Vaccine 90 (2026) 128952

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Original article

Baseline adverse birth outcomes in a prospective pregnancy cohort in Uganda: Evidence to inform maternal vaccine readiness

Hannah G. Davies [a,b,c,*], Gordon Rukundo [d], Cleophas Komugisha [d], Sam Kipyeko [d], Andrew Young [a], Jennifer Kisakye [d], Merryn Voysey [e], Robert Mboizi [d], Paul T. Heath [a], Musa Sekikubo [d,f], Kirsty Le Doare [a]

[a] Centre for Neonatal and Paediatric Infection, City St George's, University of London, London, UK
[b] Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK
[c] Department of Infection and Population Health, Institute for Global Health, University College London, UK
[d] Makerere University Johns Hopkins Research Collaboration (MUJHU), Kampala, Uganda
[e] Oxford Vaccine Group, University of Oxford, Oxford, UK
[f] Department of Obstetrics & Gynaecology, University School of Medicine, Makerere University, Uganda

ARTICLE INFO

Keywords:
Vaccine safety **a**dverse outcomes **a**dverse outcomes of special interest **n**eonatal sepsis **m**aternal vaccines

ABSTRACT

Background: Maternal vaccines have the potential to substantially reduce neonatal morbidity and mortality; however, in low- and middle-income countries (LMICs), their evaluation and implementation are hindered by the scarcity of high-quality baseline data on pregnancy and neonatal outcomes. Harmonised outcome definitions, such as those developed by the Brighton Collaboration's Global Alignment of Immunisation Safety Assessment in Pregnancy (GAIA), are essential for interpreting vaccine safety signals and supporting equitable maternal immunisation programmes.

Methods: PREPARE was a prospective pregnancy registry conducted at a tertiary maternity facility in Kampala, Uganda. Pregnant women were enrolled in the first or second trimester and followed through delivery and until nine months postpartum. Maternal, fetal, and neonatal outcomes were actively ascertained using GAIA case definitions, with independent review and expert adjudication to determine diagnostic certainty.

Results: Between September 2020 and March 2023, 3423 women were enrolled; 98.5% were followed to delivery and 95.7% retained through nine months postpartum. The stillbirth incidence was 26.3 per 1000 total births, exceeding national estimates. Preterm birth occurred in 110.9 per 1000 births, and neonatal mortality was 22.5 per 1000 livebirths, with substantially higher incidence among preterm infants. Neonatal infections were commonly identified through active surveillance. Reported rates of most neonatal outcomes were lower among births occurring outside the study site, consistent with under-ascertainment in routine settings. Conversely, through application of GAIA criteria, overdiagnosis of some intrapartum and neonatal conditions in routine clinical records was identified.

Conclusions: Prospective pregnancy registries using standardised GAIA definitions can generate robust, context-specific background rates and reveal important limitations of routine health data systems. These findings highlight the need for prospective surveillance, strengthened diagnostic capacity, and adaptation of GAIA case definitions for reliable use with electronic health record data to support the evaluation of maternal vaccines and to enhance maternal immunisation readiness in LMICs.

1. Introduction

Neonatal morbidity and mortality remain unacceptably high in many low- and middle-income countries (LMICs), constituting 47% of all under-five deaths globally [1]. Infections such as sepsis, pneumonia, and meningitis remain among the leading causes of preventable mortality in the neonatal period, accounting for an estimated 440,000 deaths each year [2]. Maternal vaccination represents a critical intervention in this context, with the potential to substantially improve both maternal and infant health outcomes. The World Health Organization (WHO) has

* Corresponding author at: City St George's University of London, Tooting, London, UK.
E-mail address: hannah.g.davies@ucl.ac.uk (H.G. Davies).

https://doi.org/10.1016/j.vaccine.2026.128952
Received 23 March 2026; Received in revised form 22 June 2026; Accepted 14 July 2026
Available online 8 August 2026

emphasised the importance of maternal vaccination within its life-course approach to immunisation, yet this remains an area in which the full public-health benefits have not yet been realised [3].

The maternal–neonatal tetanus programme demonstrated the effectiveness of maternal immunisation, with tetanus toxoid vaccination in pregnancy, in combination with improved umbilical cord care, leading to the near-global elimination of neonatal tetanus by 2020 [4]. As maternal vaccines targeting major neonatal pathogens including group B Streptococcus [5] and respiratory syncytial virus [6] advance toward late-phase trials and wider global introduction, reliable baseline data on pregnancy and newborn outcomes are essential for safety monitoring, and policy decision-making [7]. Yet high-quality prospective data from LMICs remain limited, particularly those using harmonised and internationally standardised case definitions such as the Brighton Collaboration's GAIA (Global Alignment of Immunisation Safety Assessment in Pregnancy) definitions [8], which are critical for comparability and for interpreting vaccine safety signals.

Establishing robust, context-specific background rates using GAIA-defined outcomes is therefore central to strengthening maternal-immunisation readiness, informing surveillance systems, and supporting equitable vaccine deployment [9]. To address these gaps, we established the PREPARE study, a prospective pregnancy registry at a research-active site in Uganda [10–13], to generate high-quality estimates of key maternal and neonatal outcomes using standardised GAIA definitions and to support preparedness for forthcoming maternal-immunisation initiatives.

2. Methods

2.1. Study site

The PREPARE study was based at a maternity national referral hospital - Kawempe National Referral Hospital (KNRH), in Kampala. KNRH is the largest national referral hospital for pregnancies in Kampala, Uganda's capital city, admitting high-risk pregnancies from surrounding areas and all deliveries from the local community. The neonatal unit admits preterm infants, and neonates with birth-related complications, sepsis or congenital anomalies. The neonatal unit receives approximately 11,000 admissions per year; these include inborn infants as well as referrals from other health centres and attendances from the surrounding community. There are approximately 25,000 births per year at KNRH [14].

2.2. Sample size

Background rates of adverse pregnancy outcomes used for sample size planning were informed by a post-hoc analysis of data from the ProGreSs study, a prospective cohort of approximately 6000 mother–newborn pairs conducted at Kawempe National Referral Hospital between March 2019 and April 2020 [10]. These data were used to generate empirical estimates of key outcomes to support planning for the PREPARE study, and were supported by hospital-level data, where available. Based on a target sample size of 4000 participants and an assumed stillbirth incidence of 1%, the expected absolute precision was ±0.36% at the 95% confidence level. For more common outcomes such as prematurity (7–11%), precision was approximately ±0.9%. This sample size was considered both feasible and sufficiently precise to estimate background rates for maternal vaccine safety assessments. Details of the underlying assumptions and precision estimates are provided in Supplementary Tables 1–3.

2.3. Ethical approval

Ethical approval for the study was given by the Makerere University School of Medicine Research Ethics Committee on the 4th of March 2020 (Ref 2020–089) and St George's, University of London Research Ethics Committee on the 6th of August 2020 (Ref 2020–0146). The study was registered with the Uganda National Council for Science and Technology (HS623ES). The study was registered on ClinicalTrials.gov (**NCT04653948**).

2.4. Recruitment and follow-up

Women attending antenatal care (ANC) clinics at KNRH between September 2020 and February 2022 were screened for eligibility. ANC clinics operated three days per week during the study period, and study staff aimed to screen all women attending clinic on recruitment days, as staffing capacity allowed. The study commenced during the COVID-19 pandemic, during which temporary clinic attendance restrictions were implemented to reduce overcrowding. Women attending ANC were initially provided with information about the study in group sessions and were subsequently individually assessed for likely gestational age based on last normal menstrual period (LNMP) and/or clinical examination. Women considered likely to be in the first or second trimester were offered a routine dating ultrasound scan. Those whose ultrasound-confirmed gestational age fell outside the first or second trimester were excluded. Some eligible women declined participation either before or after ultrasound assessment. Women in the third trimester were not eligible for enrolment.

Demographic, clinical, and vaccination data were collected and managed using REDCap electronic data capture tools hosted at Makerere University Johns Hopkins University (MU-JHU) Research Collaboration. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [15]. HIV and syphilis screening followed national guidelines using the SD Bioline™ Duo rapid test, with confirmatory testing for positive results. Routine measurements and laboratory tests were conducted using hospital or study-provided equipment. Provisions for urinary dipstick, blood culture and sonography were provided by the study.

Participants were followed through antenatal, delivery, and postnatal visits, with outcome data abstracted from hospital and electronic records. For participants that delivered away from the main study site, birth outcomes were collected over the phone, and copies of birth records obtained where possible. Post-pregnancy follow-up occurred by telephone within 28 days and during infant immunisation visits at 6, 10, 14 weeks and 9 months (full details of the follow-up schedule in Supplementary Fig. 1). Women experiencing pregnancy loss or infant death received psychosocial support and continued follow-up. In cases of maternal death, consent for infant participation was sought from a guardian, if consent for continued participation was not given, the infant was withdrawn from the study, with only data collected to that point retained for analysis.

2.5. Definitions

Outcomes were defined using the Brighton Collaboration's Global Alignment of Immunisation Safety Assessment in Pregnancy (GAIA) case definitions [16,17]. Potential cases were independently reviewed by two assessors and classified as levels 1–5, where levels 1–3 represent confirmed cases, level 4 indicates reported cases with insufficient evidence for classification, and level 5 indicates non-cases. Additionally, records for those with discordant results between the two independent assessors or those determined to level 4/5 were reviewed by an expert panel. This expert panel contained at least three members and one specialist (obstetrician or paediatrician). Additional information about the GAIA classification system and the selection of potential cases are provided in Supplementary Tables 4 and 5.

2.6. Data analysis

Continuous variables were summarised using means, standard deviations, medians and interquartile ranges based on normality assumptions. Categorical variables were summarised using frequencies and proportions. Incidence proportions were presented as point estimates with their associated 95% confidence intervals. The incidence calculated were the sum of outcomes that either fulfilled the GAIA outcomes at levels one to three, or that were deemed to be cases by an expert panel but did not fulfil the GAIA case definitions (level four).

3. Results

A total of 4084 women were assessed for eligibility between 1 September 2020 and 28 March 2023. Of these, 661 either did not meet the inclusion criteria or declined to provide written informed consent, leaving 3423 women who were recruited into the study (Fig. 1). Most participants were enrolled at their initial ANC appointment (84.8%). Among those recruited, 12.4% joined during the first trimester, with the remainder enrolled in the second trimester. The average gestational age at the time of recruitment was 20 weeks (IQR 17–23).

The baseline characteristics of enrolled women are summarised in Table 1. Participants had a median age of 25 years (IQR 22–29) and were predominantly Ugandan (97.3%). Few had no formal education (1.3%);

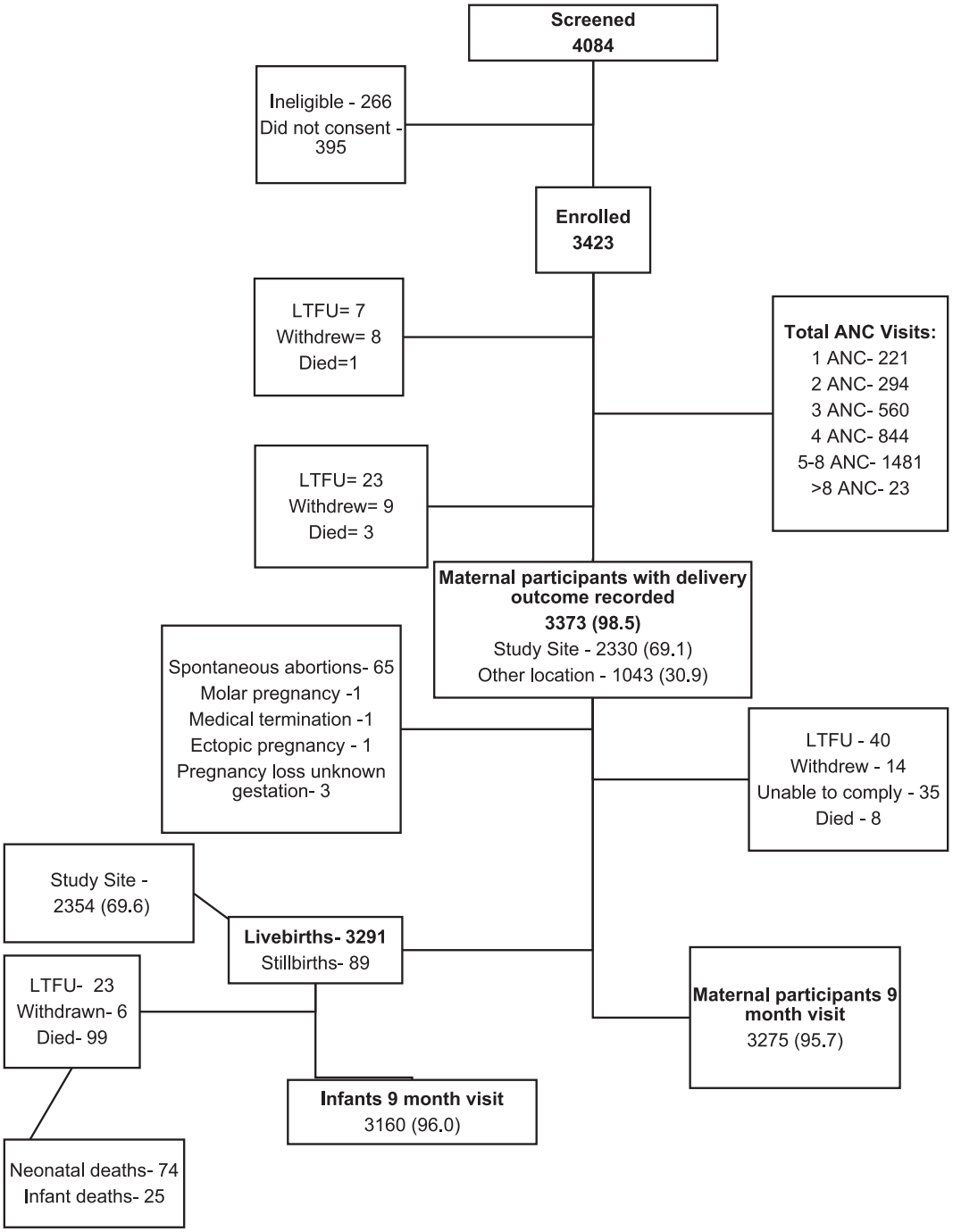

Fig. 1. Flowchart showing recruitment and follow-up of participants frequencies and (%).

Table 1
Demographic characteristics of the enrolled participants.

Characteristics	n (%)*
Total enrolled participants	3423
Visit Number at Enrolment (n = 3423)	
First ANC Visit	2904 (84.8)
Second ANC Visit	404 (11.8)
Third ANC Visit	18 (0.5)
Fourth ANC Visit	4 (0.1)
Nationality (n = 3423)	
Ugandan	3330 (97.3)
Rwandan	70 (2.0)
Other African	23 (0.6)
Education level (n = 3420)	
None	45 (1.3)
Some primary	283 (8.3)
Completed primary	363 (10.6)
Some secondary	1714 (50.1)
Completed Secondary	357 (10.4)
University/College/Tertiary	658 (19.2)
Marital Status (n = 3408)	
Single	226 (6.6)
Married/Cohabiting	3167 (92.9)
Separated/Divorced/Widowed	15 (0.4)
Religion (n = 3074)	
Christian	2249 (73.2)
Muslim	825 (26.8)
Age, years (n = 3423)	
Median, (IQR)	25 (22–29)
Age group	
14–18	149 (4.4)
19–23	1106 (32.2)
24–28	1192 (34.8)
29–33	638 (18.6)
34–38	42 (1.23)
>38	5 (0.2)
Mid-Upper Arm Circumference MUAC, cm (n = 3416)	
Mean (SD)	27.6 (3.8)
MUAC < 21 cm (malnourished)	21 (0.6)
MUAC 21-23 cm (underweight)	27 (7.9)
MUAC in normal range (>23-30 cm)	2408 (70.5)
MUAC > 30 cm (overweight or obese)	717 (21.0)
BMI Category (n = 3418)	
Underweight (< 18·5)	34 (1.0)
Normal (18·5–24·9)	1395 (40.8)
Overweight (25·0–29·9)	1206 (35.3)
Obese (≥ 30)	783 (22.9)

* Data are presented as n (%), mean (Standard deviation SD), or median (Interquartile range IQR), as appropriate.

Table 2
Table showing past obstetric and medical history of maternal participants.

.	
Primigravida? (n = 3423)	
No	2263 (66.1)
Yes	1160 (33.9)
Gestational age at enrolment (3418)	
Median (IQR)	20 (17–23)
First trimester	425 (12.4)
Second trimester	2993 (87.6)
Previous abortion? (n = 2263)	
Yes	773 (34.2)
Previous stillbirth? (n = 2263)	
Yes	141 (6.2)
Previous child death? (n = 1953)	
Any loss	194 (9.9)
Total number of deaths	215
At least one neonatal death	137 (7.0)
At least one infant death	43 (2.2)
At least one child death (<5 years)	32 (1.7)
Other child death (5–18 years)	9 (0.5)
No	1738 (89.0)
Previous Obstetric complications? (n = 3423)	
Perineal tear	106 (3.1)
Postpartum haemorrhage	24 (0.7)
Ectopic pregnancy	20 (0.6)
Pre-eclampsia	7 (0.2)
Cervical incompetence	6 (0.2)
Cervical tear	3 (0.1)
Other	17 (0.5)
Obstetric & Gynaecological Surgery (n = 3423)	
Caesarean Section	614 (17.9)
Cervical cerclage	5 (0.1)
Previous uterine evacuation (including D&C)	194 (5.7)
Blood transfusion	55 (1.6)
Laparotomy	28 (0.8)
Obstetric/gynaecological surgery	23 (0.7)
Past Medical History (n = 3423)	
Hypertension	167 (4.9)
Epilepsy	6 (0.2)
Diabetes	31 (0.9)
Gestational diabetes	2 (0.1)
Tuberculosis	8 (0.2)
Asthma	70 (2.0)
Allergy	52 (1.5)
Other medical condition	19 (0.6)
Living with HIV? (n = 3423)	
Yes	225 (6.6)
Previous history of syphilis? (n = 3364)	
Yes	22 (0.6)
Syphilis diagnosed in this pregnancy? (n = 3410)	
Yes	91 (2.7)
Interpregnancy interval	
> 24 months or primigravid	2905 (86.1)
12–24 months	322 (9.6)
< 12 months	146 (4.3)
Tetanus toxoid vaccine (n = 3423)	
At least 1 tetanus vaccine	2975 (86.9)

most had at least some primary or secondary schooling. Nearly all were married or cohabiting (92.9%), and most had normal nutritional status by MUAC (70.5%), the remainder had a mixture of overnutrition (21%) and undernutrition (8.5%). Primigravidae accounted for 66.1%. Among women with previous pregnancies, 34.2% reported a prior abortion, 6.2% a stillbirth, and 11.0% a prior infant loss. Previous obstetric or gynaecological procedures were uncommon, with caesarean section (17.9%) the most frequent. Pre-pregnancy hypertension was reported by 3%. HIV prevalence was 6.6%, only 0.6% reported past syphilis infection, whilst 2.7% tested positive on Rapid Plasma Reagin test (RPR) during the current pregnancy (Table 2).

A total of 3373 mothers (98.5%) were successfully followed through to delivery, and 3275 (95.7%) remained in follow-up until nine months after giving birth (Fig. 1). These 3373 women delivered 3291 live infants, and 3160 of these children (96.0%) completed follow-up through their nine-month EPI visit (Fig. 1). Infants were observed for a median duration of 278 days (IQR 274–289). At birth, the median gestational age was 39 weeks (IQR 38–40), and the mean birthweight was 3129 **g** (Table 3). Male infants made up 51.0% of the cohort. Most births occurred at the study facility (69.6%), with the remaining infants delivered in another health centre (27.4%), at home (1.4%), or in another setting (1.5%). There were 76 pairs of twins and one set of triplets (Table 3).

Among the 3423 enrolled women, 2975 (86.9%) received at least one tetanus vaccine during pregnancy, while 448 (13.1%) did not (Table 2). Parity was similar between women who did and did not receive tetanus vaccination (median of 2 in both groups). Women who received at least one tetanus vaccine attended more ANC visits than unvaccinated women (median 4 vs 2). No Adverse Events Following Immunisation (AEFI) following tetanus vaccine were reported.

The incidence proportions for fetal, maternal and neonatal outcomes are presented in Figs. 2 and 3. The distribution of GAIA levels of diagnostic certainty for all assessed outcomes are presented in Supplementary Tables 6 and 7 demonstrating the level of certainty achieved for each outcome classification. Spontaneous abortions occurred in 19 per 1000 pregnancies. More losses were recorded in the second trimester (n = 47) than in the first (n = 17), consistent with late presentation for

Table 3
Neonatal characteristics ($N = 3380$).

Neonatal Characteristics	
Birthweight ($n = 3315$) grams	
Mean grams (SD)	3129 (588)
[Min, max]	[300, 5000]
Sex Freq (%)	
Male ($n = 3368$)	1716 (51.0)
Gestational age[#] (weeks)	
Median (IQR)	39 (38, 40)
[Min, max]	[24, 42]
Birth number - Freq (%)	
Singleton	3225 (95.4)
Multiple[*]	155 (4.6)
Birth location - Freq (%)	
Kawempe	2354 (69.6)
Other health facility	926 (27.4)
Home	49 (1.4)
Other ^	51 (1.5)

Data are presented as n (%), mean (SD), or median (IQR), as appropriate.
^ Includes traditional birth attendant ($n = 5$), on the way to health facility ($n = 8$), unknown ($n = 27$), other ($n = 11$).
[*] Twins ($n = 152$, 76 pairs), triplet babies (n = 3, 1 trio).

antenatal care. One ectopic pregnancy, one molar pregnancy and one medically terminated pregnancy due to severe fetal anomalies were documented. Three additional fetal losses were reported, though exact gestational age at loss was unknown (Fig. 1).

Hypertensive disorders affected 222 women (82.4 per 1000). Postpartum haemorrhage (PPH) occurred in 22.3 per 1000 deliveries; among 55 affected women, 12.7% required subtotal hysterectomy and 63.6% received a blood transfusion. Dysfunctional labour occurred in 8.2 per 1000 deliveries. Non-reassuring fetal status was noted in 33.5 per 1000 births. Maternal mortality within 42 days was 2.3 per 1000. Four deaths were due to direct obstetric causes (two haemorrhage, one hypertensive disorder, one intraoperative), one woman died on the route to hospital with suspected hypertension, one death was attributed to COVID-19, and three remained unexplained. There were 89 stillbirths (26.3 per 1000 births): 46.1% antepartum (41/89), 31.5% intrapartum (28/89), and 22.5% of unknown timing (20/89).

Among 3373 women with recorded birth outcomes, 3380 infants were delivered: 3291 were liveborn (97.4%) and 89 were stillborn (2.7%). Most were singletons (95.4%), with 155 twins or triplets (Table 3). Preterm birth occurred in 110.9 per 1000 births. Median gestational age among preterm infants was 33 weeks (IQR 33–36); 3.5% were extremely preterm (less than 28 weeks), 14.8% very preterm (28 to less than 32 weeks), and 81.8% moderate to late preterm (32–37 weeks). Nearly half of stillbirths were preterm (46.1%). Low birthweight (birthweight <2500 g) occurred in 95.2 per 1000 livebirths, and small-for-gestational-age infants in 146.7 per 1000. Congenital microcephaly (head circumference < 3 percentile for GA and sex) was seen in 20.5 per 1000 infants. Congenital anomalies affected 9.3 per 1000 livebirths ($n = 26$), most commonly external defects such as polydactyly ($n = 10$) and hypospadias ($n = 4$) (supplementary table 7).

Neonatal bloodstream infection, respiratory infection, and meningitis occurred in 37, 34, and 10 per 1000 livebirths respectively. Neonatal encephalopathy occurred in 17.9 per 1000 live births; respiratory distress in 34.9 per 1000; and seizures in 10.9 per 1000. The neonatal mortality rate was 22.5 per 1000 livebirths—substantially higher in preterm infants (74.0) than in term infants (13.3). Twenty-five post-neonatal infant deaths occurred (7.6 per 1000 livebirths).

Supplementary Figs. 3 and 4 compare the incidence of adverse outcomes recorded among births occurring at the study site with those occurring at other facilities or at home. Rates of most maternal and fetal outcomes were higher for births at the study site, except for spontaneous abortion and preterm labour. For neonatal outcomes, all rates except for preterm birth and neonatal death were lower among births occurring outside the study site, most likely reflecting under-ascertainment and incomplete reporting in non–study-site settings.

Supplementary fig. 5 shows the variability in stillbirth incidence in the registry (26.3 per 1000), hospital electronic health records (50.6 per 1000) and reported national rate (15.1 per 1000).

4. Discussion

This study provides prospective, GAIA-defined baseline incidence estimates for key maternal, fetal, and neonatal outcomes in Uganda. By comparing registry-derived rates with national estimates and routine clinical data, the findings highlight important discrepancies related to data source, care setting, and outcome ascertainment. These results underscore both the value of prospective surveillance platforms and the limitations of relying on routine or retrospective data when interpreting safety signals during maternal vaccine trials and post-licensure monitoring.

Preterm birth, low birthweight (LBW), and small-for-gestational-age (SGA) births are among the most important outcomes evaluated in maternal immunisation safety studies. A particular strength of this registry was the prospective collection of pregnancy data combined with routine ultrasound assessment during pregnancy, enabling accurate gestational age determination and application of GAIA definitions. Accurate gestational age assessment is critical, as reliance on last menstrual period or clinical estimation alone can lead to misclassification of gestational age and consequently inaccurate estimates of preterm birth and growth-related outcomes. The preterm birth incidence observed in this cohort (11.1%) was similar to estimates reported by the Global Network Maternal Newborn Health Registry in East Africa, despite differences in study design and outcome classification [18]. The distribution of GAIA levels of diagnostic certainty for these and other outcomes are presented in Supplementary Tables 6 and 7.

The most recent national estimate of stillbirth incidence in Uganda was 14.5 (12.5–16.9) per 1000 total births in 2023 [19]. A decreasing trend has been observed in the last decade from an estimated 20.5 per 1000 (17.4–24.1) births in 2010 [19]. Our estimated incidence of 26.3 per 1000 total births (95% CI 21.1, 32.3) is much higher than the reported national rate (Supplementary fig. 5). Several factors are likely to explain this difference. First, our study was conducted in a tertiary referral hospital serving a population with high levels of socioeconomic deprivation, which is associated with increased risk of adverse pregnancy outcomes. Second, improved case ascertainment within the study, including prospective data collection and careful classification of outcomes, may have resulted in more complete identification of stillbirths compared with routine national reporting systems. Third, the study population may have included women referred during antenatal care for higher-risk pregnancies, which may contribute to a higher observed incidence.

Stillbirth incidence among enrolled women was similar between births occurring at the study site and those at other sites (26.8 vs 25.3 per 1000, $p = 0.08$), suggesting that the higher rate is not explained by a site-specific issue with care provision. In contrast, the higher incidence observed in hospital electronic medical record (EMR) data (50.6 per 1000) likely reflects the inclusion in those data of women transferred in during labour with complications, representing a more selected high-risk population. The observed discrepancy between site-specific and national stillbirth rates underscores the need for locally derived baseline data for safety evaluation, particularly given longstanding challenges in the accurate counting and classification of stillbirths globally [20]. Relying on national estimates in place of accurate site-level rates risks misclassifying expected events as potential safety concerns, or overlooking genuine ones, during maternal vaccine trials or post-licensure safety monitoring.

Uganda's maternal mortality ratio (MMR) was estimated at 284 per 100,000 live births in 2020 (UI 191–471), an improvement from 461 in 2000 [21]. In our registry, eight maternal deaths occurred during

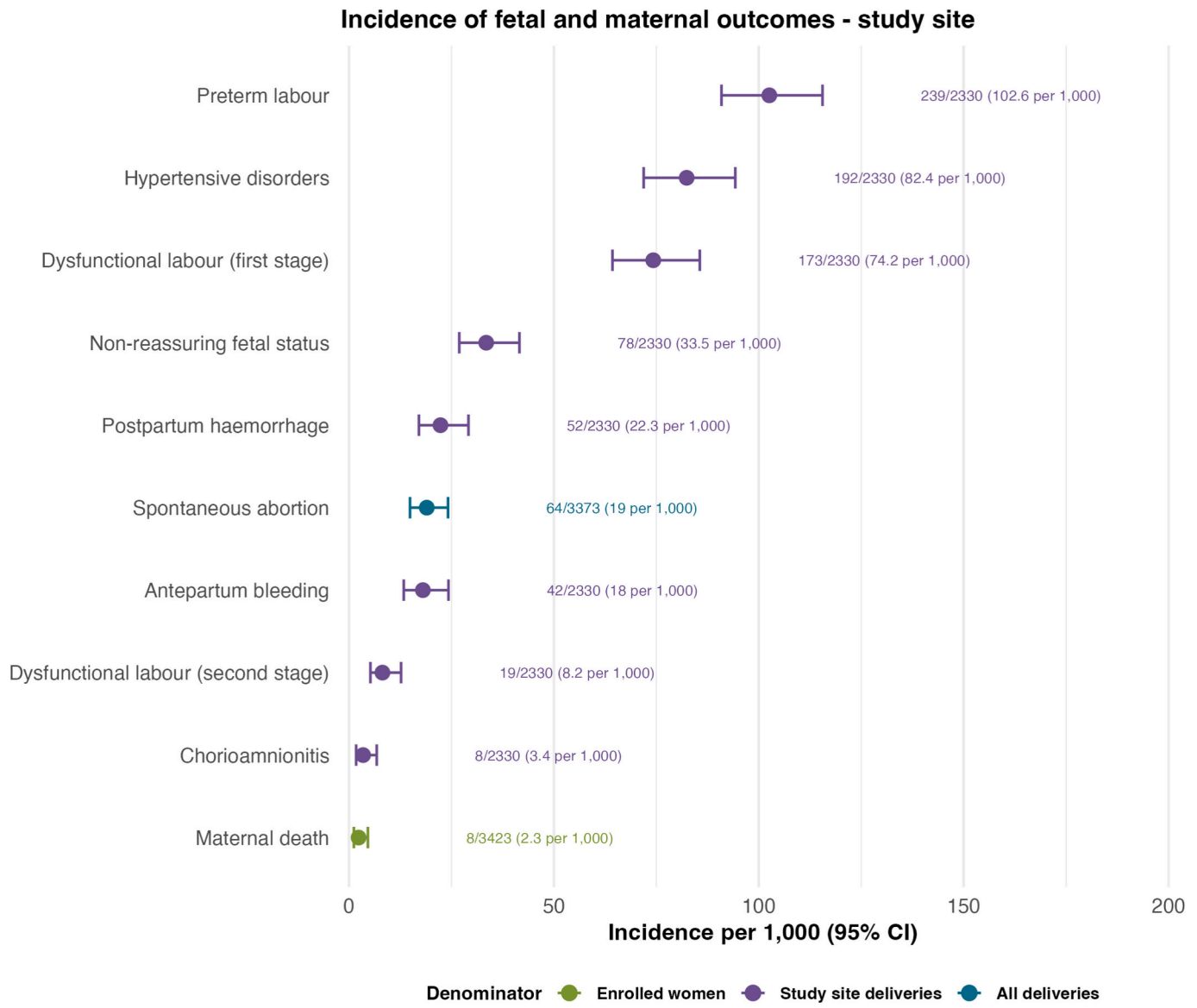

Fig. 2. Incidence of maternal and fetal outcomes (classified according to GAIA definitions levels 1–4) and associated 95% confidence intervals.

pregnancy or within 42 days postpartum, yielding an MMR of 243 per 100,000 live births (95% CI 106–478), similar to national estimates. Half of these deaths were due to direct obstetric causes—PPH, intraoperative death, or hypertensive disorders. Direct maternal deaths result from pregnancy or its management, whereas indirect deaths arise from other medical conditions worsened by pregnancy. Globally, around 70% of maternal deaths are attributed to direct obstetric causes; this proportion is lower in our registry, though three deaths of unknown cause and one suspected hypertensive case suggest the true proportion may be closer to the global pattern [22]. Hypertensive disorders were among the most common maternal complications observed in the registry affecting 82.4 per 1000 women. Their association with severe maternal outcomes, as well as preterm birth and fetal growth restriction, highlights the importance of accurate ascertainment of these conditions within maternal vaccine safety surveillance systems.

PPH remains a major driver of maternal morbidity, mortality, and near-miss events in LMICs. In our registry, PPH occurred in 22.3 per 1000 women; seven cases resulted in near-miss events requiring subtotal hysterectomy, and two maternal deaths were due to obstetric haemorrhage. Our PPH incidence is lower than that reported in a 2016 study from six Ugandan facilities (9.0%, 95% CI 7.5–10.6%), though that study defined PPH as ≥500 mL blood loss [23]. The GAIA criteria, used in our registry, define PPH as ≥1000 mL or bleeding causing hypotension, transfusion, or near-miss [24]. When the 2016 study applied a comparable "severe PPH" definition, the incidence (1.2%, 95% CI 0.6–2.0) aligned more closely with ours, underscoring the importance of consistent case definitions when comparing PPH rates across studies.

Spontaneous abortion rates are not systematically recorded even in high-income settings [25]. However, an estimated 23 million spontaneous abortions occur each year worldwide with a pooled risk of miscarriage of 15.3% (95% CI 12.5–18.7%) in all recognised pregnancies [25]. In this study, 1.8% of recognised pregnancies ended in spontaneous abortion, substantially lower than the 18.9% cumulative miscarriage probability reported by Dellicour et al. in a community-based prospective cohort in rural Kenya that identified pregnancies much earlier in gestation [26]. This difference is likely explained by the propensity for late antenatal care attendance (median gestational age at recruitment to the registry was 20 weeks (IQR 17–23)). Many early pregnancy losses would therefore have occurred before enrolment and were not captured. These findings highlight the inherent limitations of pregnancy registries initiated in the second trimester for estimating spontaneous abortion incidence and underscore the need to interpret

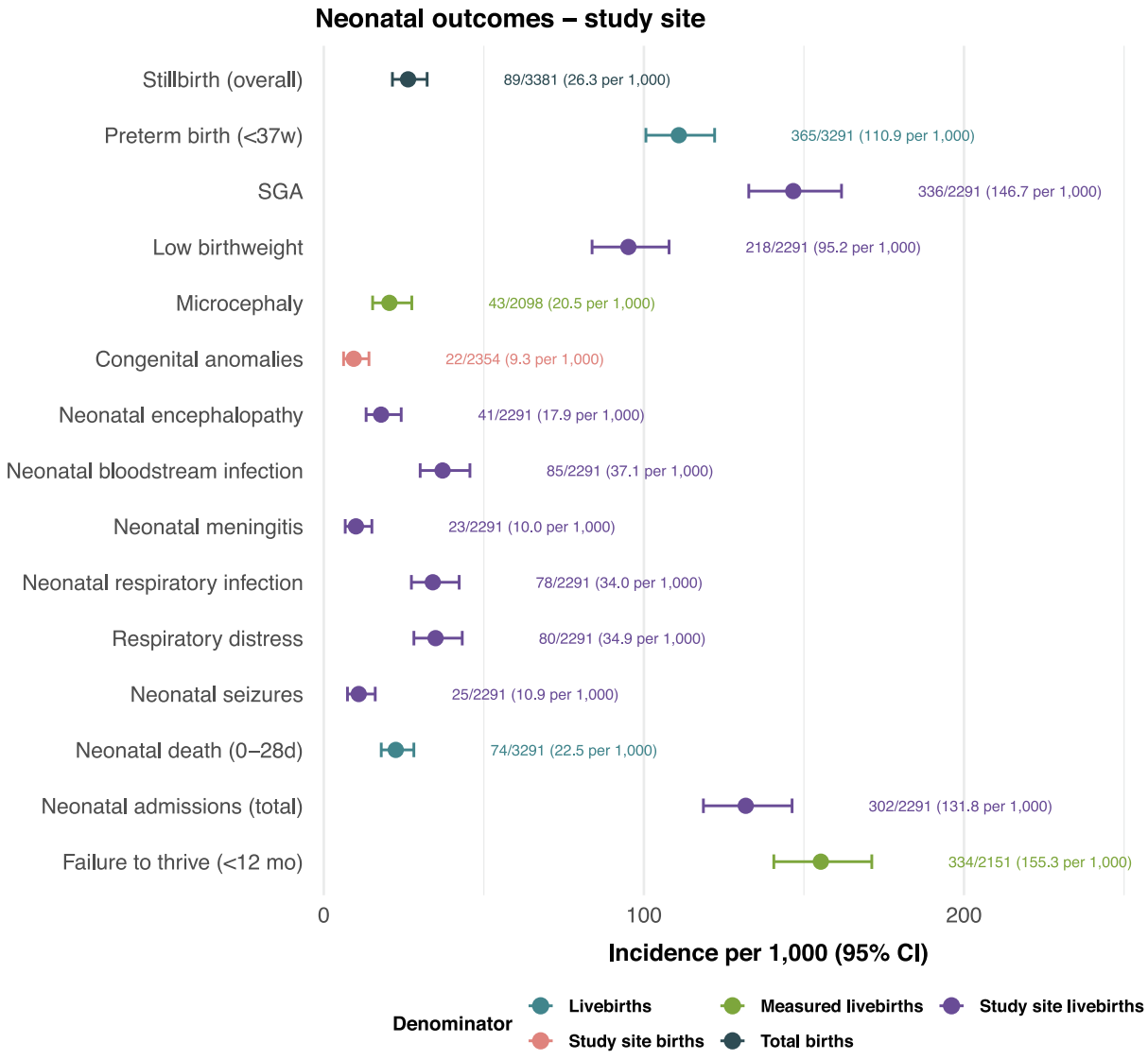

Fig. 3. Incidence of neonatal and infant outcomes (classified according to GAIA definitions levels 1–4) and associated 95% confidence intervals.

observed rates in the context of enrolment timing.

Our findings suggest substantial underreporting by women of their past medical and obstetric history. Although only 0.6% of women reported previous syphilis infection, 3% tested positive during the current pregnancy. Likewise, just 0.7% of women recalled a prior PPH across 3925 earlier deliveries, yet PPH was documented in 1.6% of deliveries within our registry. This discrepancy likely reflects both limitations of patient recall and the fragmented nature of maternity records in Uganda, where a new antenatal file is often created for each pregnancy, resulting in non-integrated documentation and increasing the risk that previous complications are missed [27]. Similar findings have been reported elsewhere, with women tending to underreport maternal complications occurring in more distant pregnancies [28]. Under-ascertainment of prior conditions may hinder timely identification of women at risk of complications and compromise continuity of care [29], while also affecting accurate eligibility assessment for clinical trials and the quality of surveillance and research data [30]. Uganda's ongoing transition to electronic medical records may help address some of these challenges in the future [31].

Although adverse outcomes from prior pregnancies were often underreported, some conditions were overdiagnosed during current admissions. Of 82 infants clinically labelled with neonatal encephalopathy, only 42 (51.2%) met GAIA criteria or were confirmed by expert review; most unconfirmed cases had low APGAR scores but no subsequent signs of encephalopathy, reflecting a lack of diagnostic reassessment as clinical information evolved. A similar issue arose with labour complications: 351 cases of prolonged labour, obstructed labour, or dystocia were documented, but only 198 were validated on review. Such discrepancies, also observed in high-income settings [32], underscore the risk of diagnostic error when standard definitions are not applied and highlights the importance of validating diagnostic codes used in health information systems if they are to underpin adverse event surveillance [32].

This study has several important strengths. High-quality prospective data on pregnancy outcomes from low- and middle-income countries remain scarce, and few settings in Africa have similarly detailed, longitudinal follow-up of maternal and neonatal outcomes. The registry achieved high retention (96%) and used harmonised data collection across mother–infant dyads, providing robust baseline incidence estimates for a wide range of key outcomes. These data are directly relevant to maternal immunisation readiness, informing the design and powering of forthcoming maternal vaccine trials—including those targeting Group B Streptococcus —and supporting interpretation of post-licensure safety signals. Integration of the registry within a research-active vaccine trial site further demonstrates the feasibility of establishing prospective safety-surveillance platforms ahead of vaccine introduction.

Methodological strengths include the prospective design, standardised procedures, and use of GAIA-aligned outcome definitions, enhancing comparability across studies and settings.

This study has several limitations. The registry was conducted at a single site, a national referral hospital where high-risk pregnancies and deliveries were over-represented, which may limit generalisability to other regions or health-system contexts. Although follow-up was high, some outcome misclassification is likely, particularly for events reliant on maternal recall or routine clinical documentation. In addition, limited diagnostic capacity in routine practice—such as restricted access to chest radiography or cerebrospinal fluid cultures—may have reduced diagnostic accuracy for certain neonatal infections. The successful application of GAIA definitions within this registry was supported by study-enhanced clinical and laboratory capacity, including routine ultrasound assessment, provision of selected point-of-care investigations, and enhanced microbiological testing. Availability of these resources may differ across routine clinical settings, and further work is needed to understand how GAIA definitions perform in diverse healthcare and surveillance contexts where diagnostic information is more limited [21]. Finally, as the study was conducted in a research-active facility, outcome rates and data quality may differ from those observed in lower-resourced or non-trial settings.

Collectively, these findings demonstrate that both reliable baseline incidence estimates and an understanding of how outcome ascertainment varies across surveillance systems are essential for accurate interpretation of maternal vaccine safety signals. Under- and over-ascertainment of key maternal and neonatal outcomes remain substantial challenges when surveillance relies on retrospective data, fragmented records, or inconsistently applied diagnostic criteria. While prospective registries provide high-quality baseline estimates essential for maternal vaccine readiness, their resource-intensive nature limits scalability. Strengthening routine electronic health information systems, alongside investment in essential diagnostic capacity, will be critical to support sustainable, high-quality surveillance. Further work is also needed to optimise the application of GAIA case definitions within routine clinical and surveillance systems, including electronic health record platforms, and to determine whether adaptations are required to support reliable case ascertainment while maintaining diagnostic validity.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT (OpenAI) to improve grammar, clarity and readability of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Hannah G. Davies: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gordon Rukundo:** Writing – review & editing, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Cleophas Komugisha:** Writing – review & editing, Formal analysis, Data curation. **Sam Kipyeko:** Writing – review & editing, Supervision, Project administration. **Andrew Young:** Writing – review & editing, Visualization. **Jennifer Kisakye:** Writing – review & editing, Validation, Data curation. **Merryn Voysey:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Robert Mboizi:** Writing – review & editing, Supervision, Project administration, Investigation. **Paul T. Heath:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Musa Sekikubo:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Kirsty Le Doare:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Funding

This work was produced by PREPARE, which is part of the EDCTP2 program supported by the European Union (grant number RIA2018V-2304). The views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the patients and families who participated in this study, as well as the clinical, nursing and research staff at Kawempe National Referral Hospital for their dedication, collaboration and support in delivering this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128952.

Data availability

Data will be made available on request.

References

[1] United Nations iInter-agency Group for Child Mortality Estimation (UN, IGME). Levels & Trends in Child Mortality [Internet]. 2021. Report. Available from: file:///C:/Users/User/Downloads/UNICEF-IGME-2021-Child-Mortality-Report.pdf.

[2] Perin HJ, Yeung MSPHD, Villavicencio F, Black RE, Liu L, Mulick A, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the **s**ustainable **d**evelopment **g**oals. Lancet Child Adolesc Health 2022;6:106–21. https://doi.org/10.1016/S2352-4642(21)00311-4.

[3] Global vaccine action plan 2011–2020 [Internet] Available from: https://www.who.int/publications/i/item/global-vaccine-action-plan-2011-2020; 2021. ISBN 978 92 4 150498 0.

[4] Yusuf N, Raza AA, Chang-Blanc D, Ahmed B, Hailegebriel T, Luce RR, et al. Progress and barriers towards maternal and neonatal tetanus elimination in the remaining 12 countries [Internet]. 2021 [cited 2023 May 24]. Available from: **www.thelancet.com/lancetghVol**.

[5] Thorn N, Karampatsas K, Le Doare K, Heath PT. Progress towards a group B streptococcal vaccine – where are we now? **Vaccine** 2025;62(June):127575. doi: https://doi.org/10.1016/j.vaccine.2025.127575 **[**PubMed PMID: 40773961**]**.

[6] Respiratory syncytial virus vaccines: the future is bright. **Lancet Respir Med** 2024;12(7):499. doi: https://doi.org/10.1016/S2213-2600(24)00184-X [PubMed PMID: 38851193].

[7] Sharan A, Stuurman AL, Jahagirdar S, Elango V, Riera-Montes M, Kashyap NK, et al. Estimating baseline rates of adverse perinatal and neonatal outcomes using a facility-based surveillance approach: **a** prospective observational study from the WHO **g**lobal **v**accine **s**afety **m**ulti-**c**ountry **c**ollaboration on safety in pregnancy. **EClinicalMedicine** 2022;50. doi:https://doi.org/10.1016/j.eclinm.2022.101506.

[8] Bonhoeffer J, Kochhar S, Hirschfeld S, Heath PT, Jones CE, Bauwens J, et al. Global alignment of immunization safety assessment in pregnancy - the GAIA project. Vaccine 2016;34(49):5993–7. https://doi.org/10.1016/j.vaccine.2016.07.006.

[9] Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang WT, et al. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety. Vaccine 2021;39(19):2712. https://doi.org/10.1016/J.VACCINE.2021.03.016 [PubMed PMID: 33846042].

[10] Kyohere M, Davies HG, Karampatsas K, Cantrell L, Musoke P, Nakimuli A, et al. Epidemiology of group B *Streptococcus*: maternal colonization and infant disease in Kampala, Uganda. Open Forum Infect Dis 2025;12(4). https://doi.org/10.1093/ofid/ofaf167.

[11] Sturrock S, Davies HG, Rukundo G, Nakabembe E, Mboizi R, Sekikubo M, et al. Sociodemographic factors associated with established and novel antenatal

vaccination uptake in a cohort of pregnant women in Uganda. Pediatr Infect Dis J. 2025;44(2S):S92–6. https://doi.org/10.1097/INF.0000000000004644. Epub 2025 Feb 14. PMID: 39951082; PMCID: PMC12178161.

[12] Nakabembe E, Greenland M, Amaral K, Abu-Raya B, Amone A, Andrews N, et al. Safety and immunogenicity of an acellular pertussis vaccine containing genetically detoxified pertussis toxin administered to pregnant women living with and without HIV and their newborns (WoMANPOWER): a randomised controlled trial in Uganda. Lancet Glob Health 2025;13(1):e81–97. https://doi.org/10.1016/S2214-109X(24)00409-1 [PubMed PMID: 39706666].

[13] Davies HG, Kyohere M, Tusubira V, Amone A, Wamawobe A, Komugisha C, et al. Etiology and **a**ntimicrobial **r**esistance of **c**ulture-**p**ositive **i**nfections in Ugandan **i**nfants: **a** **c**ohort **s**tudy of 7000 **n**eonates and **i**nfants. **Open Forum Infect Dis** 2024 11:S157–64. doi:https://doi.org/10.1093/ofid/ofae629.

[14] Le Doare K, Kyohere M, Davies HG, Musoke P, Nakimuli A, Tusubira V, et al. Seroepidemiology of maternally-derived antibody against Group B *Streptococcus* (GBS) in Mulago/Kawempe Hospitals Uganda - PROGRESS GBS. Gates Open Res 2020;4. https://doi.org/10.12688/gatesopenres.13183.2.

[15] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: **b**uilding an international community of software platform partners. **J** **Biomed Inform** 2019 95:103208. doi:https://doi.org/10.1016/J.JBI.2019.103208 **[**PubMed PMID: 31078660**]** .

[16] Davies HG, Bowman C, Watson G, Dodd C, Jones CE, Munoz FM, et al. Standardizing case definitions for monitoring the safety of maternal vaccines globally: GAIA definitions, a review of progress to date. Int J Gynecol Obstet 2023. https://doi.org/10.1002/IJGO.14843.

[17] Kochhar S, Bauwens J, Bonhoeffer J, http://www.gaia-consortium.net/ GPParticipantsE address: **Safety assessment of immunization in pregnancy**. **Vaccine** 2017;35(48 Pt A):6469–71. https://doi.org/10.1016/j.vaccine.2017.09.033.

[18] Pusdekar YV, Patel AB, Kurhe KG, Bhargav SR, Thorsten V, Garces A, et al. Rates and risk factors for preterm birth and low birthweight in the global network sites in six low- and low middle-income countries. Reprod Health 2020;17(3):1–17. https://doi.org/10.1186/s12978-020-01029-z. PubMed PMID: 33334356.

[19] The United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). STANDING UP FOR STILLBIRTH. Current estimates and key interventions [Internet]. 2024 [**C**ited 2025 Dec 15]. **Report** Available from: **https://data.unicef.org/resources/standing-up-for-stillbirth-report/**.

[20] Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: **w**here? When? Why? How to make the data count? Lancet 2011;377(9775): 1448–63. https://doi.org/10.1016/S0140-6736(10)62187-3 [PubMed PMID: 21496911].

[21] WHO, UNICEF, UNFPA, World Bank Group and UNPD. Estimates of maternal mortality ratio (MMR; maternal deaths per 100,000 live births) 2000–2020; 2023.

[22] Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. **Lancet** 2014;2:333. doi:https://doi.org/10.1016/S2214-109X(14)70227-X.

[23] Ononge S, Mirembe F, Wandabwa J, Campbell OMR. Incidence and risk factors for postpartum hemorrhage in Uganda. Reprod Health 2016 13(1):1–7. doi:https://doi.org/10.1186/S12978-016-0154-8/TABLES/2 **[**PubMed PMID: 27080710**]** .

[24] Kerr R, Eckert LO, Winikoff B, Durocher J, Meher S, Fawcus S, et al. Postpartum haemorrhage: **c**ase definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016;34(49):6102–9. https://doi.org/10.1016/j.vaccine.2016.03.039.

[25] Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 2021;397(10285):1658–67. https://doi.org/10.1016/S0140-6736(21)00682-6 [PubMed PMID: 33915094].

[26] Dellicour S, Aol G, Ouma P, Yan N, Bigogo G, Hamel MJ, et al. Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya. BMJ Open 2016;6(4). https://doi.org/10.1136/bmjopen-2016-011088. PubMed PMID: 27084287.

[27] World Health Organization. Standards for improving quality of maternal and newborn care in health facilities. [Internet]. 2016 [**C**ited 2024 Feb 9]. **Report** Available from: **https://www.who.int/publications/i/item/9789241511216**.

[28] Zimmerman LA, Shiferaw S, Seme A, Yi Y, Grove J, Mershon CH, et al. Evaluating consistency of recall of maternal and newborn care complications and intervention coverage using PMA panel data in SNNPR, Ethiopia. PLoS One 2019;14(5). https://doi.org/10.1371/JOURNAL.PONE.0216612 [PubMed PMID: 31071142].

[29] WHO recommendations on home-based records for maternal, newborn and child health. Licence: CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization; 2018.

[30] Eckert LO, Jones CE, Kachikis A, Bardají A, Silva FT Da, Absalon J, et al. Obstetrics risk **a**ssessment: **e**valuation of selection criteria for vaccine research studies in pregnant women. **Vaccine** 2020 38(29):4542–7. doi:https://doi.org/10.1016/j.vaccine.2020.05.022 **[**PubMed PMID: 32448618**]** .

[31] Cowie MR, Blomster JI, Curtis LH, Duclaux S, Ford I, Fritz F, et al. Electronic health records to facilitate clinical research. **Clin Res Cardiol** 2017 106(1):1–9. doi: https://doi.org/10.1007/S00392-016-1025-6/TABLES/3 **[**PubMed PMID: 27557678**]** .

[32] Moll K, Fingar K, Sheng M, Burrell T, Wong HL, Baer B, et al. Validating claims-based algorithms identifying pregnancy outcomes. Pharmacoepidemiol Drug Saf 2020;36th International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Virtual.29(SUPPL 3):400. http://dx.doi.org/10.1002/pds.5114.

[21] Davies HG, Bowman | Conor, Watson G, Dodd C, Jones CE, Munoz FM, et al. Standardizing case definitions for monitoring the safety of maternal vaccines globally: GAIA definitions, a review of progress to date. International Journal of Gynecology & Obstetrics 2023;00:1–10. https://doi.org/10.1002/IJGO.14843.