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Obstetric and neonatal outcomes in South Africa

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ABSTRACT

Background: Background epidemiologic population data from low- and middle-income countries (LMIC), on maternal, foetal and neonatal adverse outcomes are limited. We aimed to estimate the incidence of maternal, foetal and neonatal adverse outcomes at South African maternal vaccine trial sites as reported directly in the clinical notes as well as using the 'Global Alignment of Immunization Safety Assessment in Pregnancy' case definitions (GAIA-CDs). GAIA-CDs were utilized as a tool to standardise data collection and outcome assessment, and the applicability and utility of the GAIA-CDs was evaluated in a LMIC observational study.
Methods: We conducted a retrospective record review of maternity and neonatal case records for births that occurred in Soweto, Inner City- Johannesburg and Metro-East Cape Town, South Africa, between 1st July 2017 and 30th June 2018. Study staff abstracted data from randomly selected medical charts onto standardized study-specific forms. Incidence (per 100,000 population) was calculated for adverse maternal, foetal and neonatal outcomes, which were identified as priority outcomes in vaccine safety studies by the Brighton Collaboration and World Health Organization. Outcomes reported directly in the clinical notes and outcomes which fulfilled GAIA-CDs were compared. Incidence of outcomes was calculated by combining cases which were either reported in clinical notes by attending physicians and/ or fulfilled GAIA-CDs.
Findings: Of 9371 pregnant women enrolled, 27·6% were HIV-infected, 19·9% attended antenatal clinic in the 1st trimester of pregnancy and 55·3% had ≥1 ultrasound examination. Fourteen percent of women had hypertensive disease of pregnancy, 1·3% had gestational diabetes mellitus and 16% experienced preterm labour. There were 150 stillbirths (1·6%), 26·8% of infants were preterm and five percent had microcephaly. Data available in clinical notes for some adverse outcomes, including maternal- & neonatal death, severe pre-eclampsia/ eclampsia, were able to fulfil GAIA-CDs criteria for all of the clinically-reported cases, however, missing data required to fulfil other GAIA-CD criteria (including stillbirth, gestational diabetes mellitus and gestational

Abbreviations: GAIA, Global Alignment of Immunization Safety Assessment in Pregnancy; CD, case definitions; LMICs, low & middle income countries; MFN-AOs, maternal and foetal/neonatal adverse outcomes.

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hypertension) led to poor correlation between clinically-reported adverse outcomes and outcomes fulfilling GAIA-CDs. Challenges were also encountered in accurately ascertaining gestational age.
Interpretation: This study contributes to the expanding body of data on background rates of adverse maternal and foetal/ neonatal outcomes in LMICs. Utilization of GAIA-CDs assists with alignment of data, however, some GAIA-CDs require amendment to improve the applicability in LMICs.
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1. Research in context

1.1. Evidence before this study

Data on background rates of adverse outcomes in maternal and foetal/ neonatal participants from low- and middle-income country settings are limited and have not been standardised in its collection nor interpretation. Knowledge of the background rates of adverse outcomes in a population in which an intervention will be implemented is vital to allow for identification of possible safety signals, as well as quantification of benefits associated with the intervention.

Maternal immunization has potential benefit to the mother, but specifically to benefit her foetus/ neonate, and may contribute to reduction of maternal, foetal and neonatal infection-related morbidity and mortality.

The 'Global Alignment of Immunization Safety Assessment in Pregnancy' (GAIA) project was initiated in 2014 and has since developed and published 26 adverse outcome case definitions (CDs), modelled on the Brighton Collaboration definitions, specifically for use in maternal immunization trials. Prior to this study, only half of the definitions had been field tested, the majority in high income countries only. Utilization of the GAIA case definitions will assist in harmonizing data collected in diverse settings, and therefore, it is imperative to assess the applicability in different settings.

1.2. Added value of this study

This study provides a comprehensive overview of background rates of maternal and foetal/ neonatal adverse outcomes from three urban sites in South Africa, which can be utilized in similar settings, to assess the risks and benefits or impact of various health interventions on maternal and neonatal health, including implementation of maternal vaccination.

All of the GAIA-CDs published before 2019 were field-tested in South Africa, utilising a retrospective review of maternity medical records and associated, available neonatal records.

1.3. Implications of all the available evidence

Data generated in this study provide important background rates for maternal- and foetal/ neonatal adverse outcomes in sites conducting early phase clinical vaccine trials in South Africa. Additionally, this study has highlighted strengths and weaknesses of the GAIA-CDs, and we have provided recommendations for amendments to be made, in order to make the GAIA-CDs more functional and relevant in different clinical settings.

2. Background

Pregnancy, delivery, postpartum period and the neonatal period are challenging times for mother-foetus/newborn dyads, many of whom experience adverse outcomes, especially in Low- and Middle-income Countries (LMICs).

Maternal immunisation is an important modality for prevention of foetal, neonatal and maternal infection-related adverse outcomes [1]. Numerous vaccines are recommended and approved for use during pregnancy, including tetanus toxoid [2], pertussis [3,4], influenza [5] and SARS-CoV-2 [6,7]. A bivalent respiratory syncytial virus (RSV) Prefusion F subunit vaccine was approved in 2023 for use in pregnant women to protect infants against RSV [8]. Additionally, vaccines against group B *streptococcus* (GBS, *Streptococcus agalactiae*), which significantly affects neonatal and infant health, have been demonstrated to be safe and show promising immunogenic and efficacy profiles in clinical trials [9–11].

A challenge during implementation of any new intervention, such as roll-out of a new vaccine, is determining whether an adverse outcome is potentially related to the intervention, or may have occurred naturally, in the absence of the intervention. With benefits of maternal immunisation being recognised globally, the World Health Organization has appealed for prioritization of active safety monitoring of these immunisations [12].

Background epidemiologic population data on maternal and foetal/ neonatal adverse outcomes (MFN-AOs) are limited, especially in low- and middle-income countries (LMIC) [13,14]. Furthermore, definitions, quality, and quantity of adverse outcome data available on from clinical trials and routine maternal-foetal/ neonatal care are variable. This variability hampers interpretation of adverse outcomes in clinical trials. The Brighton Collaboration Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project was initiated in 2014 to develop standardised case definitions (CD) of MFN-AOs and guidance on collection of clinical, laboratory and other data spanning antenatal, intrapartum and postpartum periods [15]. In line with other Brighton Collaboration CDs, the GAIA-CDs have three levels of certainty (LOC), with LOC1 being the most specific and LOC3 being the most sensitive. Since 2016, GAIA-CDs for 26 MFN-AOs have been developed and published, and are being utilised in clinical trials to assist in improving comparability of data across sites.

Pregnant women in South Africa were enrolled in a phase 1/2 randomised controlled GBS vaccine trial (C1091002; NCT03765073) from early 2019, however, limited available data on background rates of MFN-AOs necessitated the conduct of this epidemiological study. This study aimed to estimate the incidence of maternal (obstetric, postpartum), foetal and neonatal adverse outcomes among (i) randomly selected pregnant women and their infants respectively (source population) and (ii) pregnant women who had characteristics similar to potential vaccine-trial participants, and their infants (trial-similar population). The GAIA-CDs were utilised as a tool to standardise data collection and outcome assessment, and the applicability and utility of the GAIA-CDs was evaluated in a LMIC observational study.

3. Methods

3.1. Study participants and oversight

We conducted a population-based, observational, retrospective medical record review of maternity case records and neonatal admission records in three regions in South Africa: Soweto, Inner City Johannesburg (ICJ), and Metro East Cape Town (MECT), South Africa.

Each site consisted of a tertiary care hospital and its referring secondary hospital(s) and/ or referring primary care delivery centres or midwife obstetric units (MOUs).

Selected sites were participating in an interventional GBS maternal vaccine trial (Clinicaltrials.gov NCT03765073). Delivery centres are public health facilities, and paper-based maternity case records (MCR) which included medical notes for the entire duration of pregnancy and delivery, were standardised nationally.

The study was reviewed and approved by the Human Research Ethics Committee of the University of the Witwatersrand (reference number: 180707) and the Research Ethics Committee of the University of Stellenbosch (reference number: N18/10/122). The study was registered on the National Health Research Database (ref GP_201811_040 & WC_201811_018). Permission was obtained from facilities and the local and provincial health authorities. As this was a retrospective review of medical records, participant written informed consent requirement was waived.

3.2. Study procedures

3.2.1. Participant selection and sample size

Electronic composite registers of births that occurred at the participating delivery centres served as a sampling frame, from which charts were randomly selected. Medical records from women who delivered at any of the delivery centres (see Table S1) affiliated to the three sites between 1st July 2017 and 30th June 2018 were included in the sampling frame.

The study statistician ensured that selection of potential participants was proportional to the number of deliveries at sites per month. This stratified random sample formed the ‘source population’, which had no exclusion criteria.

The ‘trial-similar’ cohort was a sub-population of the source population and was identified during analysis using inclusion and exclusion criteria for the GBS-vaccine trial. The “index visit” was any antenatal visit between 27 and 36 weeks gestation, which would correspond with the vaccine trial’s first vaccination visit. The trial-similar cohort included women with singleton pregnancies who had an antenatal visit between 20 and 26 weeks gestation, at least one antenatal clinic visit between 27 and 36 weeks gestation, were aged ≥18 years and ≤40 years at the time of the index visit, had no previous evidence of a selection of adverse outcomes, and did not have human immunodeficiency virus (HIV) or syphilis infection recorded at or before the index visit.

The sample size required for the trial-similar cohort to achieve a 95% confidence interval (two-sided) on an observed incidence proportion of 0·20 (20%) with a 1·5% absolute precision (width of 95% CI is 3%) was 2732 women. The intended sample composition across regions for the trial-similar cohort was proportionate to the expected region-specific enrolment for the C1091002 trial: 57% from Soweto (n = 1,588), 29% from ICJ (n = 792), 14% MECT (n = 382). Based on the assumption that only 30% of the population would be eligible for the trial-similar cohort, 9108 medical charts from the source population would be required with 5194, 2640 and 1274 charts coming from the Soweto, ICJ and MECT sites respectively.

3.2.2. Data abstraction

Between March 2019 and June 2020, study staff retrieved paper (Soweto & ICJ) or electronic (ICJ & MECT) maternity case records selected from birth registers and allocated sequential participant identifiers to maternal participants, abstracted maternal, foetal and newborn data from antenatal and delivery records onto either paper or electronic study-specific case report forms. If a maternity case record was not accessible, the subsequent randomly selected file was retrieved and reviewed.

Data were collected into a study-specific Research Electronic Data Capture (REDCap) database hosted at The University of the Witwatersrand [16,17] (see Supplementary material). For ease of data abstraction, the database aligned with maternity case records, and included all variables required for assessment of all GAIA-CDs and enabling terms published by February 2019 (Table S2). Participant identifiers were utilized by study staff to retrieve medical and laboratory records, but all identifiers were removed from data prior to analysis.

3.3. Statistical analysis

A statistical analysis plan was approved before database lock. Data were analysed using STATA version 15 (Statacorp LLC, College Station, Texas). The LOC attainable by using abstracted participant data was determined for each relevant MFN-AO in a step-wise process during analysis, from LOC1 to LOC3. For each adverse outcome, the relevant data variables were abstracted for all participants from the main database and analysed to assess whether or not the AE was present according to the most specific LOC (LOC1). If LOC1 criteria were not fulfilled, analyses were repeated for LOC2 and LOC3 criteria. Additionally, participants who did not fulfil GAIA-CD criteria, but had free-text mention of the adverse outcome in clinical notes, were included in reported incidence rates for that outcome. Incidence of adverse outcomes was calculated as cases (i) per 100,000 deliveries for maternal outcomes, (ii) per 100,000 births for stillbirths and miscarriages, and (iii) per 100,000 live births for neonatal outcomes.

3.4. Role of funding source

This work was funded by Pfizer (Inc.), and co-authors employed by Pfizer were involved in study conceptualisation and design, in interpretation of results, writing the manuscript and the decision to submit manuscript for publication.

4. Results

4.1. Participants: Source population

Of the 10,600 maternity case records originally selected, <10% were not located and were replaced with subsequent files on a random file sampling list. Of the 9389 maternity case records reviewed, 9371 were complete enough to include: 1289 from MECT, 5442 from Soweto, and 2640 from ICJ (Fig. 1, Table 1). The mean age of women at the ‘index visit’ was 27·7 years, with 10·9% (1022/9371) being under 20 years of age. Three quarters (6949/9371) of the mothers were aged 20–34 years, 10.8% (1013/9371) and 3.2% (304) were aged 35-<40 and ≥40 years, respectively, at the index visit (27-<36 weeks gestation) (Table S3).

HIV-infection status was known for more than 99% (9355/9371) of mothers, of whom 27·6% were HIV-infected. Syphilis results were recorded for 86·3% (8086/9371) of participants, of whom 1·2% (100/8086) were positive. Overall, 15·1% (1414/9371) of women had a history of at least one significant adverse outcome in a previous pregnancy (stillbirth, neonatal death, low birth weight (LBW), preterm delivery, miscarriage, congenital anomalies) (Table 1).

Just over 22% of women delivered in a primary healthcare facility and 31·8% of women (2979/9371) were primigravida. Median body mass index at index visit was 27.5 kg/m^2, 36·3% (2111/ 5822) of women were obese (BMI ≥ 30·0kg/m^2), and 6·8% (395/5822) of women were morbidly obese (BMI ≥ 40·0kg/m^2). The median number of antenatal clinic (ANC) visits was 5 (IQR 4 to 7). Only 1·6% (148/9371) of women did not attend at least one ANC visit prior to delivery, however, only 20% (1864/9371) of women had an ANC visit during their first trimester. Most women (58·6%, 5494/9371) initiated antenatal care during the second trimester of pregnancy (Table 1).

There were 9505 infants born to source population women for whom birth outcome details were available, including 140 pairs of twins and 2 sets of triplets. Mean birth weight was 2992 g, and 51·1% were males. There were 150 stillbirths and 53 miscarriages (Fig. 1, Table 1).

4.2. Participants: Trial-similar population

Thirty percent (2832/9371) of the source population fulfilled trial-similar population criteria, all of whom had singleton pregnancies, a median of 6 ANC visits (IQR 5 to 7), and 42·4% were primigravida. There were 17 (0·6%) and 4 (0·1%) women who seroconverted to HIV-

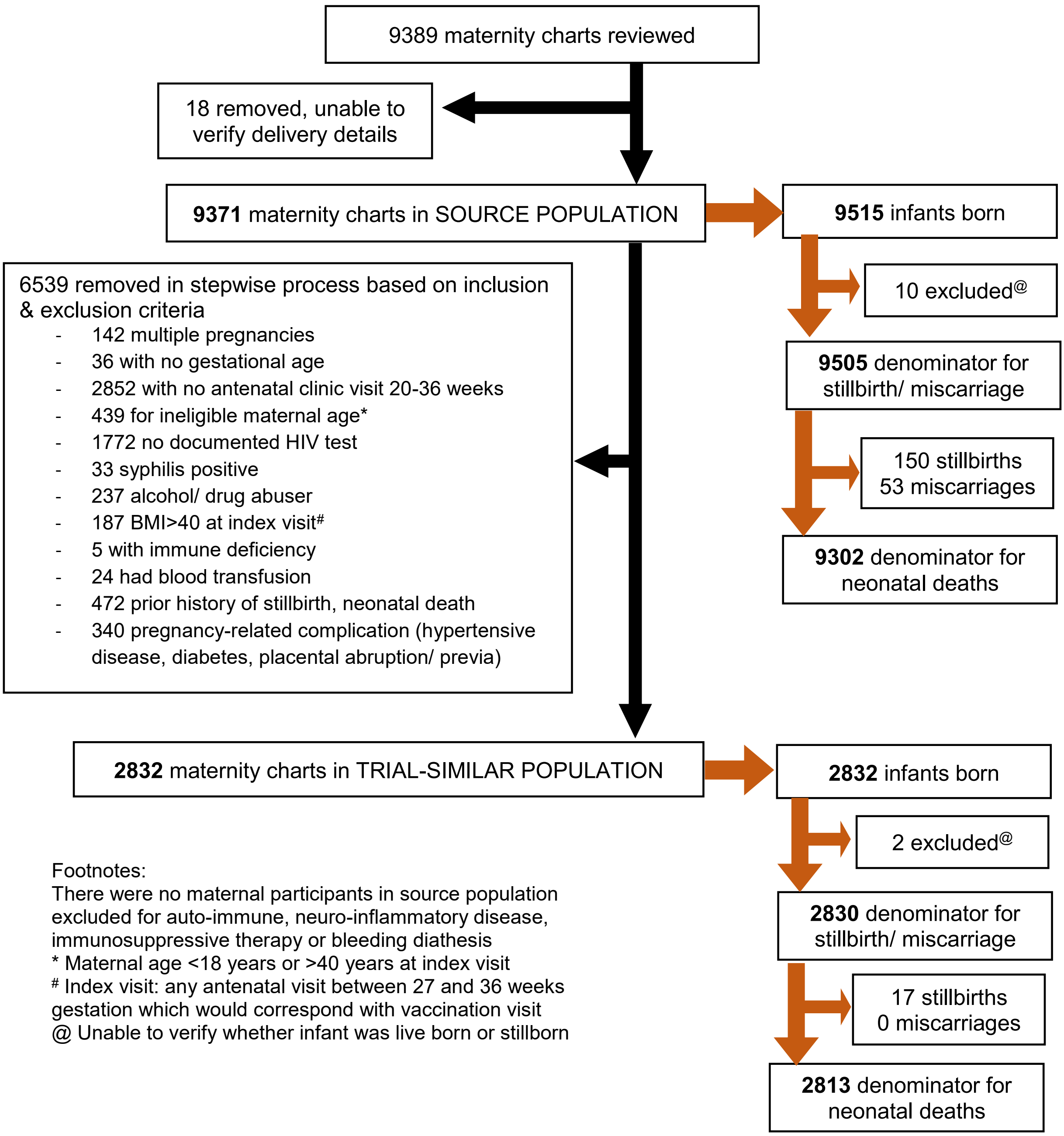

Fig. 1. Flow chart of maternal and infant participants in source population and trial-similar cohort.

positivity and syphilis seropositivity respectively between the index visit and delivery. The mean birth weight of the 2830 infants with known birth outcome was 3149 g, and 17 were stillborn (Fig. 1, Table 1).

4.3. Gestational age assessment

Gestational age (GA) could be ascertained using the GAIA-CD [18] in 94·3% (8839/9371) of women in the source population and 98·7% of women in the trial-similar population. Less than four percent and <30% of women had GA assessment fulfilling GAIA LOC 1 or LOC 2 respectively (Table 2).

4.4. Incidence of obstetric and neonatal outcomes (Tables 3 and 4)

The incidence of MFN-AOs in the source- and trial-similar populations, detailed in Tables 3 and 4, are the sum of outcomes which (i) fulfilled the requirements for GAIA-CD LOC 1, 2 or 3, and (ii) were reported in free text in the maternity case records, but didn't fulfil requirements for GAIA-CD.

Fourteen percent (1353/9371) of women in the source population had hypertensive diseases of pregnancy. The incidence (per 100,000) of gestational hypertension without complications, pre-eclampsia and severe pre-eclampsia or eclampsia were 3831, 9305 and 7022, respectively, with some overlap. Gestational diabetes mellitus (GDM) occurred in 1·3% (124) of women, 7·2% (675) had preterm premature rupture of membranes, 16% (1538) of women experienced preterm labour (Table 3) and 27% (2541) delivered by emergency caesarean section (Table S9).

There were 150 stillbirths (1·6% of 9505 newborns) in the source population, of which 20% (30/150) and 26% (39/150) of foetal deaths occurred antepartum, and intrapartum respectively, however, timing of foetal death in 54% (81/150) of stillbirths was unknown, making them

Table 1
Selected clinical and demographic characteristics of mothers and their newborns: SOURCE and TRIAL-similar populations.

Characteristic	Source population	Trial similar population
Maternal participants	**N (%)**	**N (%)**
Number	9371 (100·0)	2832 (100·0)
Demographic characteristics		
*Maternal age at index visit (years)**	27·7 ± 6·5	26·47 ± 5·2
HIV Status (N with known HIV status)	9355	2824
Positive‡	2585 (27·6)	17 (0·6)##
Syphilis Status (N with known results)	8086	2761
Positive	100 (1·2)	4 (0·1)
Body Mass index (BMI) at index visit (median (IQR)) kg/m²	27·5 (23·8–32·4)	28·0 (25·0–32·0)
BMI Category (N with known BMI)	5822	1042
Underweight (<18·5) ‡	95 (1·6)	6 (0·6)
Normal (18·5–24·9) ‡	1821 (31·3)	252 (24·2)
Overweight (25·0–29·9) ‡	1795 (30·8)	410 (39.4)
Obese (≥30) (N for obesity classes) ‡	2111 (36·3)	374 (35·9)
Obesity Class I (30·0–34·9)~	1170 (55·4)	256 (68·5)
Obesity Class II (35·0–39·9)~	546 (25·9)	118 (31·5)
Obesity Class III (≥40·0)~	395 (18·7)	0 (0·0)
Parity (median (IQR)	1 (0 to 2)	1 (0 to 1)
Primigravida	2979 (31·8)	1202 (42·4)
≥5 previous pregnancies	88 (0·9)	0 (0)
Singleton pregnancy	9229 (98·5)	2832 (100)
Multiple pregnancies- Twins	140	0
Multiple pregnancies- Triplets	2	0
Other characteristics		
Number of ANC visits- median (IQR)	5 (4 to 7)	6 (5 to 7)
Timing of first ANC visit		
1st trimester	1864 (19·9)	634 (22·4)
2nd trimester	5494 (58·6)	2178 (76·9)
3rd trimester	1843 (19·7)	20 (0·7)
Cannot be determined	22 (0·2)	0
None	148 (1·6)	0
Women with ≥ 1 Ultrasound examination during pregnancy	5179 (55·3)	1444 (51·0)
Timing of FIRST ultrasound examination		
1st trimester	402 (7·8)	96 (6·7)
2nd trimester	2742 (52·9)	868 (60·1)
3rd trimester	2031 (39·2)	480 (33·2)
Cannot be determined	4 (0·08)	0 (0)
Institution of delivery		
Tertiary hospital	5828 (62·2)	1518 (53·6)
Secondary hospital	1401 (15·0)	479 (16·91)
Primary care: Midwife Obstetric Unit	2136 (22·8)	835 (29·5)
Other (home taxi before arrival at healthcare facility)	6 (0·1)	0 (0)
History of prior Stillbirth	242 (2·6)	0
History of prior Neonatal Death	172 (1·8)	0
History of prior low birth weight or preterm deliveries	982 (10·5)	0
Prior history of infants with a known genetic disorder or major congenital anomaly	18 (0·2)	0
Diabetes at or prior to index visit	94 (1·0)	7 (0·3)@
Hypertension at or prior to index visit	339 (3·6)	31 (1·1) @
Infant participants	9515 (100)#	2832 (100)
Birth outcome known	9505 (99·9)$	2830 (99·9)
Male sex	4852 (51·1)	1418 (50·1)
Birth weight in grams (mean SD)	2992 (±640)	3149 (±470)
Stillbirths	150 (1·6)	17 (0·6)
Stillbirths (Antepartum foetal death)	30 (0·3)	3
Stillbirths (Intrapartum foetal death)	39 (0·4)	8
Stillbirths (Timing of foetal death unknown)	81 (0·9)	6
Miscarriages	53 (0·6)	0
Live births	9302 (97·9)	2813 (99·4)

* Plus- minus values are means ± SD.
‡ Participants with known results used as denominator.
# Birth information missing for 10 infants; inadequate to determine outcome status.
$ Denominator used for all infant characteristics, includes livebirths, stillbirths and miscarriages·.
@ Women with pre-existing diabetes and chronic hypertension not excluded from trial-similar cohort, in alignment with study SAP.
17 women seroconverted to HIV-infected between index visit and delivery.
~ Denominator for obesity classes is number of obese women.

Table 2
Gestational age assessment utilizing the GAIA definition [18], with two modified GAIA Level of Certainty (LOC) suggestions: Source & trial-similar populations.

GAIA level of certainty (LOC)	Source population **n (%)** **N = 9371**	Trial similar population **n (%)** **N = 2832**	**GAIA Gestation age definition criteria**
Level of certainty 1	367 (3·9)	94 (3·3)	1. Certain LMP* or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (≤13 6/7 weeks). OR 2. 1st trimester scan (≤13 6/7 weeks)
Level of certainty 2A	1363 (14·5)	458 (16·2)	1. Certain LMP* with 2nd trimester scan (14 0/7 weeks to 27 6/7 weeks). If LMP and U/S do not correlate, default to U/S GA assessment. OR 2. Certain LMP* with 1st trimester physical examination
Level of certainty 2B	1458 (15·6)	420 (14·8)	1. Uncertain LMP with 2nd trimester scan (14 0/7 weeks to 27 6/7 weeks)
Level of certainty 3A	2501 (26·7)	980 (34·6)	1. Certain LMP with 3rd trimester scan – ≥28 0/7 weeks OR 2. Certain LMP with confirmatory 2nd trimester FH. OR 3. Certain LMP with birth weight. OR 4. Uncertain LMP with 1st trimester physical examination.
Level of certainty 3B	3150 (33·6)	844 (29·8)	1. Uncertain LMP with FH. OR 2. Uncertain LMP with newborn physical assessment. OR 3. Uncertain LMP with Birth weight.
Undetermined by GAIA*	532 (5·7)	36 (1·3)	
Modified LOC3C‡	388 (4·1)	33 (1·2)	‡ Uncertain LMP with 3rd trimester fundal height
Modified LOC 3D‡	109 (1·2)	3 (0·1)	‡ Uncertain LMP with 3rd trimester ultrasound
Unknown	35 (0·4)	0 (0)	

FH- Fundal height.
LMP- last normal menstrual period.
U/S - ultrasound.
* Did not fulfil any GAIA levels of certainty. Modifications have been suggested (LOC 3C and LOC 3D).

unclassifiable by GAIA-CD (Tables 1 and 3). More than a quarter of births were classified as preterm (26·8%), 14% (1308/9302) of newborns weighed <2500 g, and 11% (1048/9302) were small for gestational age (SGA). Almost 5% (432/9302) of newborns fulfilled criteria for congenital microcephaly (Table 3).

The incidence of hypertensive disease in pregnancy (3249/100 000) and GDM (459/100 000) in the trial-similar maternal participants was lower than in the source population due to exclusion criteria. The incidence of LBW, SGA and preterm birth were also lower in the trial-similar infant population (Table 4).

Table 3
Adverse outcomes reported in medical records and/ or determined by GAIA case definitions (CD): SOURCE population.

	Total cases n (Incidence /100 000)	% with AE	Cases fulfilling GAIA LOC1 N (%*)	Cases fulfilling GAIA LOC2 N (%*)	Cases fulfilling GAIA LOC3 N (%*)	Reported in clinical notes but did not fulfil GAIA CD N (%*)	% of total fulfilling GAIA CD	Reported in clinical notes and fulfilling GAIA CD N (%*)
N for maternal participants	9371							
Gestational Hypertension	359 (3831)	3.8	1 (0·3)	92 (25·6)	N/A	266 (74·1)	25·9	39 (10·9)
Pre-eclampsia	872 (9305)	9.3	0 (0)	447 (51·3)	N/A	425 (48·7)	51·3	115 (13·2)
Severe pre-eclampsia/ eclampsia	658 (7022)	7.0	634 (96·4)	0 (0)	N/A	24 (3·6)	96·4	104 (15·8)
Any hypertensive disorder	1353 (14438)	14·4	634 (46·9)	423 (31·3)	N/A	296 (21·9)	78·1	472 (34·9)
Maternal death	5 (53)	0.05	5 (100)	0 (0)	0 (0)	0 (0)	100·0	5 (100)
Gestational Diabetes Mellitus	124 (1323)	1.3	3 (2·4)	2 (1·6)	1 (0·8)	118 (95·2)	4·8	4 (3·2)
Preterm Premature Rupture of Membranes	675 (7203)	7.2	0 (0)	12 (1·8)	424 (62·8)	239 (35·4)	64·6	82 (12·2)
Primary post-partum hemorrhage	65 (694)	0.7	11 (16·9)	14 (21·5)	9 (13·9)	31 (47·7)	52·3	21 (32·3)
Pre-term labor	1538 (16412)	16.4	620 (40·3)	600 (39·0)	0 (0)	318 (20·7)	79·3	131 (8·5)
Placental abruption	104 (1110)	1.1	59 (56·7)	7 (6·7)	N/A	38 (36·5)	63·5	15 (14·4)
N for stillbirth and miscarriage[1]	9505	..	..	..	..	..	..	..
Stillbirth	150 (1578)	1.6	..	..	..	..	..	..
Miscarriage	53 (558)	0.6	..	..	..	..	..	..
N for neonatal outcomes[2]	9302	..	..	..	..	..	..	..
Microcephaly	432 (4644)	4.6	(0)	186 (43·1)	246 (56·9)	0 (0)	100·0	27 (6·3)
Low birth weight	1308 (14061)	14.1	1308 (100)	0 (0)	0 (0)	0 (0)	100·0	0 (0)
Small for gestational age	1048 (11266)	11.3	49 (4·7)	390 (37·2)	485 (46·3)	124 (11·8)	88·2	47 (4·5)
Preterm birth	2492 (26790)	26.8	..	..	..	..	..	..
Major congenital anomaly	29 (312)	0.3	..	29 (100)[‡]	..	..	100·0	..
Neonatal encephalopathy	83 (892)	0.9	0 (0)	2 (2·4)	22 (26·5)	59 (71·1)	28·9	12 (14·5)
Neonatal bloodstream infection	161 (1731)	1.7	2 (1·2)	62 (38·5)	32 (19·9)	65 (40·4)	59·6	19 (11·8)
Neonatal meningitis	8 (86)	0.1	0 (0)	0 (0)	0 (0)	8 (100)	0·0	0 (0)
Neonatal respiratory infection	73 (785)	0.8	0 (0)	0 (0)	35 (48·0)	38 (52·1)	48·0	5 (6·9)
Neonatal death	52 (559)	0.6	46 (88·5)	2 (3·9)	4 (7·7)	N/A	100·0	0 (0)

CD- Case definition.
%*- percentage of total cases identified by GAIA definitions AND text in maternity case records, [1] 10 births excluded for lack of information, [2] Excludes stillbirths and miscarriages, [‡] Lack of recorded training of assessor in clinical notes prohibited LOC1 confirmation.

4.5. Functionality of GAIA-CDs to describe disease incidence

Discrepancies were found between the proportions of adverse outcomes reported by the healthcare workers who had completed the maternity case records as part of routine care, compared to the proportion of adverse outcomes which fulfilled GAIA-CD criteria. These discrepancies varied extensively between outcomes (Tables 3 and 4). Only 25·9% of gestational hypertension, 4·8% of GDM, 28·9% of neonatal encephalopathy, and 48% of neonatal respiratory infections fulfilled GAIA-CDs criteria. GAIA-CDs identified 64·6% of preterm premature rupture of membranes, 63·5% of placental abruption and 59·6% of neonatal bloodstream infections. All of the maternal- and neonatal deaths, severe pre-eclampsia, eclampsia, congenital anomalies and LBW cases reported in clinical notes fulfilled GAIA-CDs criteria. Conversely only 27/432 (6·3%) of congenital microcephaly cases which fulfilled GAIA-CDs criteria were also reported in clinical notes.

5. Discussion

We present a comprehensive summary of MFN-AOs incidence from urban South Africa, and results of the most extensive field testing of GAIA-CDs from a LMIC setting to date. Burden of disease background data are vital for accurate interpretation of adverse outcomes during clinical- and implementation vaccine and drug trials; the most recent example being during the COVID-19 pandemic [19].

Maternal mortality rate (MMR) in South Africa declined to 88/100 000 live births in 2020 [20]. The lower rate of MMR observed in our study population (53/100 000) may be explained by the study population being limited to urban dwelling women with institutional deliveries.

Hypertensive disorders of pregnancy (HDP), which include gestational hypertension, pre-eclampsia and eclampsia, are a leading cause of maternal death [21–23], and near-miss events [24]. Additionally, HDP contribute significantly to foetal and neonatal adverse outcomes including stillbirths [25], as well as predisposing offspring to long term adverse cardiovascular disease [26], neurodevelopmental disorders, obesity, hypertension and diabetes [27]. About 10% of African women develop HDP [14], which exceeds global estimates (5·2%- 8·2%) [28]. Over 14% of women in our study were diagnosed with HDP, with almost half of cases (658/1353) diagnosed with severe HDP (pre-eclampsia, eclampsia). Only 56·8% (768/1353) of HDP cases in our study were reported in clinical notes, suggesting that actual rates may be underestimated clinically, especially the less severe 'gestational hypertension'.

'Hyperglycaemia first detected in pregnancy' (HFDP), which includes GDM and the more severe diabetes in pregnancy [29], can lead to

Table 4
Adverse outcomes reported in medical records and/ or determined by GAIA case definitions: Trial-similar population.

	Total cases n (Incidence /100 000)	% with AE	Cases fulfilling GAIA LOC1 N (%*)	Cases fulfilling GAIA LOC2 N (%*)	Cases fulfilling GAIA LOC3 N (%*)	Reported in clinical notes but did not fulfil GAIA CD N (%*)	% of total fulfilling GAIA CD	Reported in clinical notes and fulfilling GAIA CD
N for maternal participants	2832	..	..	..	..	..	..	..
Gestational Hypertension	46 (1624)	1.6	0 (0)	17 (37·0)	N/A	29 (63·0)	37·0	8 (17·4)
Pre-eclampsia	52 (1836)	1·8	0 (0)	10 (19·2)	N/A	42 (80·8)	19·2	1 (1·9)
Severe pre-eclampsia/ eclampsia	14 (494)	0.5	12 (85·7)	0 (0)	N/A	2 (14.3)	85·7	1 (7·1)
Any hypertensive disorder	92 (3249)	3·2	12 (13·0)	27 (29·3)	N/A	53 (57·6)	42·4	16 (17·4)
Maternal death	0 (0)	0						
Gestational Diabetes Mellitus	13 (459)	0.5	0 (0)	0 (0)	0 (0)	13 (100)	0·0	0 (0)
Preterm Premature Rupture of Membranes	168 (5932)	5.9	0 (0)	2 (1·2)	112 (66·7)	54 (32·1)	67·9	10 (6·0)
Primary post-partum hemorrhage	11 (388)	0.4	0 (0)	2 (18·2)	3 (27·3)	6 (54·6)	45·5	2 (18·2)
Pre-term labor	350 (12359)	12.4	171 (48·9)	154 (44)	0 (0)	25 (7·1)	92·9	17 (4·9)
Placental abruption	11 (388)	0.4	10 (90·9)	0 (0)	N/A	1 (9·1)	90·9	0 (0)
N for stillbirth and miscarriage[1]	2830	..	..	..	..	..	..	..
Stillbirth	17 (601)	0.6	..	..	..	..	..	..
Miscarriage	0 (0)	0	..	..	..	..	..	..
N for neonatal outcomes[2]	2813	..	..	..	..	..	..	..
Microcephaly	140 (4977)	5.0	(0)	68 (48·6)	72 (51·4)	0 (0)	100·0	0 (0)
Low birth weight	185 (6577)	6.6	185 (100)	0 (0)	0 (0)	0 (0)	100·0	0 (0)
Small for gestational age	284 (10096)	10.1	14 (4·9)	109 (38·4)	138 (48·6)	23 (8·1)	91·9	10 (3·5)
Preterm birth	531 (18877)	18.9	..	..	..	..	..	..
Congenital anomaly	7 (249)	0.2	..	7 (100)	..	..	..	..
Neonatal encephalopathy	25 (889)	0.9	0 (0)	0 (0)	7 (28)	18 (72)	28·0	3 (12)
Neonatal bloodstream infection	24 (853)	0.9	0 (0)	11 (45·8)	4 (16·7)	9 (37·5)	62·5	3 (12·5)
Neonatal meningitis	2 (71)	0.1	0 (0)	0 (0)	0 (0)	2 (100)	0·0	0 (0)
Neonatal respiratory infection	17 (604)	0.6	0 (0)	0 (0)	4 (23·5)	13 (76·5)	23·5	2 (11·8)
Neonatal death	14 (498)	0.5	13 (92·9)	0 (0)	1 (7·1)	N/A	100·0	0 (0)

%*- percentage of total cases identified by GAIA definitions AND text in maternity case records, [1] 2 births excluded for lack of information, [2] Excludes stillbirths and miscarriages.

significant perinatal morbidity and cognitive impairment in children born to women with HFDP, as well as progression to type-2 diabetes mellitus, obesity and cardiovascular disease in women [30]. The diagnosis of HFDP is challenging, especially in LMICs, as the gold-standard diagnostic Oral Glucose Tolerance test (OGTT), is expensiveand not widely available [31]. Almost 45% of pregnant South African women are obese or morbidly obese, which is significantly associated with HFDP [32]. The prevalence of HFDP in the past decade in South Africa ranges from 1·6%-25·8% [30–31], compared to 1·3% (124/9371) noted in this study. These differences may be attributed to varied sensitivity of glucometers and laboratory tests, and facilities at which patients were enrolled (primary vs. tertiary).

Postpartum haemorrhage (PPH) is a significant contributing cause to maternal morbidity and mortality, especially in LMICs [33], with a pooled prevalence in Sub-Saharan Africa of 4.4% (95%CI 3.0–6.0) and 3.6% (95%CI 2.0–5.6) in South Africa [13]. PPH prevalence in Soweto between 2014 and 2016 was 5.8% [34]. Only 0.7% of our study participants experienced a PPH.

Differences between previously reported MFN-AO rates and rates observed in this study highlight the importance of having local data available for interpretation of impact of new interventions in communities. The estimates observed for PPH and HFDP in this study are lower than previously reported, suggesting that the source population in this study, selected from both primary- and tertiary- healthcare facilities, is healthier than previous populations studied.

The stillbirth rate in our study (15·8/1000 births) is similar to rate reported in South Africa for 2015–2017 (16·1/1000) [35]. Maternal medical conditions, placental and foetal infections and acute obstetric events are the main causes of stillbirth in South Africa [25].

There is a high but variable prevalence (3·4%-49·4%) of preterm birth reported in sub-Saharan Africa. Extensive use of last normal menstrual period for gestational age assessment jeopardises assessment accuracy, and may lead to underestimation of GA [36], with subsequent over-reporting of preterm birth. There is poor concordance between GA assessed by ultrasound (US-GA) and GA assessed clinically, with wide variability in accuracy of clinical estimates of GA leading to both over- and under-estimation of GA [37]. Over a quarter of all deliveries in our study were preterm, contributing to associated high rates of LBW (14·1%).

Despite there being no cases of clinically-diagnosed microcephaly, 4.6% (432/9302) of all newborns fulfilled GAIA-CD criteria for microcephaly, raising concerns that microcephaly is either under-reported, or anthropometric measurements are poorly done. Further investigations with larger population-based databases is recommended. Neonatal infection-related outcomes in this study are similar to the global burden previously reported (2202/100,000 live births) [38], despite probable under-reporting due to challenges associated with linking of mother and neonatal patients in this study.

The GAIA-CDs were developed to provide standardised definitions of MFN-AOs during pregnancy, delivery and postpartum in mothers and their newborns, to assist in harmonising safety data collection and MFN-AO reporting [39].

The GAIA-CDs were developed specifically for use in vaccine trials, however, we used them in this observational study to evaluate alignment between clinical trial results and background adverse outcome rates, and obtain important information on availability and completeness of data in medical records.

In maternal immunisation trials, understanding background rates assists in the detection of both safety signals, and the benefits of an intervention. Since most GBS-vaccine trials will not be powered to demonstrate efficacy for every potential neonatal outcome, background rates are critical to help understand whether vaccination may confer additional benefit beyond prevention of invasive GBS disease or if they are associated with risk.

Testing of GAIA-CDs for observational studies, including to describe background incidence rates of AEs, assists in (i) identifying deficiencies in documentation of adverse outcomes in medical records, and/ or data abstraction and (ii) determining the applicability of GAIA-CDs in various settings. Prior to this study, field testing and recommendations for modification of definitions had only been done for 13 of the 26 published GAIA-CDSs and one enabling term [40–43].

We estimated incidence rates of MFN-AOs in South Africa, by combining all cases identified through fulfilment of GAIA-CDs, and/or through abstraction of free text noted by the attending clinician. Some adverse outcomes, including maternal- and neonatal death, severe pre-eclampsia/ eclampsia, LBW and congenital anomalies fulfilled the GAIA-CDs, but identification of other adverse outcomes using GAIA-CDs was limited. Almost 78% of gestational hypertension cases did not fulfil GAIA definition criteria [44], as medical notes lacked confirmation of normal blood pressure in the first half of pregnancy, or antenatal care initiation occurred after 20 weeks gestation, which led to the inability to exclude or confirm pre-existing chronic hypertension, and distinguish it from gestational hypertension. Less than 5% of clinically diagnosed GDM cases fulfilled any GAIA LOC. The strict criteria in the GAIA definition for confirming absence of pre-gestational diabetes, which includes (in the absence of a previous diagnosis of DM) an elevated HbA1c or fasting blood glucose in the first trimester [45], significantly hampered clinically-confirmed cases from fulfilling GAIA-CDs, as only 20% (1864) of women attended antenatal care in the first trimester. Despite the data collection sites being either at or affiliated with tertiary academic hospitals, which offer specialist care to women with HFDP, the difficulty in diagnosing HFDP in pregnancy, and the lack of consensus between clinicians regarding diagnostic guidelines [30] probably contributed to lower-than-previously-reported prevalence of clinically-reported GDM in this cohort than in previous studies.

Many of the GAIA-CDs utilise gestational age (GA) assessment. As most (80%) women in our study only booked for antenatal care after 1st trimester, and only 55% of women had an ultrasound examination, very few women (<4%) had a GA LOC1; most (>60%) women's highest LOC for GA was level 3, which affected achievable LOC of other adverse outcomes. In a recently published retrospective study from high income settings, GA was assessable at LOC1 for 78% of maternal participants [40], which is in stark contrast to the <4% attainable in our study. About 30% of our study population fulfilled level 2 for GA. Alternative methods of GA assessment should be considered, including utilisation of trans-cerebellar diameter measurements from second trimester ultrasounds [46], blind ultrasound sweeps [47] and machine learning [48].

Only half of the clinically-diagnosed cases of PPH fulfilled GAIA-CDs criteria, mainly due to lack of documentation of volume of blood lost.

Despite deliveries taking place in healthcare facilities, only 46% of stillbirths could be classified by GAIA-CD, as timing of foetal death is not well recorded. Challenges with confirming timing of foetal death in LMICs, and recommendations for amendments to the GAIA stillbirth definition have been made previously [41].

6. Strengths and limitations

This study, which collected over 2300 variables from maternity and neonatal medical records, is uniquely placed to evaluate all of the GAIA-CDs. Challenges with retrospective medical chart review were exacerbated in this LMIC by the limited accessibility to paper-based medical records, and limited documentation of pre-existing conditions, including chronic hypertension and Type 2 diabetes mellitus. Reasons for missing files included patient referrals to other facilities, misfiling and removal of paper files from filing rooms for use by other healthcare workers. Paper-based file tracking processes impacted time taken to establish why a required medical chart was not available in filing system. Two sites (MECT and tertiary hospital in ICJ) had access to scanned paper medical charts, however, benefits of access to electronic files were offset by scanning errors including missed, mis-ordered or overlapping pages, and incorrectly named files. Lack of a standardised patient identification system and exclusion of maternal hospital identifiers in neonatal medical charts posed challenges in linking maternal participants to their admitted neonates, especially if neonatal admission occurred several days or weeks post-delivery. This could have led to under-estimation of certain neonatal outcomes.

Data were abstracted onto either paper or electronic case report forms. Limited internet connectivity at healthcare facilities affected direct electronic data abstraction, however, the offline facility in REDCap allowed data to be captured electronically and uploaded later. Established working relationships between researchers and medical facilities were vital for ensuring access to facilities and medical records. The standardised maternity case record template utilised nationally assisted in ensuring that there was minimal cross-site variability in the data collection.

7. Conclusion

This large study describes the incidence rates of adverse outcomes during pregnancy and the newborn period in urban South African settings. Data available for some adverse outcomes, (including maternal- & neonatal death, severe pre-eclampsia/ eclampsia), were able to fulfil GAIA-CDs criteria for the majority of clinically-reported cases, however, missing data required to fulfil other GAIA-CD criteria (including stillbirth, gestational diabetes mellitus and gestational hypertension) led to poor correlation between clinically-reported adverse outcomes and outcomes fulfilling GAIA-CDs. Despite challenges encountered, this study provided vital background rate data for MFN-AOs, important for interpretation of clinical trial data and highlighted the applicability of the GAIA-CDs in varied settings.

Recommendations have been made to amend the GAIA case definitions to improve their utility in LMICs (Table 5).

Author contributions

JA, VF, JS & CLC conceptualised the study; CLC is the national principal investigator and supervised study teams nationally; CLC, SB & LF are site principal investigators and provided supervision for all study aspects on site; SS led data curation and formal analysis of data; AI prepared randomisation lists and assisted with data curation and formal analysis; JLR assisted with data analysis; SS, JLR and CLC were responsible for data curation and validaiton, CV, JDJ & KEKM provided Project administration and supervision of data collection teams, BJ & SM contributed to funding acquisition and sponsor oversight of study. CLC wrote original drafts of manuscript, and all authors critically reviewed and edited manuscript. All authors approved final version of manuscript.

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Table 5
Recommendations for amendments to GAIA definitions.

	% of total fulfilling GAIA CD	Criteria that were challenging to fulfil	Challenge	Recommended change
Gestational Hypertension	25·9	Evidence of normal BP (<140 & <90) prior to 20 weeks gestation 24 h urine collection (LOC1)	Most women present after 20 weeks for 1st ANC/ booking visit 24 h urine collection not done routinely/not recorded	Add LOC3, which allows for hypertension diagnosed at ≥20 weeks gestation, no previous history of hypertension No proteinuria (any method)
Pre-eclampsia	51·3	Same as gestational hypertension but is mitigated by super-imposed pre-eclampsia that does not require evidence of normal BP prior to index visit	Most women present after 20 weeks for 1st ANC/booking visit 24 h urine collection not done routinely/not recorded	Add LOC3, which allows for hypertension diagnosed at ≥20 weeks gestation, no previous history of hypertension
Severe pre-eclampsia/ eclampsia	96·4	Not applicable, CD worked well		
Maternal death	100·0	Not applicable, CD worked well		
Gestational Diabetes Mellitus	4·8	1st trimester documented raised HbA1c or fasting blood glucose required to rule out pre-gestational DM	Many women do not have 1st trimester ANC visits, and therefore it is challenging to confirm 'absence of pre-gestational DM in 1st trimester'	Amend LOC 3 to allow for 'absence of pre-gestational DM' defined as no known history of DM prior to pregnancy, or during 1st, 2nd or 3rd trimester. In section 2.1, remove the words 'The absence of' from 'The absence of pre-gestational DM….'
Preterm Premature Rupture of Membranes	64·6	Visible arborization on microscopy not routinely performed – specific to LOC 1 & 2. Ultrasound with oligohydramnios not routinely performed – specific to LOC 1 & 2. Most diagnostic tests for documented membrane rupture are not used in routine clinical settings – specific to LOC 1	Free text mention of premature or preterm ROM is a clinical definition with low specificity may have led to over diagnosis of PPROM	
Primary post-partum hemorrhage	52·3	>1000 ml of blood loss through genital bleeding after delivery not well documented	Specific volume of blood loss is not documented – clinical judgement is used.	*Recommend improvement of recording of estimated blood volume loss in medical records
Pre-term labor	79·3	Documented uterine contractions per hour determined by a tocodynometer for LOC1 & 2 is not routinely performed. Documentation of Cervical changes and uterine contractions during late labour.	Cervical changes and uterine contractions when mom is already bearing down during an advanced phase of labour, may not be documented.	Explicit or implied documentation of advanced stage of labour (head on perineum or bearing down) should be added to LOC 3
Placental abruption	63·5	Features of labour, hypovolemic shock, uterine tenderness, retroplacental clot and placental infarcts are generally not well documented as part of the pathway to diagnosis.	The combination of requirements for LOC1 and LOC2, may exclude cases where clinical diagnosis of abruption is clear but not explicitly documented	Free text mention of abruption AND (at least 1 other clinical sign documented)
Stillbirth	46	Timing of foetal death	Intrapartum/antepartum often not recorded	See Kochhar et al 2019
Microcephaly	100·0	Not applicable, CD worked well	Potential over diagnosis with GAIA, or under-recognition clinically	
Low birth weight	100·0	Remove scale graduation & SOP from individual BW, rely on institutional guidelines		
Small for gestational age	88·2	Assumptions made about weight <24 h after birth as that standard practice though not documented. Scale resolution and calibration was not applied	Unclear how strictly clinical diagnosis (derived from free text only) from birth charts was applied	
Major congenital anomaly	100·0	Not applicable, CD worked well		
Neonatal encephalopathy	28·9	Features of encephalopathy (alertness, lethargy, depressed tone) are either not well documented as part of the pathway to diagnosis or may not have been captured well from the medical records.		Add 'clinically recorded encephalopathy' to LOC3
Neonatal bloodstream infection	59·6	2 blood cultures from 2 different sites or at 2 different times.	Neonate with 1 positive blood culture and only 1 clinical sign would be excluded. LOC3 has fewer clinical criteria than LOC2	Should allow 1 blood culture with 1 clinical sign. Include all LOC2 clinical signs in LOC3.
Neonatal meningitis	0·0	CSF pleocytosis definition was too strict and number of clinical signs in the absence of lumbar puncture or sample.	GAIA definition too strict	Reduce number of clinical criteria required for LOC3b to 2
Neonatal respiratory infection	48·0	CXR and pathogen requirements with at least 3 clinical signs for LOC1. CXR with 4 or more clinical signs for LOC2. Lack of LOC2 signs in LOC3.	Clinical signs are inconsistent between the 3 LOCs	
Neonatal death	100·0	Not applicable, CD worked well		

BJ, JS and JA) work/ worked for funder during study conduct. The funder was involved in study conceptualisation and design, results interpretation and revision of this manuscript. Funder was not directly involved in data collection or analysis. The views expressed in this publication are those of the authors and not necessarily those of the funder. All authors had access to data from this study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Clare L. Cutland reports financial support was provided by Pfizer Inc. Clare L. Cutland reports a relationship with Wits Health Consortium Pty Ltd that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.054.

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