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Cohort profile: measuring adverse pregnancy and newborn congenital outcomes (MANGO) study in Kenya

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ABSTRACT

Purpose Pharmacovigilance (PV) systems to assess the safety of antiretroviral treatment used periconception and during pregnancy are lacking in low-resource settings with high HIV burdens, and strategies to guide their implementation are limited. We implemented the Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO) study in Kenya to address these gaps.

Participants In MANGO, we ascertained delivery outcomes for pregnant women living with HIV (WLH) and not living with HIV (WNLH) enrolled in care at Moi Teaching and Referral Hospital (MTRH) through two cohorts: C1, a prospective cohort of 1:1 matched WLH and WNLH attending antenatal clinic; and C2, a cross-sectional cohort of all deliveries, including among those who did not attend antenatal clinic at MTRH.

Findings to date 24 205 deliveries were recorded from October 2020 to September 2023 (853 in C1 and 23 352 in C2). Median maternal age was 32 years, 4.5% were WLH and 2.6% of deliveries were stillbirths. Among liveborn infants, 17.2% were preterm (<37 weeks), and 15.1% were low birth weight (<2.5 kg). Prevalence of ≥1 major congenital abnormality was 73.9/10 000 births (47.7 in C1 and 76.1 in C2). Assessing implementation barriers/facilitators, lack of national PV policy was a barrier overcome through establishing partnerships with the Kenya Ministry of Health. The facility's size and complexity were barriers to newborn surface exam coverage overcome through staff training and cocreation of a standardised form for newborn surface exam documentation. High staff turnover was addressed by involving head nurses to champion implementation and incentivising staff participation with medical education credits. Use of audit/feedback cycles and focusing on PV as a way to improve care quality facilitated PV institutionalisation at MTRH.

Future plans The MANGO model is a multifaceted strategy with replicative potential in other settings. Research is needed to understand the model's opportunities for implementation in other settings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Measuring Adverse Pregnancy and Newborn Congenital Outcomes study is a pharmacovigilance strategy to address the knowledge gap in antiretroviral safety data at conception and during pregnancy.
⇒ The study's prospective and retrospective cohorts allow for detailed data collection on pregnancy exposures and maternal and infant outcomes, and expert adjudication of congenital abnormality diagnoses.
⇒ The study's implementation and maintenance are enhanced by its focus on enhancing healthcare service delivery, clinical leadership involvement and training and incentivisation of healthcare providers.
⇒ The study's reliance on paper files and patient-held medical records as primary data sources may limit exposure ascertainment compared with electronic pharmacy data systems.

INTRODUCTION

Pharmacovigilance (PV) is an evidence-based intervention defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[1] PV systems to monitor the safety of antiretroviral treatment (ART) and other drugs used periconception and during pregnancy are established in high-income countries. However, in sub-Saharan African settings with high HIV burdens, PV in pregnancy is lacking, and strategies to guide its implementation are limited.[2 3] This implementation gap was acutely highlighted in 2018 when a study in Botswana reported an unexpected association between neural tube defects (NTD) among infants born to women living with HIV (WLH) and maternal exposure to dolutegravir-containing ART at conception.[4] Although this association was based on few NTD cases from a single study, it prompted the WHO to issue interim guidance restricting the use of dolutegravir among WLH of reproductive potential.[5] What

followed was a global disparity in dolutegravir uptake among women of reproductive potential compared with other populations.[6] Data refuting the association between dolutegravir and NTDs would eventually emerge, and in 2019, dolutegravir was recommended for all adults living with HIV.[7–10] Still, the events surrounding the 2018 dolutegravir safety signal are a bellwether of the need for PV implementation in sub-Saharan Africa and the significant impact of PV on public health.

Filling the PV implementation gap in sub-Saharan Africa will necessitate the expansion of surveillance systems to examine large populations of exposed and unexposed individuals. While this has been achieved through electronic medical record (EMR) and pharmacy systems in high-income countries, such systems are less well established in sub-Saharan Africa.[11 12] Sentinel site surveillance with review of paper-based medical records and expert classification of congenital abnormalities, as used in Botswana, is an alternative approach to PV implementation in settings without established EMRs.[4] However, this approach is resource-intensive and scaling it in multiple health facilities is challenging. Tertiary referral facilities are desirable for PV implementation given their large sample sizes relative to lower-level facilities, which enhances statistical precision when assessing associations with rare events like congenital abnormalities. However, PV implementation at tertiary facilities risks case ascertainment bias due to their higher level of care and referrals from lower-level facilities, which can limit their generalisability to the population. The WHO has issued general guidance for PV in pregnancy and congenital abnormality surveillance.[13] Lacking, however, is practical guidance addressing real-world implementation challenges in PV and congenital abnormality surveillance in resource-constrained settings.

The goal of this report is to describe the Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO) study in Kenya, a PV implementation strategy developed to address the knowledge gap in antiretroviral safety data at conception and during pregnancy. The objectives of the MANGO study are to (1) determine associations between HIV status and dolutegravir exposure and adverse pregnancy and infant outcomes, including congenital abnormalities; (2) establish PV infrastructure for future antiretrovirals and other drugs and (3) develop standardised protocols and outcome definitions to facilitate multiregional analyses within the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium.[14] In this report, we use an implementation research logic model to synthesise MANGO implementation processes;[15] highlight barriers and facilitators to PV implementation using the Consolidated Framework for Implementation Research (CFIR);[16] and discuss outcomes related to the MANGO PV model using the reach, effectiveness, adoption, implementation and maintenance (RE-AIM) framework.[17]

COHORT DESCRIPTION

Setting and population

The MANGO study was implemented at Moi Teaching and Referral Hospital (MTRH) in western Kenya. In this region, HIV prevalence among women 15–49 years is approximately 5%.[18] MTRH is the second largest national referral hospital in Kenya, with a catchment of 24 million people, and managing approximately 12 000 deliveries per year. Site-level resources include a newborn intensive care unit staffed by neonatologists but not a clinical geneticist. Within MTRH is an antenatal clinic and postnatal clinic that offer integrated HIV services.

MTRH is the headquarters of the Academic Model Providing Access to Healthcare (AMPATH), a USAID-funded HIV care and treatment programme and participating site in the IeDEA East Africa consortium.[14 19] AMPATH facilities provide standard-of-care HIV treatment services based on national guidelines.[20] Outpatient clinical data for people living with HIV enrolled at MTRH and other AMPATH-affiliated sites are collected in the EMR;[21] however, at the time this project was implemented, there was not a comprehensive EMR for the MTRH maternity ward, antenatal or postnatal clinic.

Description and operationalisation of the MANGO study

A detailed description of the methods is available at clinicaltrials.gov (#NCT04405700). The full study protocol can also be accessed on the WHO Antiretrovirals in pregnancy research toolkit website (www.who.int/tools/antiretrovirals-in-pregnancy-research-toolkit). In brief, MANGO involves three cohorts (figure 1). Cohort 1 (C1) involves prospective recruitment of all pregnant WLH and pregnant women not living with HIV (WNLH) enrolled in antenatal clinic at MTRH, matched 1:1 by age because of the well-established association with older maternal age and adverse birth outcomes including congenital abnormalities, and pregnant WLH being older than pregnant WNLH.[22 23] Enrolled participants are interviewed by a research assistant who records their clinical information, including medication exposures during and within a year prior to pregnancy. Follow-up study visits are conducted after each routine antenatal clinic visit. Delivery and infant data for participants who deliver at MTRH are captured at the facility. For participants who do not deliver at MTRH, phone contact and community tracing are conducted to ascertain pregnancy and infant outcomes.[24]

Cohort 2 (C2) is a cross-sectional cohort of all pregnant women who deliver at MTRH, irrespective of whether they attended antenatal clinic at MTRH or any other facility. For C2, the study team extracts relevant data from each woman's maternal and child health (MCH) handbook and paper medical file (colocated with the infant's file), typically within 24 hours post partum (table 1). The MCH handbook is a Kenya Ministry of Health (MOH) tool that women are instructed to carry whenever they visit a health facility and is a primary source for pregnancy exposure data. Non-live births <28 weeks gestation are excluded as

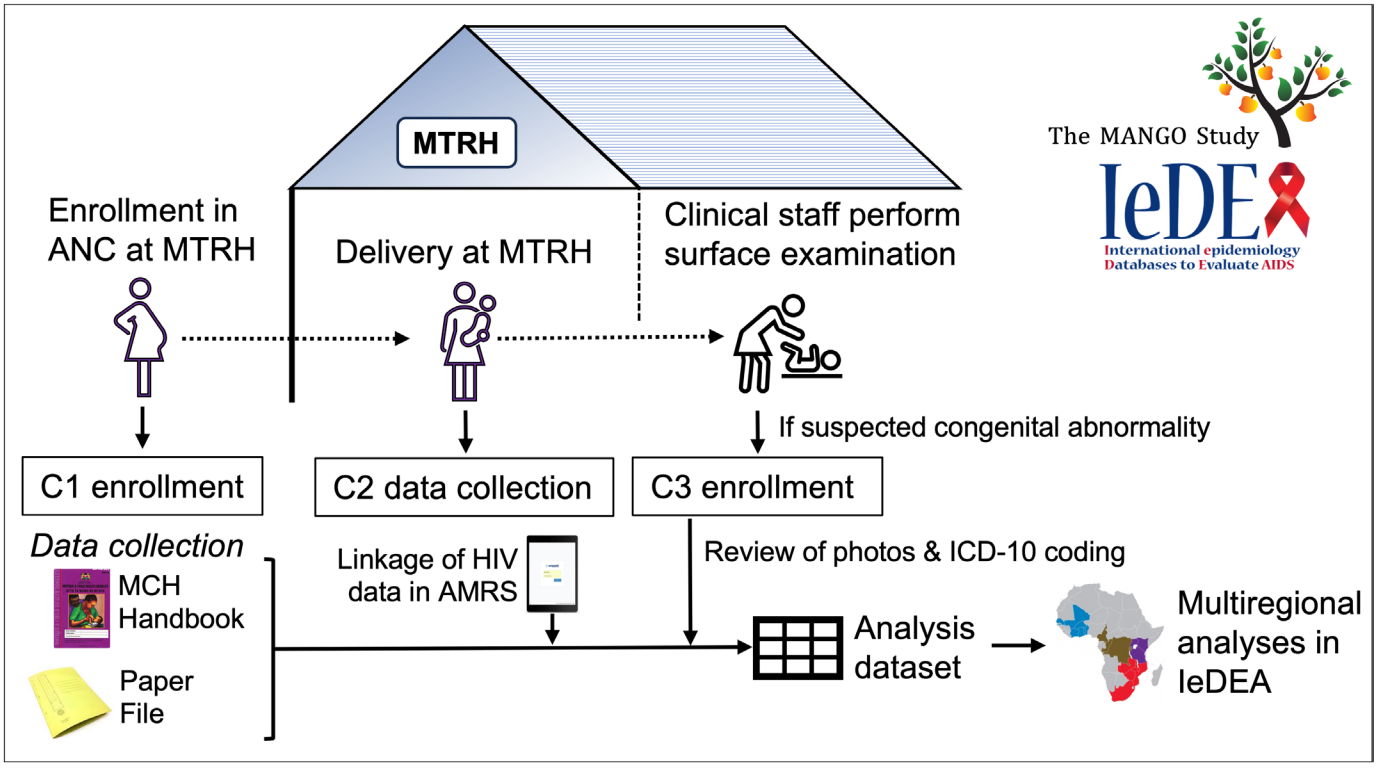

Figure 1 Schematic of the MANGO study in Kenya. AMPATH, Academic Model Providing Access to Healthcare; AMRS, AMPATH Medical Record System; ANC, antenatal clinic; ICD-10, International Classification of Diseases, 10th Revision; IeDEA, International Epidemiology Databases to Evaluate AIDS; MANGO, Measuring Adverse Pregnancy and Newborn Congenital Outcomes; MCH, maternal-child health; MTRH, Moi Teaching and Referral Hospital.

they are considered miscarriages rather than stillbirths at MTRH.[25] Deliveries that occur outside MTRH are excluded to reduce referral bias. C2 represents the major PV implementation focus of the study, while C1 enables statistical adjustments for potential bias in outcome ascertainment at MTRH, a tertiary referral facility.

Cohort 3 (C3) is a prospective cohort of live and stillborn infants included in C1 and C2 who have major congenital abnormalities on surface examination.[26] Photos and videos of eligible infants are taken by a research assistant using a standardised approach.[27] As the goal of C3 is to accurately classify the abnormalities, the photos/videos are reviewed by an expert panel that includes a neonatologist and obstetrician/gynaecologist at Moi University and a geneticist at Indiana University, then diagnoses are assigned using International Classification of Diseases, 10th Revision (ICD-10) codes. In C1, the time window for identifying abnormalities was from birth to 2 weeks postdelivery to accommodate community tracing for out-of-facility deliveries. In C2, the time window was between birth and hospital discharge, typically within 24 hours after delivery.

Data management

Research assistants collected data from various sources (table 1) then entered data into customised REDCap forms using a tablet. The forms were developed and piloted in collaboration with MoH representatives. To facilitate future multiregional analyses, the study team collaborated with IeDEA investigators implementing a parallel pregnancy exposure registry in South Africa to ensure standardisation of data collection and outcome definitions.[12] Reports were generated biweekly to track data collection and quality, including comparisons of the total deliveries entered in REDCap with the facility's maternity register to ensure completeness of data capture. For analyses, REDCap data were cross-linked with the HIV data in the EMR using unique identification numbers assigned to each patient enrolled in HIV care at AMPATH. The photo/video media in C3 were securely stored in Microsoft OneDrive.

Analysis

Prevalence of adverse pregnancy outcomes in MANGO was compared with relevant indicators derived from Kenya Demographic and Health Survey data for 2022 and other sources as available.[23] Major congenital abnormalities were defined as those visible on surface exam with medical, surgical or cosmetic significance according to the WHO definition, and reported as frequency per 10 000 births with 95% CIs.[28] For the purposes of this report, we included chromosomal trisomies (eg, Down syndrome) identified on the basis of physical characteristics, as well as abnormalities inside the mouth (eg, cleft palate) and anus (ie, imperforate anus) which are detectable on surface exam but likely underdetected.[26]

Within the logic model, we used CFIR constructs to highlight barriers and facilitators to implementation of

Table 1 Data elements and sources used in cohorts 1, 2 and 3 of the MANGO study

Data elements	Data source	Definition and comments
Maternal demographics		
Identifying information	H, F	Full name, date of birth, hospital number, national identification number
Contact information*	H, F	Phone number (primary and alternate); owner of phone (self, partner, other person), county of residence
Locator information*	H, F	Specific address at the subcounty and street level.
Antenatal		
Date of antenatal clinic enrolment	H	Date of first visit to the antenatal clinic at any facility
Last menstrual period	H	Date
Transfer in	H	Indicate whether the mother transferred to MTRH from another facility during the current pregnancy and the reason for transfer
Date of antenatal clinic visit*	H	Date of each antenatal clinic visit during the current pregnancy
Weight*	H	Weight at each antenatal clinic visit
Blood pressure	H	Blood pressure at each antenatal clinic visit
Obstetric/medical history	H, F	Indicate any history of pregnancy complications, communicable and non-communicable diseases and dates of diagnosis for each
Parity, gravidity	F	Indicate the number of prior pregnancies and any history of miscarriage
History of congenital abnormalities	F	Indicate whether there is a family history of congenital abnormalities and the types of abnormalities and affected family member
Current medical history	H, F	Indicates all diagnoses within a year prior to pregnancy and the estimated month of diagnosis for each
Medications	H, F	Indicates all medications taken during pregnancy, including chronic medications started within a year prior to pregnancy and the estimated start/stop dates for each
Antenatal clinic profile results	H	A panel of labs tested at antenatal clinic enrolment includes haemoglobin, blood group/Rh, RPR, urinalysis and HIV test) and dates for each
HIV status	H, F	HIV test result during pregnancy and date of HIV test (recorded as part of antenatal clinic profile)
ART history	A	For WLH, includes all ART regimens and start/stop date for each regimen
ART adherence	A	Self-reported adherence (yes/no) and using the 8-item Morisky Medication Adherence Scale
Cotrimoxazole	A	For WLH, indicates exposure to cotrimoxazole prophylaxis and start/stop date
CD4 count	A	In cells/mm^3 and dates prior to and during pregnancy
Viral load	A	Copies/mL and dates prior to and during pregnancy
Foetal ultrasound	F	Fetal ultrasound results in hand-written reports
Substance use	H, F	Includes alcohol, tobacco, or other illicit drugs (ie, marijuana, heroin, other)
Peripartum		
Date of delivery	H, F	
Time of delivery	F	24-hour time of delivery
Location of delivery*	H, F	Categorical as per booklet: MTRH, home or other facility
Mode of delivery	H, F	Categorical: spontaneous vaginal delivery; spontaneous breech delivery; elective caesarean section; emergency caesarean section; assisted vaginal delivery;
Induction of labour	F	Categorical: yes; no
Number of infants delivered	F	Includes live and stillborn infants
Pregnancy outcome	F	Categorical for each infant delivered: live birth; stillbirth (≥28 weeks gestation); miscarriage (<28 weeks gestation); termination of pregnancy; ectopic pregnancy; molar pregnancies.
Blood loss	F	Indicates estimated blood loss in millilitres during delivery
Peripartum complications	F	Free text field to indicate complications during delivery for mother or infant

Continued

Table 1 Continued

Data elements	Data source	Definition and comments
Umbilical cord appearance	F	Categorical: normal, abnormal (and comment if abnormal)
Placenta appearance	F	Categorical: normal, abnormal (and comment if abnormal)
Postdelivery—maternal		
Maternal vital status	F	Indicates vital status at the time of file review or hospital discharge, whichever occurred first
Date of death	F	Date of death (if occurred)
Cause of death	F	Free text
Postdelivery—infant		
Date of review	R	Date of medical record review and REDCap data entry
Reviewer	R	Name of MANGO staff completing data entry
Sex	F	Categorical: male, female, ambiguous
Estimated gestational age (EGA)	F	As indicated on medical records;
Mode of EGA assessment	F	Categorical: last menstrual period
Birth weight	F	In kilograms to the second decimal (eg, 3.45 kg); used to calculate low birth weight (<2500 g) and small for gestational age (weight <10th percentile for gestational age)
Anthropomorphic data	F	Body length, foot length, head circumference in centimetres
Birth outcome	F	Categorical: live birth, fresh stillbirth, macerated stillbirth
APGAR score	F	APGAR score documented at 1 and 5 min
Surface examination	F	Head-to-toe surface exam results with any abnormalities noted (see online supplemental table S1)
Description of possible congenital abnormality	F	Free text box to document comments for the congenital abnormality diagnosis
ICD-10 code	R	ICD-10 plugin in REDCap for entry of congenital abnormality diagnosis
Certainty of ICD-10 diagnosis	R	For each ICD-10 code, indicate certainty of diagnosis: definite, probable, possible, uncertain
C3 consent†	R	Indicates whether the mother consents for enrolment in C3, which includes photos/videos of congenital abnormalities and longitudinal phone follow-up
Photo/video upload†	R	Fields to allow for photo/video upload into REDCap
HIV test	F	Indicates HIV DNA PCR testing date and result for neonate (if performed)
Vital status at discharge	F	Indicates vital status at the time of file review or hospital discharge, whichever occurred first
Date of death	F	Date of death (if occurred)
Cause of death	F	Free text

*Indicates data collected in C1 only.
†Indicates data collected in C3.
A, AMRS (AMPATH Electronic Medical Record System); AMPATH, Academic Model Providing Access to Healthcare; APGAR, Appearance, Pulse, Grimace, Activity and Respiration; ART, antiretroviral treatment; F, maternal medical file; H, MCH handbook; ICD-10, International Classification of Diseases, 10th Revision; MANGO, Measuring Adverse Pregnancy and Newborn Congenital Outcomes; MTRH, Moi Teaching and Referral Hospital; R, research team; WLH, women living with HIV.

the MANGO PV model (figure 2).[16] The CFIR constructs include the outer setting (environment and policy context), inner setting (facility where the model is implemented), individuals (roles and characteristics of those involved in the model's implementation) and implementation process (activities involved in the model's implementation). The strategies used to implement the MANGO PV model are also described in the logic model, along with their hypothesised mechanisms of influence. These strategies and mechanisms are described under each CFIR construct below. However, in reality, these strategies target multiple determinants across different CFIR constructs. In the discussion, we assess the preliminary implementation outcomes of the MANGO PV model using the RE-AIM framework.[17]

Written informed consent was obtained from women participating in C1 and for their infant's participation in C3. A waiver of consent was granted for the activities in C2 because they involved minimal risks. C3 is encompassed within C1 and C2; however, these identifiable data are

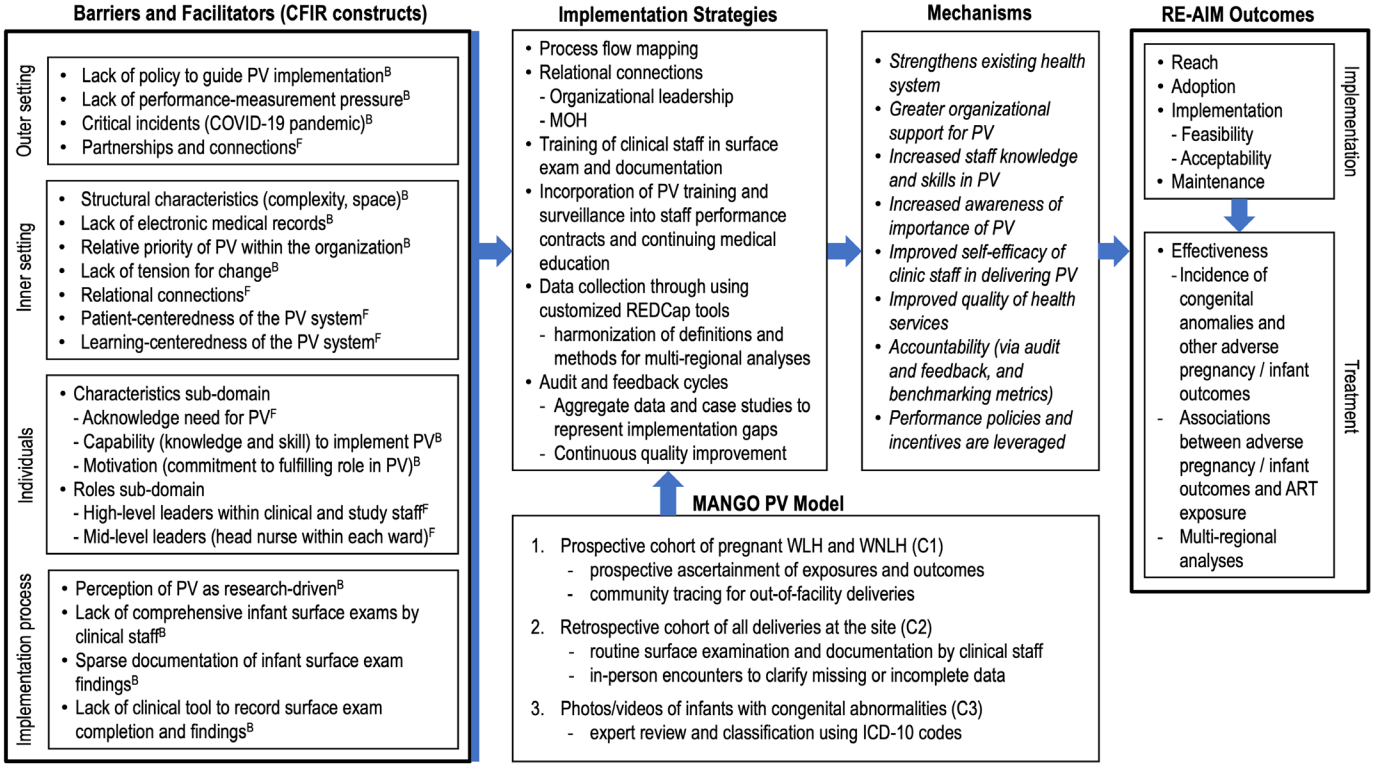

Figure 2 Implementation research logic model for the MANGO study. ART, antiretroviral treatment; B, barrier; CFIR, consolidated framework for implementation research; F, facilitator; ICD-10, International Classification of Diseases, 10th Revision; MANGO, Measuring Adverse Pregnancy and Newborn Congenital Outcomes; MOH, Ministry of Health; PV, pharmacovigilance; RE-AIM, reach, effectiveness, adoption, implementation, maintenance; WLH, women living with HIV; WNLH, women not living with HIV.

stored separately in a secure, online Google at IU Secure Storage account, which is authorised for sensitive data, including protected health information.

FINDINGS TO DATE

From October 2020 to September 2023, there were 24 205 deliveries entered into the MANGO REDCap database (853 in C1 and 23 352 in C2), representing 87% of all registered deliveries at the site (table 2). A total of 956 pregnant women were approached to participate in C1, and 103 (10.8%) declined, including 71 WLH and 32 WNLH. Of the 80 women who provided reasons for declining, 68 (85%) cited lack of time or interest and 12 (15%) wished to consult their male partner before participating. Recruitment was also impacted by the COVID-19 pandemic, which imposed social and economic strain on patients and limited their ability to engage with the health system.[29] Thus, 839 women (419 WLH, 420 WNLH, median age 32 years) were enrolled in C1 and followed through delivery. Median (IQR) gestational age for WLH was 22 (16–29) months vs 28 (22–34) weeks for WNLH.

A waiver of consent was granted for C2. Median maternal age was 32 years, 4.5% were WLH, 23.3% of deliveries were by elective or emergency caesarean section and 97.3% of deliveries resulted in live births and 2.6% in stillbirths. Median infant gestational age at delivery was 40 weeks, 17.2% were preterm (<37 weeks) and 15.1% were low birth weight (<2.5 kg). Overall, the prevalence of ≥1 major congenital abnormality was 73.9/10 000 births (95% CI 63 to 85). Among liveborn infants, 150 (0.62%) suffered neonatal death prior to hospital discharge.

Barriers and facilitators to PV implementation

Outer setting

The lack of national or local PV policies was an initial barrier to implementation as there were limited incentives or performance-measurement pressures to drive integration of PV into routine care. This was compounded by the COVID-19 pandemic, which overlapped with the MANGO implementation process. Establishing relationships with MOH staff, along with the site's long-standing collaborations with AMPATH leadership, helped overcome these barriers by elevating the perception of the surveillance strategy as a public health priority among MTRH staff despite the ongoing COVID-19 pandemic, and by ensuring that our data collection tools aligned with MOH and MTRH priorities. Understanding MOH's ongoing and planned PV activities through our MOH collaboration helped contextualise the MANGO study and position it for future sustainability at the site. Lessons learnt within the outer setting construct are that the development of clear national or local policies for PV could help promote its integration into routine public healthcare services, potentially enhancing PV resilience

Table 2 Characteristics of the MANGO cohort at delivery, October 2020 to September 2023

Indicator	MANGO N=24 205	Kenya aggregate data (Ref.)
Maternal age at delivery (years), n (%)		
<20	1947 (8.0)	13.0%*
20–34	18 315 (75.7)	74.1%*
35–49	3892 (16.1)	12.9%*
Missing	51 (0.2)	--
Women living with HIV, n (%)	1084 (4.5)	5.2%†
Transfer in for delivery, n (%)	1754 (7.2)	n/a
Caesarean section delivery, n (%)	5641 (23.3)	23.8%‡
Missing	14 (0.06)	
Stillbirth, n (%)	627 (2.6)	1.6%§
Per 1000 births	25.9	15.8
Missing	16 (0.07)	
Premature birth (<37 weeks), n (%)	4161 (17.7)¶	12.3%§
Low birth weight (<2.5 kg), n (%)	3643 (15.5)¶	10.0%**
Major congenital abnormality, n (%)††		
C1 (n=839)	4 (0.48, 95% CI 0.13 to 1.22)	--
C2 (n=23 004)	175 (0.76, 95% CI 0.65 to 0.88)	--
Total (n=24 205)	179 (0.74, 95% CI 0.63 to 0.85)	--
Total per 10 000 births		--
C1	47.7 (95% CI 13 to 122)	--
C2	76.1 (95% CI 65 to 88)	--
Total	73.9 (95% CI 63 to 85)	--

*From Kenya National Bureau of Statistics (KNBS) data 2022,[23] includes livebirths only N=6847.
†From Kenya HIV Estimates Report 2018,[40] includes females 15–49 years.
‡From KNBS data 2022,[23] includes elective and emergency caesarean sections; caesarean section rates in urban areas 23.8% and 12.3% in rural areas of Kenya.
§From KNBS data 2022,[23] among all births n=6957.
¶Among 23 546 live births.
**From UNICEF-WHO Low birthweight estimates, 2023.[41]
††Among live and stillborn infants.
MANGO, Measuring Adverse Pregnancy and Newborn Congenital Outcomes.

to external disruptions and fostering collaborative efforts between healthcare facilities and government entities.

Inner setting

The large size and complexity of the maternity hospital at MTRH was an initial implementation barrier, as patients resided on multiple wards and frequently transferred between them. This made it difficult to track delivery outcomes, patient files for data entry and to ensure that comprehensive newborn surface exams were performed on all infants. Additionally, clinical staff trained to conduct standardised newborn surface exams and surveillance for congenital abnormalities perceived these activities to be of low priority compared with their other daily responsibilities. This resulted in limited motivation for change within the inner setting of the organisation. To overcome barriers associated with implementation, we used process flow mapping to create a visual representation of the flow of patients and their files throughout the hospital from admission to discharge. This facilitated data collection by pinpointing missing files and missed surface exams. Relationships between the research team and members of the Department of Reproductive Health at MTRH also facilitated the introduction of comprehensive newborn surface examination and documentation into the standard performance contract for clinical staff, enhancing prioritisation and accountability to PV implementation within the organisation. A lesson learnt in the inner setting was that PV implementation at large referral facilities will require strategies to break down complex clinical systems into more manageable components to facilitate implementation and define factors driving inefficiencies in surface examination and data collection. Additionally, leveraging relationships within the organisation can be used to foster PV prioritisation and accountability, enhancing uptake.

Individuals

At the individual level, frequent staff turnover, partly related to the COVID-19 pandemic, was a barrier to PV implementation as it required frequent retraining of clinical staff in PV activities. Some clinical staff members demonstrated varying capacity and motivation to participate in PV activities, as well as limited knowledge and skills in congenital abnormality detection and documentation. These elements posed individual-level barriers to rigorous PV implementation. The need for PV training was addressed in several ways. First, the study engaged high-level leaders (ie, obstetrician-gynaecologists) within the Department of Reproductive Health to better understand and anticipate staffing changes. Second, the study engaged head nurses within each of the wards to act as implementation leads who championed newborn surface exams and helped identify staff in need of training. To motivate attendance at the training sessions, the study team worked with departmental leadership to ensure that the sessions fulfilled the requirements for Continuing Medical Education. Offering credits for attendance at the sessions increased staff motivation and attendance. Lessons learnt at the individual level were that understanding the capabilities, training needs and motivations of the clinical staff enhanced PV implementation by increasing staff knowledge and skills in PV, awareness of its importance and self-efficacy in delivering PV.

Implementation process

Insufficient space for documentation of newborn surface examinations in the paper obstetric records was a barrier to PV implementation at the onset of the study. To address this, the study team worked with clinical staff to co-create a standardised form for newborn surface examination and documentation (online supplemental table S1). This form was adopted and included in all paper files at admission and completed for all infants after delivery. The completion of the form was tracked by the research team, leading to the discovery of suboptimal completion rates (ie, 60%–75%) in some units. Monthly audit and feedback meetings were subsequently implemented with nursing staff from affected units. In these meetings, aggregated monthly data on surface exam completion rates were presented by the research assistants, fostering open discussions on root causes of individual and team performance, action plans to address root causes and establishing performance accountability through benchmarking. Over the following 3 months, comprehensive newborn surface exam completion rates increased to ≥90%.

During the study, research assistants also identified several cases of infants with major congenital abnormalities that were not documented by clinical staff, including cleft palate and imperforate anus. These missed diagnoses served as examples of the importance of comprehensive newborn surface examination and documentation and motivated clinical staff to participate in congenital abnormality surveillance. Over time and through the audit and feedback meetings, clinical staff perceptions shifted from seeing the study as research-driven to seeing it as continuous quality improvement in comprehensive newborn surface examination and reporting, enhancing both the patient-centredness and learning-centredness of the PV strategy. This shift substantially improved the acceptability and adoption of the MANGO PV activities among the clinical staff, illustrating a key lesson learnt during the implementation process.

DISCUSSION

As new antiretroviral and other drugs enter the global marketplace, PV systems are needed to determine the safety of these agents in pregnant persons, a demographic often excluded from drug efficacy studies. The MANGO PV model is a viable strategy to address this need. Though, generalisability may be limited, since our cohort is reflective of an urban, tertiary hospital with higher caesarean section rates compared with rural areas and higher prevalence of preterm birth than countrywide estimates.[23 30] These differences will need to be considered when making inferences about the broader population, particularly in more rural settings.

The prevalence of major congenital abnormalities in our cohort was 73.9/10 000 births (95% CI 63 to 85). This is slightly higher than estimates from a hospital-based birth surveillance study in Uganda (66.2/10 000 births) and nationwide birth surveillance study in Botswana (60/10 000).[8 10] This difference may also reflect MTRH's tertiary/referral status, as our sample may be enriched with individuals at increased risk of adverse birth outcomes, including congenital abnormalities, compared with the general population. The lower observed prevalence of congenital abnormalities in C1 (48/10 000) compared with C2 (76/10 000) also supports this, as the outcomes for those in C1 were prospectively measured and included community tracing for out-of-facility deliveries, which may be more akin to a general population. It is also possible that the COVID-19 pandemic influenced this outcome by reducing the number of women with healthy pregnancies who delivered at home rather than at MTRH during lockdowns.[31] These estimates should be considered preliminary, as we are still cleaning and analysing these data to confirm these findings and investigate factors associated with congenital abnormality detection, including HIV and ART exposures. Nevertheless, the overall prevalence of congenital abnormalities is comparable to other studies and supports the reliability of our cohort.

MANGO is feasible to implement based on our early experience and analyses. However, it is resource-intensive with data collection reliant on research assistants, data managers and training clinical staff, resulting in limited reach (ie, the ability to capture all deliveries at the site). Maintaining and scaling the MANGO model to achieve sufficiently large samples to rule out associations between specific ART exposures and rare outcomes such as NTDs

would be challenging without the advantages of EMR data.[32 33] Indeed, many of the studies following the initial dolutegravir safety signal were underpowered to refute associations with NTDs.[34 35] Moreover, stretching available resources to expand surveillance at additional sites could increase samples at the expense of data quality.[36] To overcome these barriers within MANGO, we have developed a priori plans to merge and analyse multiregional data in the future, which could simultaneously enhance statistical power while maintaining data quality.[37] Alternative strategies for hospital-based PV include the use of dedicated mobile applications and nurse midwives for data collection, incorporating PV elements into standard MOH reporting tools, and promoting the implementation of EMRs and pharmacy systems.[9 38] Based on our experience, stakeholders interested in developing PV systems should explore strategies that leverage routine data, incorporate PV into standard reporting tools, and promote EMR adoption to enhance PV sustainability and effectiveness.

In our experience, a programme's adoption of PV is enhanced by activities that provide value to frontline providers. Supporting providers in the acquisition of new knowledge and skills in congenital abnormality detection, incentivising PV participation through performance benchmarks and medical education credits and implementing PV as a care quality improvement effort are examples of this, and similar concepts were reported in hospital-based birth defects surveillance in Uganda.[39] These activities also enhance the effectiveness of the PV system at the site by prioritising data quality and ensuring comprehensive surveillance. By integrating PV into routine clinical practices and emphasising its role in improving patient care, programmes can foster a culture of accountability and engagement among providers. Doing so strengthens the adoption of PV while also contributing to the overall improvement of healthcare delivery and patient outcomes.

STRENGTHS AND LIMITATIONS

The strengths of the MANGO study are its unique design and prioritisation of data quality and reliability using logic checks in REDCap, expert adjudication of congenital abnormality diagnoses and trained research assistants for data collection. The comprehensiveness of the MANGO data collection strategy has enabled it to serve as a parent study to several prospective cohorts to determine factors predictive of child neurodevelopment among children exposed and unexposed to HIV,[39] understand programme outcomes among postpartum WLH and their infants, and validate the Desire to Avoid Pregnancy scale in the Kenyan population. Limitations of the study include the reliance on paper files and MCH booklet for exposure ascertainment, which, although primary source data, may be less complete compared with an electronic pharmacy database. This is also the case with the use of over-the-counter or herbal drugs that are common in the community but difficult to track. The lack of birth defect ascertainment among stillbirths or pregnancy terminations <28 weeks, while consistent with hospital policy, reduces the sensitivity of surveillance. At MTRH, pregnant women <28 weeks gestation are admitted to the gynaecology ward, not the maternity ward, which is in a separate building on the medical campus. Due to study resource constraints, it has not been feasible to cover the gynaecology ward. The surveillance system also does not conduct diagnostic imaging for internal birth defects (eg, congenital heart defects) or testing for functional or genetic defects, although such diagnoses are captured if present in the paper files. Finally, gestational age dating was estimated using last menstrual period rather than first trimester ultrasound in most cases, which may impact the accuracy of outcomes such as preterm birth. We plan to conduct subanalyses including only those with appropriate pregnancy dating when assessing outcomes.

COLLABORATION

Our long-term plans are to maintain the MANGO cohort as a surveillance platform for assessing associations between adverse pregnancy outcomes, including congenital abnormalities and pregnancy exposures such as HIV and antiretrovirals, within the IeDEA consortium. We have now established the infrastructure to collect longitudinal data on pregnancy exposures and birth outcomes at MTRH, the second largest national referral hospital in Kenya. This hospital has now transitioned to a novel EMR system in the maternity ward, antenatal and postnatal clinics, and we have incorporated our surveillance tools (eg, birth surface exam forms, congenital abnormality documentation fields) into the EMR to enable sustained and complete data collection for this cohort in the future. This offers a unique and important opportunity to conduct analyses to assess the safety of novel antiretrovirals and other drugs during pregnancy in sub-Saharan Africa, where few such cohorts currently exist.

Deidentified, aggregated data for the MANGO cohort are available to investigators through a concept-driven process within the East Africa IeDEA consortium (see https://globalhealthequity.iu.edu/research/iedea-main-page/index.html). Aggregated data are also made available to clinical staff and hospital administrators at MTRH and AMPATH for quality improvement and to representatives of the Kenya MOH for epidemiological investigations.

CONCLUSIONS

The MANGO PV model in Kenya is a unique approach to address the PV implementation gap in Africa. The lessons learnt through the implementation process are instructive to researchers, programme implementers and policy-makers involved in developing PV systems in resource-constrained settings. Advanced planning and data management are required for the integration of

PV into routine clinical care, to strengthen the health system and provide direct value to those responsible for PV delivery, and to optimise data quality. More research is needed to explore PV implementation and scalability challenges and models in resource-constrained settings.

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