of results was notoriously incomplete. Turnaround times between testing and receiving HIV results were quite long, approximately 60 days in both

intervention and control facilities. In intervention and control facilities, the proportion of HIV-positive infants who initiated ART by 20 weeks of age was quite low, below 50 per cent. Only seven control facilities and eight intervention facilities identified any HIV-positive infants by 16 weeks of age.

Table 4: Distribution of pre-intervention period outcome values by treatment arm

	Control			Intervention			
	n health facil-ities	Mean	SD	n health facili-ties	Mean	SD	p-value
Outcome: The proportion of known HIV-exposed infants that were tested for HIV by 16 weeks of age	14	0.95	0.03	14	0.92	0.06	0.05
Outcome: The proportion of infants tested for HIV by 16 weeks of age that received their results by 20 weeks of age*	3	0.88	0.12	7	0.70	0.19	0.2
Outcome: Turnaround time (days) between testing and receiving HIV result among those who tested by 16 weeks of age	3	60.9	6.5	7	63.6	21.9	0.9
Outcome: The proportion of HIV-positive infants that initiated on ART by 20 weeks of age	7	0.43	0.45	8	0.44	0.42	1.0
Outcome: Turnaround time (days) between HIV test result collection and ART initiation among those who initiated by 20 weeks of age	0	-	-	2	0.5	0.71	-
Outcome: Age at ART initiation (days), among those who initiated by 20 weeks of age	5	90.2	47.2	5	79.0	20.8	0.6

Note: *The health facilities that were missing date information were not included in these outcomes.

4.2 Impact of the intervention

During our study period, we observed no significant difference in the HIV testing at 16 weeks of age, receipt of test results by 16 weeks of age and ART initiation by 20 weeks of age between the two arms. Table 5 displays the unweighted t-tests for outcomes 1.a–3.c for the study period. Similar to the pre-intervention period, the control group tended to have slightly better outcome measures for the proportional outcomes compared to the intervention arm during the study period. Though not significant, the proportion of infants receiving HIV tests by 20 weeks of age was higher in the control than in the intervention group (83% versus 75%; p = 0.5). Similarly, the proportion of HIV-positive infants initiated on ART was higher in the control arm than the intervention arm (36% versus 28%; p = 0.6). In comparison (though not significant), the continuous outcomes tended to

be better in the intervention arm than the control arm. The turnaround time between HIV testing and receiving test results was lower in the intervention arm than the control arm (56.9 days versus 64.2 days; p = 0.2), and the age at ART initiation was lower in the intervention arm (83.3 days versus 96.8 days; p = 0.4). Similar results were found for the bi-variable comparisons, accounting for varying cluster sizes and ln-transformed comparisons.

Table 5: Distribution of study period outcome values by intervention arm

	Control			Intervention			
	n health facil-ities	Mean	SD	n health facil-ities	Mean	SD	p-value
Outcome: The proportion of known HIV-exposed infants tested for HIV by 16 weeks of age	14	0.93	0.06	15	0.91	0.05	0.4
Outcome: The proportion of infants tested for HIV by 16 weeks of age that received their results by 20 weeks of age*	13	0.83	0.10	15	0.75	0.20	0.2
Outcome: Turnaround time (days) between HIV testing and receiving HIV results among those who tested by 16 weeks of age	13	64.2	13.5	15	56.9	15.2	0.2
Outcome: The proportion of HIV-positive infants that initiated on ART by 20 weeks of age	11	0.36	0.39	13	0.28	0.43	0.6
Outcome: Turnaround time (days) between HIV test result collection and ART initiation among those who initiated by 20 weeks of age	5	0	0	4	0.38	0.75	0.3
Outcome: Age at ART initiation (days), among those who initiated by 20 weeks of age	6	96.8	23.8	5	83.3	24.6	0.4

Note: *This missing date information was not included in these outcomes.

Overall, the difference-in-difference analysis, as presented in Table 6, did not show any statistically significant improvements from the pre-intervention period to the study period due to the intervention. The proportion of infants who received HIV test results by 20 weeks of age increased for the intervention arm, whereas it dropped in the control arm (absolute difference: 10 percentage points; p = 0.6). The turnaround time between testing and receiving results received dropped by 3.5 days in the intervention arm, compared with an increase in 0.5 for the control arm. Only two control health facilities were able to estimate a change in the age at treatment initiation, finding a decrease of 23 days (standard error 25); the 6 intervention facilities in the comparison arm had a 5-day decrease (standard error 13.2) in the age at treatment initiation.

Table 6: Difference in the change over time between treatment arms

	n health facili-ties	Difference- in-difference	Stan-dard error	p-value
Outcome: The proportion of known HIV-exposed infants who were tested for HIV by 16 weeks of age	28	0.02	0.03	0.5
Outcome: The proportion of infants tested for HIV by 16 weeks of age who received their results by 20 weeks of age	10	0.10	0.18	0.6
Outcome: Turnaround time (days) between testing and receiving HIV results among those who tested by 16 weeks of age	10	–4.0	11.0	0.7
Outcome: The proportion of HIV-positive infants who initiated ART by 20 weeks of age	14	–0.05	0.28	0.9
Outcome: Turnaround time (days) between HIV test result collection and ART initiation among those who initiated by 20 weeks* of age	2	-	-	-
Outcome: Age at ART initiation (days), among those who initiated by 20 weeks of age	6	17.8	25.1	0.5

Note: * Too few health facilities had data to calculate an estimate.

Given the potential small (though not statistically significant) differences in sex, as well as health facility-level outcomes during the pre-intervention period, we adjusted for these characteristics in individual-level, mixed effect logistic models that accounted for clustering at the facility level. We found similar results, in that there was no significant difference in the odds of an infant being tested for HIV by 16 weeks of age, and receiving the test result and being initiated on ART by 20 weeks of age. Similarly, we did not find a significant difference in the odds of our outcomes when we restricted our sample to non-Harare laboratories or for outcomes after 1 January to examine a per protocol effect. Finally, we did not see any evidence of the heterogeneity of the effect based on the sex of the infant or the presence of NGOs (data not shown).

For the sensitivity analysis and to estimate known HIV-exposed infants using multiple register sources more effectively (rather than simply using the HIV infant diagnosis register, which may not capture all known exposed infants at the health facility), we found that the number of known exposed infants was similar between the two data sources (HIV infant diagnosis register versus PNC/ANC and HIV-exposed infant registers). Eight of the 11 health facilities had known HIV-exposed infant estimates from

the PNC/ANC register that were within 15 units of the total number of HIV-exposed infants recorded in the HIV infant diagnosis register. Only one health facility had a noticeable difference, with the HIV infant diagnosis register recording 67 more infants than the PNC, ANC, and HIV-exposed infant registers combined. Notably, in the intervention arm, the HIV infant diagnosis register had more infants on average than the ANC, PNC, and HIV-exposed infant registers combined (mean difference: 11 more infants; SD: 17 infants), whereas the control arms had fewer infants, on average, in the HIV infant diagnosis register than the combined ANC, PNC, and HIV-exposed infant registers (mean difference: 14 fewer infants; SD: 28 infants). As there was no evidence that using additional data sources led to substantially different numbers, additional analyses were not carried out with these numbers.

In a non-inferiority analysis examining outcome 4, the coverage of infants receiving pentavalent 1 over the study period for the intervention arm versus the control arm was not significantly different (absolute difference of –4.6%; 95% confidence interval: –21.1%, 11.8%). While the mean difference was not larger than the 5% boundary established for non-inferiority, the confidence interval for the mean difference in coverage did cross the 5% boundary, likely failing the non-inferiority test due to high variance rather than reduced vaccination rates.

Due to the fact that we did not observe an impact on infant HIV testing or ART initiation with the intervention, it was not possible to calculate the outcome on cost per additional HIV test by 16 weeks of age and the outcome on cost per additional ART initiation by the age of 20 weeks.

Given the lack of effect observed between the study arms, we did not further tease apart the data to examine the heterogeneity of this effect.

4.3 Caregiver and healthcare worker perspectives

A total of 143 infant caregivers were interviewed during endline data collection (74 from intervention facilities and 69 from control facilities). While caregivers were interviewed across provinces, most were from Mashonaland Central (35%) followed by Harare (29%), Manicaland (11%), Masvingo (10%), Midlands (7%), Mashonaland West (3.5%) and finally Matebeleland South Province (3.5%). The median age of the respondents was 27 years; the oldest participant was 50 and the youngest was 17. Most caregivers (more than 50%) were visiting the health facility for infant EPI services, and most came on foot. The median number of children per caregiver was two and the maximum was seven. Key findings on caregiver attitudes are provided in Table 7.

Table 7: Caregiver attitudes on HIV testing and service integration

HIV testing	Control	Intervention
Overall, they believe **the healthcare workers at this health facility provide high-quality services**	88%	93%
Would get an HIV test **if offered at her/his health facility**	100%	97%
Do not trust **healthcare workers at her/his health facility to keep** HIV status confidential	7%	11%
Know mothers who are concerned with being recognised while receiving HIV services	41%	33%
Know mothers who fear HIV testing	43%	38%
Integration		
Agree it is a good idea to…		
ask HIV status for **mothers** coming for EPI services	96%	93%
offer HIV testing for **mothers** coming for EPI services	97%	96%
offer HIV testing for **infants** coming for EPI services	97%	93%
Believe that mothers who fear HIV testing may not come for EPI **if offered HIV testing during EPI visit**	58%	41%

In addition to the statistics in Table 7, when asked about their level of satisfaction (dissatisfied, neutral, or satisfied), most caregivers appeared to be satisfied with the care they were receiving (92% in intervention facilities and 87% in control facilities), but key issues noted by some caregivers included long wait times and inadequate human resource capacity. Only 39 per cent of caregivers in intervention facilities reported noticing changes in how the health facility operated over the previous year. Of those who noted changes (n = 18 in control facilities; n = 29 in intervention facilities):

- Compared with caregivers at control facilities, caregivers at intervention facilities were more likely to report noticing more healthcare workers at the health facility in the last year (62% versus 33%);
- Caregivers at control facilities were more likely to report the health facility being less crowded over the previous year (39% versus 14% reported by caregivers in intervention facilities); and
- About one-third of caregivers in intervention facilities (34%) and in control facilities (39%) noted more availability of supplies than previously, and around half (41% in intervention facilities and 56% in control facilities) noted shorter waiting times than previously.

The aim of the healthcare worker interviews was to identify successes and challenges with HIV and EPI integration and understand other key perspectives from healthcare staff working on the ground. All but two of the 48 healthcare workers interviewed were key to delivering infant HIV care procedures.

Of those interviewed at intervention facilities, all nurses indicated that they had successfully implemented EPI and paediatric HIV services. Overall, most healthcare staff felt that integration was a positive initiative and should be expanded to all facilities. As one healthcare worker said, ‘Integration of services reduce[d] missed opportunities’ in

identifying HIV-positive mothers and infants. Staff members noted the following positive changes due to service integration:

- Increase in retesting for mothers, since healthcare workers were able to capture them when they visited for EPI;
- Identification of mothers who defaulted on ART;
- Identification of mothers who tested negative during ANC but seroconverted later; and
- Potential vertical transmissions averted by identifying HIV-positive mothers and getting them on treatment and/or putting infants on prophylaxis.

Other positive aspects of integration identified by health facility staff included the following:

- Children received all of the services they needed in one visit;
- Caregivers' burden was reduced, because they did not have to make multiple trips to the health facility;
- Healthcare workers and caregivers had a better rapport, because the healthcare worker was providing more comprehensive care;
- Caregivers did not have to go to as many points in the health facility, making life easier for staff and patients alike;
- Integration enabled the identification of children born at home who would otherwise be missed; and
- There was potential for earlier ART initiation among HIV-positive children.

However, a number of challenges were identified. For example, one healthcare worker noted,

> 'The environment is very difficult to do DBS. The schedule of EPI is tight and it is difficult to dry the sample and we are forced to ration service provision. Even ... [HIV testing and counselling] is difficult; we don't have tents to provide privacy. Village healthcare workers are responding by preparing some shades but it is difficult to provide a conducive environment for testing.'

In general, healthcare staff interviewed for this evaluation reported two main challenges:

- Delays in the turnaround of HIV test results: many results were not received by the health facility within four weeks; therefore, it was difficult to link results with EPI visits. There were some reports of patient frustration with laboratory delays after repeated follow-ups at the facility.
- Lack of human resources, which made it difficult for nurses to integrate services and meant longer waiting times for patients. In some cases, this staffing shortage prevented staff members from offering HIV testing or discouraged patients from waiting for an HIV test.

Besides these key issues, the following challenges were also reported to have affected the successful implementation of service integration:

- Infrastructure was a challenge at some health facilities, and it was difficult to offer HIV testing within the EPI area;
- There was a lack of resources to conduct regular EPI services;
- Some facilities had shortages of paediatric HIV drugs;

- The transient patient population, without accurate contact information, made it difficult to follow up at some facilities;
- Multiple registers made it difficult for some staff to record timely, accurate data;
- Some caregivers refused to be tested for HIV or to initiate their child on ART (rare); and
- There was a shortage of rapid diagnostic HIV tests (noted at one health facility only).

Clearly, these challenges need to be addressed before service integration can reach its full potential impact on patient testing coverage and linkages to care in this environment. Additionally, it is important to consider that the impact of integration may be smaller and more difficult to estimate in a low-prevalence environment. Other key points related to the HIV testing and counselling and EPI programmes, as identified by healthcare workers, were:

- The number of children testing HIV positive has declined because of successful PMTCT programmes;
- Poor male partner participation and/or stigma around HIV status disclosure continues to be a problem, and likely negatively affects mother and child testing and treatment adherence. One healthcare worker noted that mothers bringing their partners with them for HIV testing got priority in the waiting line; they had success with this approach;
- Some women may avoid returning to the health facility to collect their children's results out of fear that they are HIV-positive. Therefore, it is important to communicate the importance of initiating treatment early so that women understand that early treatment offers hope for their children;.
- There are challenges with EPI coverage in some religious communities, such as the Apostolic sect, due to distrust of vaccines. Therefore, outreach efforts are needed to cover this population; and
- Strong counselling programmes are needed to prevent HIV patients defaulting from treatment, which is relatively common.

Despite the challenges of integrating EID and EPI services, healthcare workers were overwhelmingly positive towards the approach and felt that integration could be successful with increased staff support. Figure 4 presents more quotes from healthcare worker interviews.

Figure 4: EID and EPI integration in the words of healthcare workers

'Some of the mothers are not willing to come on their own for HIV testing, but if we integrate these services together, that means every woman who is HIV positive [can be counseled] for HIV.'	'We have noted [that] if mothers get tested [as HIV] negative in [the] labour ward, they do not continue to come for testing until the next pregnancy. So when they come for EPI we give them information [and] they are opting to get tested after [us] telling them the benefits.'
'At first, we were afraid that this would increase our workload [but] as time went on we found that it was actually lessening our burden as all the under-fives were seen… and offered… services in one room. It has helped us track all our [HIV-] exposed infants and most of them got their ART as soon as they received their results.'	'If we manage to integrate EPI and HIV properly it will help in the reduction in new infections in paediatric services.'

4.4 Intervention cost

The total cost of the intervention, as implemented, was US$44,104 (see Table 8). This figure excludes roughly US$19,000 spent on personnel costs and US$17,500 spent on administrative costs. Our intervention did not involve changes to infrastructure or staffing in the EID or EPI programmes, but rather focused on using EPI as a mechanism to increase referral to EID testing. While we did not see cost differences or administrative savings from integrating the two programmes, with the additional activities for the EPI staff we may have experienced an increase in the administrative costs or staffing costs.

Table 8: Cost of intervention

Item activity	Cost (US$)	
		USD
Site support visits	**9,568**	**9,568**
Airtime for client follow-up	435	435
Site support team meals and accommodation	7,124	7,124
Fuel	343	343
Car hire	1,666	1,666
	34,000	
Training costs	26,908	**34,000**
Conference	1,367	26,908
Printing of training material	5,725	1,367
Training facilitation fees for government partners		5,725
	536	
Printing costs	536	**0**
Printing of service integration job aid for integration sites		
	44,104	0
Total		

Given that HIV positivity is low in this population, and that we did not see an impact on additional HIV-positive infants identified in the intervention arm (compared with the

control arm), even if our study underestimated the impact of the intervention, the cost per additional HIV-identified infant and per HIV-positive infant treated would be high compared with other interventions. Service integration, in the way it was executed in this study, would need to be carefully considered before scaling up nationally and adjustments would be necessary for it to be done in a cost-effective way.

5. Discussion

Overall, this cluster-randomised controlled trial of the integration of EPI and EID services in Zimbabwe clinics from October 2015 to April 2016 did not have a statistically significant impact on the EID of HIV, nor any discernible impact on early initiation on ART. With respect to early HIV testing for infants, we observed that the level of testing of known HIV-exposed infants by 16 weeks of age was similar between the intervention and control arms of the trial, as was the proportion of those tested by 16 weeks who then received their results by 20 weeks of age. A very small number of HIV-positive infants were identified in both trial arms, likely due to the successes of the Option B+ programme in Zimbabwe, leading to smaller numbers of infants seroconverting.

Among the HIV-positive infants, similar proportions were initiated on ART by 20 weeks of age in the two trial arms, and the turnaround time between testing for HIV and receiving results was similar, as was the age (in weeks) at treatment initiation. From a qualitative perspective, healthcare workers both approved of and supported EPI and EID integration. However, the interviews and discussions with caregivers identified important challenges, including continued laboratory delays, staff turnover and limited human resource capacity, and inadequate time to document patient information.

From these results, we conclude that given the successes of Option B+ and the current challenges in Zimbabwe's laboratory and healthcare system, EPI and EID integration did not increase early diagnosis of HIV or early ART initiation.

5.1 Strengths

The strengths of this impact evaluation included its randomised study design to minimise confounding, clustering by health facility to minimise spillover effects, relatively long timeframe (seven months), triangulation of data across several sources and sensitivity analyses to examine the robustness of the findings. In addition, frequent study monitoring and interviews with caregivers and healthcare workers provided contextual information to better understand the study results and ways to strengthen integration programmes in the future.

5.2 Challenges and limitations

The lack of impact that we observed in this trial may be attributed to implementation challenges and study limitations, which likely affected the internal and external validity of the findings. With respect to implementation, a number of important challenges may have contributed to the lack of impact. Key challenges included limited human resources to maintain records and keep up with service demands. Health facility staff reported being overstretched and unable to spend adequate time on recording patient dates and other information across multiple registers, and some caregivers reported long waiting times. High staff turnover also may have led to a dilution of knowledge about the

intervention and a de-emphasis of EID and EPI integration in the face of other health facility training priorities. Another challenge was the inability to integrate testing facilities nearby or within the EPI service stations at many facilities, due to infrastructure limitations. As such, staff members were unable to confirm that referred mothers from the EPI station were indeed attending the HTS for testing. Integration was limited to EPI services occurring within the health facility; EID testing did not occur during outreach activities, which are an important part of immunisation programme coverage. Some healthcare workers noted transient patient populations, making patient follow-up difficult. Finally, one of the most pressing implementation challenges was laboratory delays and reagent shortages, which severely limited the ability to provide timely results to patients.

With respect to the limitations of this study, although there was considerable effort to ensure high-quality data capture, the data collected was incomplete due to challenges with record-keeping at health facilities. In particular, it was difficult to identify the total number of infants exposed to HIV who came through a given health facility, given the multiple entry points to the facility. Hopefully the mother-infant pair registry system planned in Zimbabwe will help to streamline identification of known HIV-exposed infants. Additionally, the dates of sample collection and results received were missing for many patients. As we did not find a difference in the distribution of missing dates between the intervention arm and control arm, missing data did not appear to be related to exposure group.

Therefore, we believe the inference of this study is not dependent on missing data. Regardless, data incompleteness is a systemic problem and should be addressed not only for further programme research, but also for improved programme monitoring and delivery. In addition, if the intervention did have an impact, it may have been more salient if we had been able to assess more accurately the total number of infants exposed to HIV who came through the health facility, and also to establish true testing dates without errors or missing data.

Potential risks to the study included healthcare workers behaving differently simply because they knew they were being observed (Hawthorne effects) or behavioural effects on control facilities (John Henry effects), as healthcare workers at control sites knew they were part of a study on service integration, received baseline SOC training and received visits from data collection teams. We attempted to minimise bias by holding the SOC training first (for control and intervention sites), followed by the intervention training after control site staff had returned to their health facilities.

Further, we accounted for changes from baseline by conducting a difference-in-difference analysis. In addition, visits to health facilities by government and NGOs are routine, and data collection activities were relatively uniform across intervention and control sites. There was also risk of contamination introduced by control and intervention arm sites in the same district having a common district health executive responsible for support and supervision. The intervention team had contact with sites only on three occasions over the seven-month implementation period, whereas the district health executives interact with sites at least monthly, and their influence on site performance may have been greater than our site support visits.

Although the study explicitly excluded sites where active research was being carried out by other NGOs, it was difficult to account for the potential confounding effect of financial incentives paid by some development partners under the Results Based Financing programme on study outcomes. That programme, which is funded by the World Bank's multi-donor Health Results Innovation Trust Fund at the request of the government of Zimbabwe, provides subsidies to health facilities and hospitals based on their performance in delivering a package of free health services to pregnant women and children under five years of age. The pervasiveness of the Results Based Financing programme is a possible explanation for why there is no difference between the performance of control and intervention sites across some outcomes in our study.

The external validity of the study is limited to Zimbabwe and the health facilities examined. This is particularly important given the differences in health facility design and patient flow between EPI and HTS that may occur in different locations, as well as differences in the laboratory networks and systems. Additionally, the prevalence of HIV-positive children was low in our sample; in locations where HIV-positive children are more common, the flow of patients may have altered the integration process and the results.

5.3 Policy recommendations

This study did not conclusively determine that integrating EPI and EID would not have an impact on early infant HIV testing and initiation of ART in any setting. Instead, we attempt to explain the limitations and challenges that arose during implementation, which other work should consider and attempt to mitigate while further investigating this question. As such, we hope that the challenges identified and lessons learned from this work will be useful for future investigations. The extreme importance of finding and initiating HIV-positive infants on to ARVs requires examination of this question in different settings, and potentially addressing some of the limitations of the design and implementation.

Specifically, future work investigating this question would benefit from: incorporating more intensive training with additional buy-in from health facility staff; focusing on facilities with adequate staffing; solving the laboratory challenges that result in delay; and assuring that the study includes ample facilities, given the low prevalence of HIV-positive infants at this time. More importantly, integration activities may be better focused, and have a greater impact, in high-HIV prevalence areas, rather than spread throughout all health facilities with HIV testing activities. A greater impact might be seen in areas with a higher prevalence of HIV in infants. At this stage, the integration as implemented here is not scalable in Zimbabwe, as multiple challenges with integration and laboratory systems need to be addressed.

We observed a relatively high EID coverage among known HIV-exposed infants in both the intervention and control health facilities. Although there were limitations with the data in estimating the number of known HIV-exposed infants at a given health facility – and thus the absolute values of these results cannot be interpreted in a literal fashion – the number of undiagnosed HIV-positive infants may be lower than previously thought. This area deserves further investigation.

Note that our study did not estimate the number of HIV infections averted due to EID and EPI integration. One potential benefit of the integration programme was greater identification of HIV-positive mothers and enhanced linkage to ART services, thereby potentially reducing vertical transmissions in this community. Measuring and estimating these outcomes was outside of the scope of this study but could be explored in future evaluations.

We did not find an improvement in EID or early ART initiation of HIV-positive infants as a result of our intervention to support the integration of EID and EPI. The intervention cost roughly US$43,000 to implement, which is high given the lack of impact. With a relatively low HIV prevalence in this population, and given that we did not identify additional HIV-positive infants in the intervention arm compared with the control arm, the cost per HIV-identified infant and per HIV-positive infant treated was relatively high even if our study underestimated the impact of the intervention.

Ultimately, although we did not observe an impact of EID and EPI integration in this trial in Zimbabwe, we do not believe that these results definitively show that EID and EPI integration does not, or cannot, work in any setting. Rather, given the relatively small number of HIV-positive infants in Zimbabwe due to the successes of the Option B+ programme, in conjunction with continued challenges in Zimbabwe's conventional laboratory testing system, we conclude that EID and EPI integration as implemented may not have the desired impact at this time. Addressing the challenges noted above could more accurately forecast the potential impact of integrating EID and EPI on paediatric HIV testing and ART initiation. In addition, providing of point-of-care HIV testing for EID will remove many of the challenges associated with EID laboratory testing and transporting samples, and therefore should be examined as a potentially important strategy to make an integrated programme more effective.

Integrating HIV testing and immunisation services could still be an effective way to improve health outcomes among HIV-exposed infants and increase the number of mothers who know their HIV status and are able to take appropriate actions for their health and the health of their children. Additional thought is needed at all levels to address the system-level challenges that may have contributed to the lack of effect seen in this study. Further efforts are needed to address the challenges of the low coverage of EID testing for infants and delays in treatment initiation for children.

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Although there have been successes in implementing an early infant diagnosis of HIV programme in Zimbabwe, challenges remain in linking mother-infant pairs to HIV testing, counselling and treatment services.

This report evaluates the impact of an intervention implemented by the Clinton Health Access Initiative to integrate Early Infant Diagnosis of HIV into routine Expanded Programme of Immunisation (EPI) services on infant HIV testing, test result turnaround time, time for treatment initiation for positive infants and on the volume of EPI services. The authors found no significant difference between the intervention arm and the control arm in the HIV testing rates, receipt of results or treatment initiation. They noted that, due to high levels of prior testing, there were very few newly identified HIV-positive infants. The intervention did not reduce test result turnaround time due to laboratory challenges.

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