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Capability and feasibility of the Global Alignment of Immunisation Safety Assessment in pregnancy criteria for the assessment of pregnancy and birth outcomes in Kinshasa, Democratic Republic of the Congo: a prospective cohort study

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ABSTRACT

Introduction There is an urgent need to investigate the capabilities of active surveillance in strengthening the development of pharmacovigilance (PV) systems in low-resource settings. Here, we assess the capability and feasibility of prospectively collected data to document maternal immunisation and adverse birth outcomes across delivery centres in Kinshasa, Democratic Republic of the Congo (DRC) according to the Global Alignment of Immunisation Safety Assessment in pregnancy (GAIA) definitions.

Methods We conducted a facility-based prospective cohort study that enrolled mothers via convenience sampling either during their antenatal care visit or following their delivery. Demographic and clinical information as well as postpartum details related to the index pregnancy were collected after delivery; all mothers were also contacted via telephone 30 days postdelivery to determine if certain outcomes occurred after health facility discharge. Adverse birth outcomes of interest and maternal tetanus immunisation were categorised according to the GAIA criteria, and the level and impact of loss to follow-up (LTFU) was also evaluated.

Results The study population consisted of 2675 mothers. The proportion of adverse birth outcomes ranged from 1.6% (for neonatal death) to 15.8% (for small for gestational age). Evidence of maternal tetanus immunisation during the index pregnancy was found for 637 mothers of newborns with any adverse birth outcome. GAIA diagnostic certainty was high for low birth weight and preterm birth, but much lower for stillbirth and neonatal bloodstream infections. Additionally, LTFU was high: only 47.9% of all mothers were successfully followed up via phone call.

Conclusion Our investigation highlighted some of the challenges associated with the utilisation of the GAIA criteria in (prospective) observational studies within health facilities in Kinshasa, DRC (eg, data quality, LTFU and selection bias). Nevertheless, active surveillance remains a promising tool for future PV activities in DRC and beyond.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has shown that archival birth records from delivery centres in Kinshasa, Democratic Republic of the Congo (DRC) can be feasibly used to screen for stillbirth and maternal tetanus vaccination and to accurately classify preterm birth, low birth weight, small for gestational age and congenital microcephaly according to the Global Alignment of Immunisation Safety Assessment in pregnancy (GAIA) definitions.

⇒ However, there is limited information on the feasibility of applying GAIA criteria to prospectively collected birth outcomes data for the longitudinal assessment of maternal and neonatal outcomes in DRC.

WHAT THIS STUDY ADDS

⇒ We found that screening for cases of adverse birth outcomes via active surveillance is generally feasible in Kinshasa, DRC but that gaps exist in the ability to classify outcomes such as stillbirth, neonatal death and neonatal bloodstream infections according to the GAIA criteria due to data quality limitations and difficulty tracking newborns across the full neonatal period.

⇒ Additionally, this study demonstrated the value of phone-based follow-up methods for the capture of adverse outcomes across the full neonatal period and revealed associated issues with loss to follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our investigation highlighted some of the challenges associated with the utilisation of the GAIA criteria in prospective observational studies within a low-resource setting and illustrated that active surveillance represents a promising tool for future pharmacovigilance (PV) activities in DRC.

⇒ These results thus have implications for researchers and policymakers working to strengthen PV systems and/or improve the measurement of maternal and neonatal health outcomes globally.

INTRODUCTION

Pharmacovigilance (PV) systems for the detection of adverse events associated with various drugs and vaccines are well-established in high-income countries (HICs).[1] In contrast to the continued growth of PV capabilities in HICs, robust PV systems are lacking in other parts of the world, particularly in low-income and middle-income countries (LMICs).[2–5] In the Democratic Republic of the Congo (DRC) specifically, a national PV centre was created in 2009 following a recommendation by WHO.[6] Active surveillance—the direct and targeted collection of health information in order to generate more complete estimates of adverse events[7]—may enhance the overall PV infrastructure in DRC and thus contribute to surveillance efforts around the safety of newer therapeutics and/or novel immunisation strategies, such as maternal immunisation.[8–10]

Although maternal immunisation represents an innovative tool for public health programmes, its prevalence and safety remain particularly understudied in LMICs, where a large number of vaccine-preventable diseases remain endemic.[8 11] As a result, there is an urgent need to investigate the capabilities of active surveillance methods in strengthening the development of PV systems explicitly designed for maternal immunisation monitoring in LMICs.[12] In light of these concerns regarding maternal immunisation research, the Global Alignment of Immunisation Safety Assessment in pregnancy (GAIA) project created standardised guidelines and case definitions for the identification of maternal immunisation and neonatal outcomes that allow for the robust evaluation of maternal immunisation safety both within and across countries. Due to the advent of the GAIA criteria, researchers are now better situated to synthesise findings from a variety of countries and ultimately generate an accumulation of evidence on vaccine safety, particularly in LMICs.[13]

We previously used GAIA case definitions in Kinshasa, DRC to evaluate the feasibility and utility of retrospectively extracting information from archival medical records for PV purposes both immediately prior to and during the early months of the COVID-19 pandemic.[14 15] These investigations concluded that it is generally feasible to use archival medical records to screen for and classify adverse birth outcomes such as preterm birth and low birth weight (LBW) as well as maternal tetanus immunisation. However, there were some challenges in linking maternal tetanus immunisation to birth and neonatal health outcomes using archival medical records alone.[14 15] Active safety surveillance through prospective data collection may represent a monitoring method better suited to link maternal immunisation with potential adverse birth outcomes. However, there is limited information on the feasibility of applying GAIA criteria to prospectively collected birth outcomes data for the longitudinal assessment of maternal and neonatal outcomes, especially in LMICs. As the GAIA criteria and guidelines were initially developed in the context of clinical trials,[13] it is important to assess their utility as tools for observational research and surveillance activities.

In response to this knowledge gap, we prospectively surveyed mothers and applied GAIA case definitions to maternal tetanus immunisation and adverse birth outcomes over a 6-month period across delivery facilities in Kinshasa province. Our primary aim was thus to assess the capability of such prospectively collected data to document maternal immunisation and adverse birth outcomes according to GAIA definitions; we additionally identified any challenges encountered, with a particular focus on loss to follow-up (LTFU) and data quality issues, to further elucidate the capability and feasibility of these prospective data for surveillance purposes.

METHODS

Study design and procedures

We conducted a facility-based prospective cohort study using convenience sampling, representing the last phase of a larger PV study in Kinshasa, DRC that included both retrospective and prospective arms.[14–16] In this prospective study arm, participants were actively recruited from 17 August 2020 through 31 January 2021. We recruited potential eligible participants (aged 18 years or older) at two time points:

1. While expectant mothers were visiting selected facilities for regular antenatal care (ANC) at 32 weeks or beyond in their pregnancy.
2. Following a postpartum mother's delivery once all medical necessities had been met, but while the mothers and their infant(s) remained in the health facility area for recovery and observation prior to discharge.

Regardless of recruitment timing, all women were followed through the postdelivery period until 30 days after birth. After their delivery but before their discharge, all mothers were administered an electronic questionnaire by trained study staff that captured demographic and clinical information and collected postpartum details related to the index pregnancy and birth outcome measures. Medical records were also consulted in order to collect detailed information on the variables necessary for GAIA classification (eg, neonatal body length, head circumference, last menstrual period (LMP), etc).

All mothers were also contacted once via telephone 30 days postdelivery to determine if any neonatal end points

of interest (specifically, neonatal death or neonatal bloodstream infection) took place in the first month of life after the mother and child(ren) were discharged from the delivery facility (online supplemental figure 1); in order to increase the likelihood that mothers would respond to the phone-based follow-up, study coordinators provided them with the phone number of the study team member in charge of the follow-up call. If study coordinators were not able to contact someone after their first attempt, a second attempt was made in order to increase the likelihood of successful phone follow-up.

Site selection

The overall study site selection procedures have been described elsewhere.[14–16] Briefly, we obtained a complete list of all health facilities in Kinshasa, DRC from an administrative unit of the DRC Ministry of Health called the Division Provinciale de la Santé de Kinshasa. From this list, 10 health facilities that (1) were designated as delivery centres, (2) recorded at least 1000 annual deliveries in 2018 and (3) archived their birth records on site were randomly selected: Bomoi, Bondeko, Lisanga, Siloe Bdom and Bosembo Health Centers; Esengo, Mokali, Saint Joseph and Kinshasa General Hospitals; and Ngaliema Clinic.

Outcome measures

The study's outcomes included adverse birth outcomes and maternal antenatal immunisation. The seven adverse birth outcome end points were as follows: neonatal bloodstream infection, (congenital) microcephaly, LBW, preterm birth, small for gestational age (SGA), stillbirth and neonatal death. Cases of each adverse birth outcome identified during enrolment were tabulated at initial case screening, and then refined and subcategorised according to level of diagnostic certainty using GAIA case definitions; additionally, for all identified cases of adverse outcomes, maternal antenatal immunisation was assessed and associated GAIA classifications were generated.[17–23]

Instances of stillbirth, neonatal infection and neonatal death were screened by maternal indication of these outcomes in the postdelivery screening questionnaire. Neonatal infections and neonatal death were also screened by maternal indication during follow-up phone calls. Cases of LBW were identified in the screening questionnaire by the mother when she indicated a birth weight <2500 g (as per WHO criteria). Similarly, preterm births screened positive if (1) the mother explicitly indicated that the birth was preterm, (2) the mother reported a gestational age at birth recorded as <37 weeks in the electronic questionnaire or (3) medical records indicated a preterm birth on physical examination for those women who did not know their LMP. No known country-specific paediatric growth charts exist in DRC against which to categorise infants according to head circumference or weight-by-term; thus, previously used methods to screen for SGA and microcephaly were replicated here.[14 15] To capture maternal antenatal immunisation, data collectors requested the mother's vaccination card or ANC logbook and recorded information directly from this written record where available. Separately, the questionnaire also asked each mother to assess antenatal vaccine history via recall; in situations where a mother's vaccination card and/or ANC logbook were not available, her self-reported immunisation history on the questionnaire was used to determine maternal immunisation status.

Each identified case as well as each instance of maternal immunisation was classified according to GAIA case definition criteria, which are stratified into multiple levels of diagnostic certainty: level 1 represents the highest specificity, while level 4 represents insufficient information for confirmation of the case; detailed information on how each term is defined according to the GAIA criteria is provided elsewhere.[17–23] As in our previous studies of GAIA application feasibility in DRC, we also added an additional category, level 5, to describe cases identified in the electronic questionnaire for which further information was either missing or not thorough enough to meet any diagnostic certainty standards. Additionally, a recording of any LMP date was considered as meeting the GAIA data element 'certain LMP', while missing LMP date was considered 'uncertain LMP'.[14 15]

Statistical analysis

Basic demographic/clinical information on the mothers and their newborns was tabulated; means with SDs and/or medians with ranges were calculated for continuous variables while frequencies and percentages were provided for categorical variables. Descriptive statistics were also generated for maternal tetanus immunisation (including its GAIA classification scheme) and adverse birth outcome variables identified via phone-based follow-up. Visual displays of the GAIA classification schemes were generated both for each facility and at the overall level for the adverse birth outcomes. Additionally, adverse birth outcomes of interest were assessed for both intrasite proportion and an overall proportion over the study period. Furthermore, the level of LTFU was calculated, and demographic characteristics for those LTFU were compared with those who remained in the study via Student's t-test or Pearson's χ^2 test (as appropriate). Statistical analyses were performed using R V.4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), and the statistical significance level was set at 0.05.

Informed consent and ethical approval

Prior to the enrolment period, clinical practitioners from selected study sites were contacted and visits were made to educate, sensitise and inform them about the details of the research project so that the clinicians felt comfortable assisting in informing their patients about potential participation and recruiting them for study involvement. Oral informed consent took place at the time of enrolment in either French or Lingala—a local language widely spoken throughout Kinshasa—due to the fact that many participants were illiterate. Participants were informed about the

purpose of the study, the data that would be collected and the potential risks and benefits of participation. Importantly, it was made clear to the participants that their decision surrounding participation would not affect the care they received at study site delivery centres. Lastly, a copy of the consent form was provided to each participant.

Patient and public involvement

Study participants were not involved in the design, recruitment or implementation of this study. There are no direct plans to disseminate the results to study participants. However, the results of this study were disseminated within each participating health facility. We have also shared the results during a large dissemination workshop that included stakeholders in charge of maternal healthcare within the DRC Ministry of Health, the Expanded Programme for Immunisation and participating health facilities.

RESULTS

Study population

Initially, 3169 mothers were enrolled in the study; however, among the expectant mothers who were enrolled at ANC (n=973), 494 (50.8%) were LTFU between ANC enrolment and their index delivery; the primary reason for this LTFU was that these expectant mothers did not return to a study health facility for their index delivery (and thus presumably delivered at a different health facility/at home or experienced some form of a pregnancy loss). Those LTFU provided no information on their delivery/birth outcomes and were excluded from all analyses. Thus, the final study population consisted of 2675 total women: 2196 (82.1%) mothers enrolled post partum and 479 (17.9%) mothers enrolled at ANC (figure 1).

The average age of the cohort was 29.2 years (SD 6.1), and the median number of previous pregnancies was 3 (range 0–17). Most of the women (85.9%) had vaginal deliveries, and delivery complications were noted among 15.6% of participants; delivery complications included haemorrhage, retained placenta and obstructed labour. Lastly, recruitment at the health facilities was highly

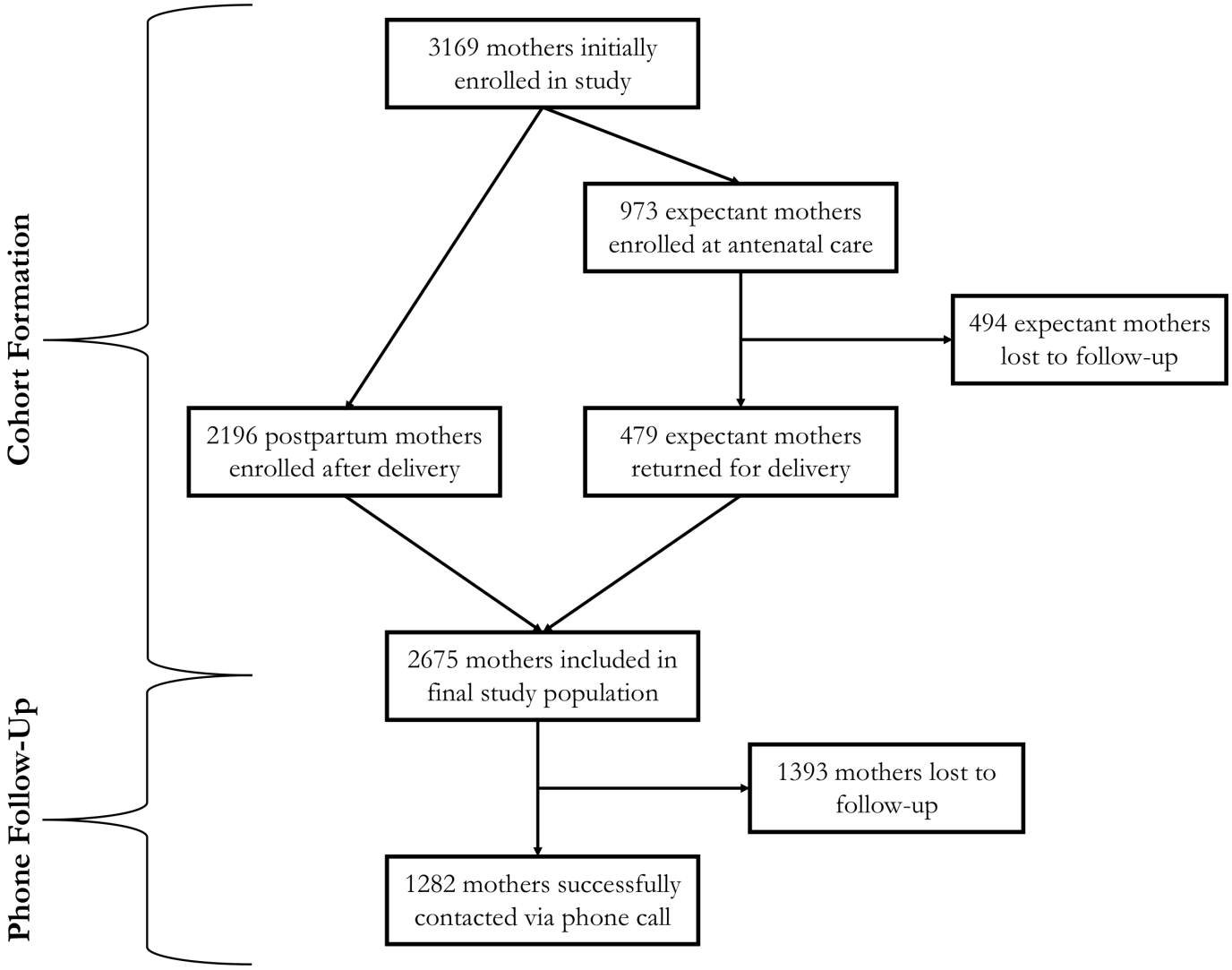

Figure 1 Study flow chart.

Table 1 Overall demographic and clinical characteristics among enrolled mothers

	N*	%*
Total mothers	2675	100.0
Enrolment type		
Post partum	2196	82.1
At antenatal care visit	479	17.9
Health facilities		
Bomoi Health Center	468	17.5
Bondeko Health Center	267	10.0
Lisanga Health Center	344	12.9
Siloe Bdom Health Center	252	9.4
Bosembo Health Center	90	3.4
Esengo General Hospital	347	13.0
Mokali General Hospital	128	4.8
Saint Joseph General Hospital	219	8.2
Kinshasa General Hospital	238	8.9
Ngaliema Clinic	322	12.0
Number of previous pregnancies		
0	3	0.1
1–2	1234	46.1
3–5	1048	39.2
6–8	238	8.9
9–17	28	1.0
Missing	124	4.6
Median (range)†	3 (0–17)	
Delivery type		
Vaginal	2298	85.9
Caesarean section	377	14.1
Delivery complications		
Missing	16	0.6
No	2241	83.8
Yes	418	15.6
Haemorrhage	58	13.9
Retained placenta	2	0.5
Obstructed labour	49	11.7
Other/Not specified	309	73.9
Mother's age (years)		
Age available	2314	86.5
Mean†	29.2	
SD†	6.1	

*Except where specified.
†Among those without missing data.

Table 2 Adverse birth outcome estimates among newborns

	N	%
Total births	2835	100.0
Adverse birth outcomes		
Stillbirth	76	2.7
Preterm birth	197	7.0
LBW	281	9.9
SGA	447	15.8
Microcephaly	404	14.3
NBSI	132	4.7
Neonatal death	45	1.6

LBW, low birth weight; NBSI, neonatal bloodstream infection; SGA, small for gestational age.

variable with some facilities (such as Bosembo Health Center and Mokali Hospital) contributing relatively few participants to the final study population (table 1); the main reasons behind this variability included discrepancies in health facility size (ie, larger health facilities tended to recruit more participants) and differences in health facility resources (ie, some health facilities were understaffed, thereby resulting in challenges in the study recruitment process).

Adverse birth outcomes

Overall, 2835 total births were observed during the study period due to the fact that 6.0% of participants gave birth to twins or triplets. About one-third (n=988, 34.9%) of recorded births met at least one case definition for an adverse event. The proportion estimates of the adverse birth outcomes ranged from 1.6% (for neonatal death) to 15.8% (for SGA) (table 2). However, there was heterogeneity in the proportion estimates by study site. For example, only 4.0% of births were identified as LBW at Bomoi Health Center, but 25.7% were classified as such at Kinshasa General Hospital; similarly, microcephaly proportion estimates were >10% at all health facilities except Lisanga Health Center and Ngaliema Clinic, which recorded proportion estimates of 1.1% and 7.2%, respectively (online supplemental table 1).

Follow-up for neonatal outcomes

About half (47.9%) of all participating mothers were successfully followed up via phone call and asked about any instances of neonatal bloodstream infection and/or neonatal death that occurred within 30 days of the index delivery (figure 1). When stratified by enrolment status, we saw that only 46.2% of mothers enrolled post partum were successfully followed up via phone call compared with 55.7% of mothers enrolled at ANC (p=0.0002). Additionally, differential follow-up was observed across the health facilities. For example, 41.3% of mothers were LTFU at Ngaliema Clinic compared with 81.1% at Bosembo Health Center. Furthermore, the average age of the mothers successfully contacted via phone was slightly higher than the mothers who were LTFU (ie, 29.7 vs 28.7 years of age, p<0.0001) (online supplemental table 2). Lastly, due to our inability to contact these mothers, it

should be noted that we were not able to determine the ultimate reason(s) behind their phone-based LTFU.

Neonatal outcome identification via phone-based follow-up drastically increased the number of neonatal bloodstream infections and neonatal deaths observed in this study. For instance, 50 neonatal bloodstream infections and 15 neonatal deaths were identified from the postdelivery screening questionnaires; however, an additional 82 neonatal bloodstream infections and 30 neonatal deaths were identified via phone-based follow-up. Thus, more than three-quarters (82.2%) of all identified neonatal bloodstream infections and neonatal deaths were identified through the phone-based follow-up mechanism (data not shown).

GAIA classification schemes

Diagnostic certainty of adverse birth outcomes varied greatly within the final study population. Specifically, all cases of screened LBW met some level of GAIA standard, with about half categorised at level 1 (50.9%), and the remaining cases falling into levels 3 (18.5%) or 4 (30.6%). Virtually all birth screening positive for preterm birth (98.5%) were classifiable according to GAIA standards; among these classifiable cases, 32.5% met level 3B criteria, 39.2% met level 3A criteria and 28.4% met level 2A criteria. Almost half of all stillbirth cases identified in the postdelivery screening questionnaire were not classifiable by GAIA standards (44.7%); lack of any information on fetal signs of life (eg, Apgar scores, ultrasound information and auscultation measurements) was the primary reason that these stillbirth cases did not reach any level of GAIA diagnostic certainty. Of the remaining stillbirth cases that were classifiable, the majority (83.3%) were classified at level 4 while 2.4% were classified at level 3, 4.8% were classified at level 2 and 9.5% were classified at level 1. Of screened SGA cases, a majority were categorised at level 3A (54.6%) with remaining cases falling into level 4 (40.3%), level 2A (3.6%) or level 1 (1.6%). About half (56.4%) of microcephaly cases were classifiable at level 3A, with almost all remaining cases at level 4 (42.8%); only three screened microcephaly cases (0.7%) reached the level 1 classification of highest diagnostic certainty (figure 2).

Most cases identified as neonatal bloodstream infections through the screening questionnaire were categorised at level 5 (84.0%); however, 8.0% were categorised at level 1 with another 8.0% categorised at level 3.

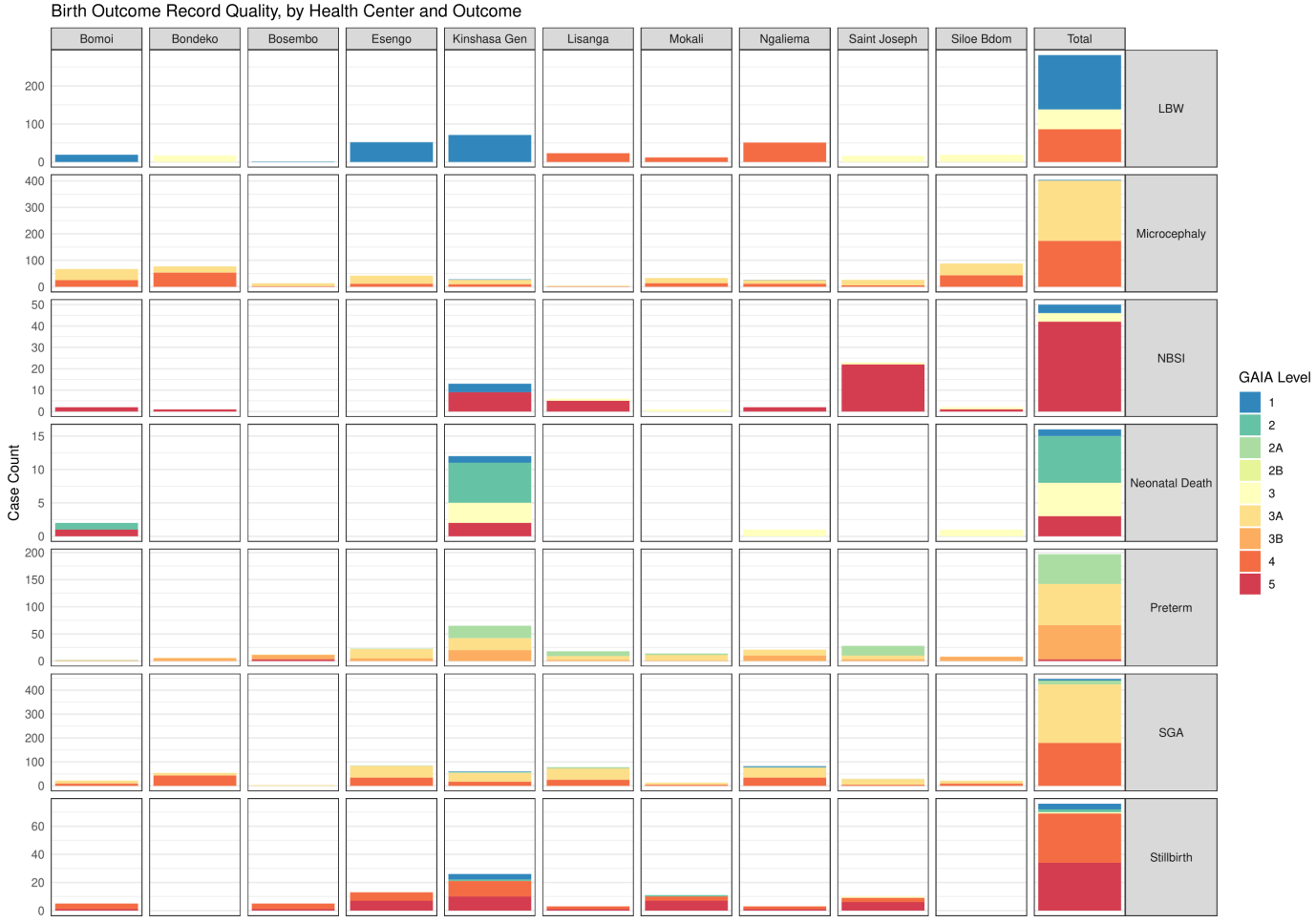

Figure 2 Adverse birth outcomes by study site and overall at initial screening, according to GAIA classification of diagnostic certainty. GAIA, Global Alignment of Immunisation safety Assessment in pregnancy; LBW, low birth weight; NBSI, neonatal bloodstream infection; Preterm, preterm birth; SGA, small for gestational age.

Although few cases were identified as neonatal deaths through the screening questionnaire, a variety of GAIA classifications were observed: 6.7% at level 1, 46.7% at level 2, 33.3% at level 3 and 13.3% at level 5 (figure 2). A majority of neonatal bloodstream infections and neonatal deaths were identified after health facility discharge (ie, via phone-based follow-up), but it was not feasible to gather sufficient information to classify these outcomes according to GAIA diagnostic certainty levels. Thus, GAIA criteria were not applied to the neonatal bloodstream infections and neonatal deaths identified after health facility discharge.

Maternal tetanus immunisation

Evidence of maternal tetanus immunisation during the index pregnancy was found for 637 mothers of cases. However, only two instances of maternal immunisation were classified at GAIA level 1, both of which occurred at Mokali Hospital. Lack of any information on tetanus vaccine name, manufacturer and/or lot number prevented the majority of maternal immunisation instances from reaching the highest level of GAIA classification. Additionally, 38.0% were classified at level 2 and 61.7% were classified at level 3 of diagnostic certainty. However, the breakdown of level 2 and level 3 classifications varied widely across health facilities. For example, virtually all maternal immunisations at Bomoi Health Center were classified as level 2, yet nearly all maternal immunisations at Siloe Bdom Health Center were classified as level 3. The primary reason level 3 maternal tetanus immunisations did not reach level 2 was that they did not have an exact date associated with vaccine administration. Furthermore, no maternal tetanus immunisations during the index pregnancy were identified at Esengo General Hospital; therefore, corresponding GAIA classifications were not able to be applied (table 3).

DISCUSSION

This study enrolled 2675 mothers and their 2835 newborns over a 6-month period throughout Kinshasa, DRC in order to assess the capability and feasibility of prospectively collected data for the monitoring of adverse birth outcomes and maternal immunisation and to also describe challenges that we encountered. Like our previous investigations using archival medical records alone,[14 15] we found that screening for cases of adverse birth outcomes via active surveillance is generally feasible in this low-resource setting but that gaps exist in the ability to classify outcomes such as stillbirth, neonatal death and neonatal bloodstream infections with a high degree of diagnostic certainty. We also observed high levels of LTFU (ie, approximately 50%), both from enrolment to index delivery among mothers enrolled at ANC and from index delivery to phone-based follow-up among the entire study population. Nonetheless, this study demonstrated the value of phone-based follow-up methods for proper capture of neonatal deaths and neonatal bloodstream infections across the entire neonatal period (ie, 28 days), thereby helping to mitigate the effects of reporting bias.

Compared with our previous retrospective investigations of delivery outcomes using archival medical records alone,[14 15] we saw somewhat disparate results in terms of the proportion of the adverse birth outcomes and rates of maternal immunisation as well as the breakdown of the GAIA classification schemes. For instance, in this investigation compared with the previous two retrospective studies, the overall proportion of stillbirth (2.7% vs 3.5%–3.5%, respectively), preterm birth (7.0% vs 8.6%–11.5%,

Table 3 Maternal tetanus immunisation among case mothers during index pregnancy classified by GAIA criteria, by study site and overall

	GAIA definition met							
	Level 1		Level 2		Level 3		Total	
Health facility	N	%	N	%	N	%	N	%
Bomoi Health Center	0	0.0	75	96.2	3	3.8	78	100.0
Bondeko Health Center	0	0.0	0	0.0	89	100.0	89	100.0
Lisanga Health Center	0	0.0	62	72.1	24	27.9	86	100.0
Siloe Bdom Health Center	0	0.0	1	1.5	64	98.5	65	100.0
Bosembo Health Center	0	0.0	2	11.1	16	88.9	18	100.0
Esengo General Hospital	0	–	0	–	0	–	0	–
Mokali General Hospital	2	4.8	28	66.7	12	28.6	42	100.0
Saint Joseph General Hospital	0	0.0	8	14.3	48	85.7	56	100.0
Kinshasa General Hospital	0	0.0	5	4.6	103	95.4	108	100.0
Ngaliema Clinic	0	0.0	61	64.2	34	35.8	95	100.0
Total	2	0.3	242	38.0	393	61.7	637	100.0

GAIA, Global Alignment of Immunisation Safety Assessment in pregnancy.

respectively), LBW (9.9% vs 12.4%–12.9%, respectively) and SGA (15.8% vs 17.8%–18.5%, respectively) were all slightly lower. Conversely, the overall proportion of microcephaly (14.7% vs 10.1%–10.7%, respectively) was higher in this study compared with the previous two retrospective analyses. The overall proportion of neonatal bloodstream infections (4.7% vs 1.3%–1.4%, respectively) was also higher in this study, as expected given that the prior retrospective analyses were not able to incorporate active follow-up methods to span the entire neonatal period and thus often only captured a few days of postdelivery information on newborn outcomes. Neonatal death could not be studied in the retrospective cohorts for reasons described elsewhere.[14 15]

Discrepancies between the prospective and retrospective evaluations,[14 15] including proportion estimates, were likely related to the convenience sampling strategy used in this prospective study; additionally, differences in data collection methods (ie, abstraction from archival medical records alone in the retrospective studies as opposed to direct questionnaires in conjunction with medical records here) and study periods (ie, July 2019 through August 2020 in the retrospective analyses as opposed to August 2020 through January 2021 here) likely also played a role. Furthermore, maternal tetanus immunisation information for the index pregnancy was only able to be recovered for about a quarter to a third of case mothers in the retrospective cohort studies,[14 15] while we were able to recover such information for a much larger fraction of case mothers in this current assessment. The ability to directly ask women for their vaccination card or about their maternal immunisation history was likely a key contributor to the higher maternal immunisation rate documented in this study and demonstrates that records-based assessments of prenatal immunisation are almost certainly underestimating true rates of vaccine uptake in this population.

With regard to GAIA classification schemes, the level of diagnostic certainty was higher for every outcome except microcephaly in this study compared with the previous two retrospective investigations that used archival medical records alone. However, the level of diagnostic certainty for microcephaly appeared approximately the same across all three evaluations. The ability of the prospective data collection to actively inquire about additional data elements, such as LMP and ultrasound measurements, that may be neglected during routine clinical care likely contributed to the generally higher levels of diagnostic certainty in this study. While active surveillance led to more successful recovery of maternal immunisation information, in terms of GAIA classification, there was no clear pattern of change seen for maternal immunisation between active and passive surveillance strategies, as the percentage of level 3 classifications found here (61.7%) fell between the range from the previous two retrospective analyses (52.4%–84.2%).[14 15]

Compared with other investigations in Africa that have used the GAIA framework, our results are generally consistent with respect to diagnostic certainty. For instance, a survey of Ugandan healthcare practitioners from Iganga-Mayuge district concluded that most preterm births could be diagnosed at level 3A or level 2A and that challenges existed in the classification of stillbirth at some health facilities. However, that survey found that neonatal bloodstream infection could be diagnosed at a higher level than that reported here.[24] Similarly, an examination of pregnant participants in randomised controlled trials of maternal immunisation in South Africa and The Gambia reported that '71% of the identified stillbirths (including antepartum and intrapartum) could not be classified' according to the GAIA criteria, thereby mirroring our challenges with properly classifying this outcome. The authors also reported that the GAIA criteria were useful for capturing most cases of preterm birth,[25] a finding in line with our experience here.

Indeed, the low levels of diagnostic certainty for certain outcomes observed in our evaluation are not unique to the African setting. For example, a large-scale prospective cohort that examined all births occurring in 21 sites in six LMICs (ie, Ghana, Tanzania, Zimbabwe, Iran, India and Nepal) and one HIC (ie, Spain) found that virtually all cases of LBW, preterm birth and neonatal death were classifiable per GAIA criteria, but the authors reported challenges associated with SGA, stillbirth, neonatal bloodstream infections and microcephaly. Moreover, the investigation also found that most instances of maternal immunisation were only able to be classified at level 2 or level 3.[26] Even investigations restricted to HICs alone report significant problems in the ability to accurately diagnose outcomes according to the GAIA criteria—as evidenced by a 2021 examination of study sites in the USA, the UK and Australia that described 'difficulty in retrospectively ascertaining cases from clinical records' and reported low levels of diagnostic certainty for certain outcomes (eg, microcephaly and SGA).[27]

Beyond GAIA, this investigation also revealed the value of phone-based follow-up as this method allowed us to present a less biased estimate of the proportion of both neonatal bloodstream infections and neonatal death. Nonetheless, it must be highlighted that 52.1% of mothers did not respond to our phone-based follow-up attempts, so the proportion estimates are therefore likely subject to selection bias. These estimates might be even further biased if the likelihood of participating in the follow-up surveys was influenced by neonatal health status (eg, if mothers were less likely to continue participation in the study if grieving the death of their infant). In order to improve phone follow-up for future investigations, we recommend that investigators explicitly include possession of a phone contact and willingness to receive calls as part of the study inclusion criteria (an approach that we did not pursue here).

Moreover, other follow-up methods, such as the deployment of community health workers (CHWs) or the subsidisation of participant travel costs by the study team, may

be useful in reducing overall LTFU, thereby improving outcome measurement. CHWs have been used in a variety of settings in sub-Saharan Africa to augment patient participation and engagement. For example, CHWs have been used to increase antiretroviral therapy adherence and follow-up in Rwanda,[28] to improve linkage to hypertension care in Kenya[29] and to enhance maternal caretaking in rural South Africa.[30] In DRC specifically, CHWs have been used throughout the country in a range of contexts, such as non-communicable disease control,[31] maternal health services[32] and Ebola outbreaks.[33] Additionally, CHWs may be able to better facilitate data collection quality in the postdelivery period, thereby potentially resulting in improved GAIA diagnostic certainty for variables such as neonatal bloodstream infections and neonatal death.

Our study succeeded in piloting an active safety surveillance strategy for the detection of adverse birth outcomes and maternal immunisation using the GAIA case criteria among a large population in Kinshasa, DRC. However, this investigation should be interpreted in light of its limitations. As previously discussed, selection bias due to LTFU (both from enrolment to index delivery among mothers enrolled at ANC and from index delivery to phone-based follow-up among the full cohort) likely impacted our proportion estimates. Additionally, our study used a convenience sampling design, thereby limiting the generalisability of the results. Indeed, our study sample contained a relatively high percentage of twins/triplets, potentially providing some evidence of selection bias; on that note, it should be highlighted that this increased twin/triplet representation likely led to slightly elevated proportion estimates for the adverse birth outcomes (as twins/triplets are at an increased risk for such outcomes). Somewhat similarly, our study team was only present at the health facilities during certain hours and on certain days; therefore, we were not able to enrol all women who attended ANC or delivered outside these hours (eg, late at night or on the weekends), thereby further limiting the generalisability of the results.

Moreover, regarding the nature of the data collection, several variables were collected via self-report and thus may suffer from measurement error. Furthermore, the phone-based follow-up calls simply asked whether a neonatal death or neonatal bloodstream infection occurred (without providing any information regarding the clinical definition of these outcomes to the mothers); consequently, this approach may have resulted in added measurement error. Likewise, none of the phone-based follow-up calls asked for extra information needed to classify the outcomes identified through this mechanism per GAIA criteria; thus, we were not able to adequately assess the diagnostic capabilities of this phone-based follow-up method.

CONCLUSION

This prospective cohort study demonstrated the suitability of the GAIA criteria to classify a wide array of adverse birth outcomes (ie, LBW, preterm birth and SGA) as part of active surveillance for maternal immunisation in Kinshasa, DRC. However, limitations remain in terms of required data elements for adequate GAIA classification of stillbirth, neonatal death and neonatal bloodstream infections. Additionally, we revealed problems related to LTFU and provided recommendations (eg, the utilisation of CHWs) aimed at improving follow-up levels for future active surveillance studies within LMICs. Ultimately, our investigation highlighted some of the challenges associated with the utilisation of the GAIA criteria in (prospective) observational studies within a low-resource setting (eg, data quality and selection bias) and illustrated that active surveillance represents a promising tool for future PV activities in DRC and beyond.

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Contributors PJA, CD, AG, DMN, NH, DKab and AWR contributed to the study design. PJA, CD, AG, DMN, NH and ALB contributed to data analyses. CD, DMN, NH, DKam, MB and DKab oversaw the data collection procedures and quality controls. PJA, CD, AG, DMN and NH drafted the manuscript with input from DKam, MB, ALB, H-LW, SA, DKab and AWR. DKab and AWR are the guarantors of the study. All authors read and approved the final manuscript.

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Competing interests PJA was a part-time contractor for Pfizer during the conduct of the study. H-LW and SA are employees of the US Food and Drug Administration, which funded this study. CD, AG, DMN, NH, ALB, DKam, MB, DKab and AWR have no competing interests to declare.

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