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REVIEW ARTICLE

Obstetrics

Standardizing case definitions for monitoring the safety of maternal vaccines globally: GAIA definitions, a review of progress to date

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Abstract

In 2014, the Global Alignment on Immunization safety Assessment in pregnancy consortium (GAIA) was formed, with the goal of developing a harmonized, globally-concerted approach to actively monitor the safety of vaccines in pregnancy. A total of 26 standardized definitions for the classification of adverse events have been developed. The aim of this review was to identify and describe studies undertaken to assess the performance of these definitions. A literature search was undertaken to identify published studies assessing the performance of the definitions, and reference lists were snowballed. Data were abstracted by two investigators and a narrative review of the results is presented. Four studies that have evaluated 13 GAIA case definitions (50%) were identified. Five case definitions have been assessed in high-income settings only. Recommendations have been made by the investigators to improve the performance of the definitions. These include ensuring consistency across definitions, removal of the potential for ambiguity or variations in interpretation and ensuring that higher-level criteria are acceptable at lower levels of confidence. Future research should prioritize the key case definitions that have not been assessed in low- and middle-income settings, as well as the 13 that have not undergone any validation.

KEYWORDS
adverse events, maternal vaccination, neonatal infections, pharmacovigilance, pregnancy, vaccine safety

1 | INTRODUCTION

Despite significant gains in reducing under-5 mortality under the Millennium Development Goals (MDGs), neonatal mortality remains unacceptably high, now accounting for 47% of all under-5 deaths globally.[1] Implementing interventions to reduce this burden has therefore become an important part of the Sustainable Development Goal targets for 2030.[2] Maternal vaccination is an important intervention that has the potential to improve both maternal and infant health. It has been highlighted by the WHO in its life-course approach to immunization and is an area where the full benefits have yet to be realized.[3] The maternal-neonatal tetanus program has demonstrated the potential of this approach. First implemented in 1989, by 2020, all but 12 targeted countries had reached elimination status. This has contributed to a resurgent interest in maternal vaccination as a means of protecting infants through their vulnerable first months. Promising new maternal vaccines for group B *Streptococcus*[4] and respiratory syncytial virus[5] are under development,[6] alongside those that may be of particular benefit for pregnant women such as SARS-CoV-2, ebola virus, lassa fever and hepatitis E.[7,8] Implementation of these vaccines requires robust safety monitoring, including in low- and middle-income countries (LMICs). Safety data generated to monitor maternal vaccine safety must be accurate and comparable globally, necessitating consistency in the terms and case definitions (CDs) used to quantify adverse events following immunization (AEFI).

The Brighton Collaboration founded in the year 2000 has developed standardized CDs and guidelines for vaccine adverse event data collection, analysis, and presentation via participation of more than 500 experts from 57 countries from public health, clinical care, academia, regulatory organizations and industry.[9] For each health outcome that could be an AEFI, a document is developed, including a background preamble to highlight the current knowledge on the outcome, the rationale and essential decisions made to develop and utilize the CD. The CD itself is structured in a format with three levels of diagnostic certainty, considering current scientific evidence and resources available in different research and geographic settings. Guidelines for data collection, analysis, and presentation of a given AEFI are provided, along with references for selected points discussed in the preamble (https://brightoncollaboration.us/about-old/the-brighton-method/).

In 2014, the Global Alignment on Immunization safety Assessment in pregnancy (GAIA) consortium was formed, with the goal of developing a harmonized, globally-concerted approach to actively monitor the safety of vaccines and immunization programs in pregnancy. This consortium, part of the Brighton Collaboration, has developed 26 standardized definitions for the classification of adverse obstetric and infant events. These CDs were developed with the aim of achieving sufficient applicability for monitoring immunization safety in pregnancy globally.[10]

The selection of these outcomes was prioritized based on recommendations from global experts convened by the WHO in 2014.[10] The definitions categorize the outcomes into levels of diagnostic certainty (LOC) 1–3, with greatest specificity at the highest level (level 1) and increasing sensitivity through the lower levels, while still maintaining an acceptable specificity. The CDs have been developed in this way to accommodate the resources and diagnostic capabilities available in different locations (Table S1).

The definitions were designed primarily for use in maternal vaccine trials whereby information could be prospectively collected to classify and report important maternal, fetal, and infant outcomes. The definitions also incorporated clinical assessment methods commonly used in LMICs to optimize the ability to classify cases from these settings.[9] Given that health systems in many LMICs are overburdened and access to diagnostic tools is limited, the extent to which routine care and documentation will need to be strengthened to diagnose these outcomes with certainty in these settings is not clear.

Given that pregnant women are routinely excluded from clinical vaccine trials (unless a vaccine is specifically designed for use in pregnancy), there is a marked reliance on post-implementation safety studies. An understanding, therefore, of whether the definitions can be applied in retrospective datasets is an important consideration. Since their publication, a significant amount of work has been undertaken to assess the utility of the GAIA definitions, particularly their ability to classify outcomes in resource-limited settings. This review brings together this research, highlighting the progress that has been made in field-testing these definitions in clinical trial and observational research contexts, prospective and retrospective datasets and identifies areas that require further research.

2 | METHODS

A literature search was conducted in Ovid Medline using a combination of MeSH terms and keywords on the topics of immunization, safety, maternal or pregnancy and CDs (Table S2). The results were reviewed by a single reviewer (HGD) and assessed for inclusion. Studies that assessed performance of GAIA definitions using real-world data (routine or research) were included in the review and studies were included regardless of whether they used retrospective or prospectively collected data. Studies that applied the definitions, for example, in vaccine trials or safety studies, but did not assess performance or utility were not included. Reference lists of all relevant studies were also scrutinized. Studies that met these criteria were reviewed and data abstracted into an Excel workbook; they were checked by a second reviewer (CB) to ensure they were correctly abstracted. If data were not available with sufficient detail in the published manuscripts, then the authors were contacted to request further information.

Abstracted data were used to create a series of tables and figures. The study setting, number of sites, country income status, and data types used were identified. The number of CDs assessed as well as the number of individual cases included were abstracted. The numbers and proportions falling into the LOC (1–3) as well as reported cases with insufficient data to classify (level 4), those determined

not to be a case (level 5), and those with insufficient documentation to distinguish between levels 4 and 5 (unclassifiable cases) across all studies were presented (classification in Table S3). A narrative summary of challenges identified with the CDs was compiled as well as recommendations made by the authors for modifications to the CDs. Differences in the interpretation or application of the definitions in the individual studies or sites were also described.

3 | RESULTS

Members of the GAIA working group have developed 26 pregnancy and neonatal outcomes to monitor safety of maternal vaccines. Ten were published in 2016, 12 in 2017, and a further 4 in 2019 (Table 1).

A total of 110 results were returned from the database search (Table S2). Three studies were identified from this source and a fourth from reference list review. Four published studies have assessed the performance of the CDs using clinical data, assessing a total of 10061 outcomes (Table 2). The first, a retrospective feasibility assessment conducted by the WHO and published in 2018,[36] led to a prospective multi-country collaboration project that assessed seven CDs, published in 2021.[37] A study from South Africa and The Gambia assessed three CDs and one enabling term – gestational age (GA) in retrospective data from two randomized controlled trials.[38] The most recently published study focused on applicability of 10 definitions in retrospective data from high-income settings.[39]

Two studies assessed the definitions using routine clinical data, one using research data and one using a mix of both. A combination of data from both high-income (four countries) and LMIC settings (eight countries) have been used to test the definitions, with a total of 12 countries contributing data. Three studies assessed medical records retrospectively and one study recruited participants prospectively. The majority of participants were recruited prospectively

TABLE 1 Published Global Alignment on Immunization safety Assessment in pregnancy consortium (GAIA) case definitions, date of publication, target of the definition, inclusion in published studies, and number of cases assessed.

GAIA outcome	Focus	Publication date	Included in a published study?	Cases assessed (*N*)[a]
Stillbirth[11]	Neonate	2016	Yes	1194
Neonatal death[12]	Neonate	2016	Yes	813
Maternal death[13]	Pregnancy	2016	No	–
Congenital anomalies[14]	Neonate	2016	No	–
Congenital microcephaly[15]	Neonate	2017	Yes	228
Fetal growth restriction[16]	Pregnancy	2017	Yes	132
Non-reassuring fetal status[17]	Pregnancy	2016	Yes	113
Antenatal bleeding[18]	Pregnancy	2017	No	–
Dysfunctional labor[19]	Pregnancy	2017	Yes	126
Gestational diabetes[20]	Pregnancy	2017	No	–
Hypertensive disorders in pregnancy[21]	Pregnancy	2016	Yes	181
Pathways to preterm birth[22]	Pregnancy	2016	Yes	126
Spontaneous abortion[23]	Pregnancy	2017	No	–
Ectopic pregnancy[23]	Pregnancy	2017	No	–
Postpartum hemorrhage[24]	Pregnancy	2016	No	–
Neonatal encephalopathy[25]	Neonate	2017	No	–
Failure to thrive[26]	Infant	2017	No	–
Low birth weight[27]	Neonate	2017	Yes	2173
Preterm birth[28]	Neonate	2016	Yes	2192
Respiratory distress[29]	Neonate	2017	Yes	126
Small for gestational age[30]	Neonate	2017	Yes	1592
Neonatal infections[31]	Neonate	2016	Yes	1065
Chorioamnionitis[32]	Pregnancy	2019	No	–
Neonatal seizures[33]	Neonate	2019	No	–
Neurodevelopmental delay[34]	Infant	2019	No	–
Postpartum endometritis[35]	Pregnancy	2019	No	–

[a]Some case definitions have not been assessed in any studies.

TABLE 2 Published research studies that have assessed field performance of the Global Alignment on Immunization safety Assessment in pregnancy consortium (GAIA) outcomes since publication.

Reference	Number of CDs tested	Study setting (income)	Countries (*N*)	Study setting (countries)	Sites (*N*)	Data	Case identification	Classification method	Case definitions assessed
Stuurman et al.[36]	4	Low-, middle- and high-income	8	Ghana, South Africa, Tanzania, Zimbabwe, Spain, India, Iran	24	Routine data	Retrospective	Algorithm	Preterm birth, neonatal death, neonatal invasive bloodstream infections
Kochhar et al.[38]	4	Low- and middle-income	2	South Africa, Gambia	2	Research data (RCT)	Retrospective	Manual review of case records	Preterm birth, stillbirth, hypertension, GA assessment (enabling term)
Stuurman et al. (2021)[37]	7	Low-, middle- and high-income	7	Ghana, Tanzania, Zimbabwe, Iran, India, Nepal, Spain	21	Routine data	Prospective	Algorithm	Low birth weight, preterm birth, small for gestational age stillbirth, neonatal death, neonatal infections (bloodstream, respiratory, meningitis), congenital microcephaly
Watson et al.[39]	10	High-income	3	USA, UK, Australia	7	Research and routine data	Retrospective	Manual review and case logic	Preterm birth, low birth weight, small for gestational age, respiratory distress, congenital microcephaly, preterm labor, fetal growth restriction, pre-eclampsia, non-reassuring fetal status, dysfunctional labor

Abbreviations: CD, case definition; GA, general anesthetic; RCT, randomized controlled trial.

(95%) and information on outcomes was collected from their routine clinical data sources (Table 2).

A total of 13 of the definitions have undergone field-validation after being selected for their relevance, one enabling term (GA assessment) has also been assessed. Five out of 13 (38.5%) pregnancy or obstetric outcomes and eight out of 13 (61.5%) neonatal/infant outcomes have been assessed in published research studies (Table 1).

The number of individual cases assessed varied according to the definition. Preterm birth (2192 cases), low birth weight (2173 cases), and stillbirth (1194 cases) have been most frequently assessed, while non-reassuring fetal status and dysfunctional labor have been assessed in only 113 and 126 subjects, respectively. Overall neonatal infections have been assessed in 1065 cases; the majority of these have been bloodstream infections (BSIs) with only 64 cases used to assess the neonatal meningitis sub-definition and 155 cases of respiratory infections.

Investigators from the two WHO-led projects developed algorithms for classifying the cases entered into the electronic case report forms.[36,37] The retrospective randomized controlled trial (RCT)-based study utilized medical personnel from the sites to manually review the medical notes and assign a LOC.[38] Finally, the study from high-income settings used a combination of a Brighton Collaboration-developed automated tool (ABC Case-logic) and review by medical abstractors to assign LOCs.[39]

3.1 | Performance

Performance of the definitions is summarized in Table 3, Figure 1, and Table S4. These demonstrate that large numbers of cases identified retrospectively and which utilized routine care data were unclassifiable. The neonatal CDs for neonatal death, preterm birth, bloodstream infections, and low birth weight were assessed in more than one study and generally performed well, regardless of whether the cases classified were retrospectively or prospectively selected.

Watson et al.[39] assessed positive predictive value (PPV) of the CDs compared with ICD-10 codes. Microcephaly, pathways to preterm labour, non-reassuring fetal status and dysfunctional labor performed poorly with PPVs of below 50%, but this was mainly driven by the quality of documentation and quantity of missing data available in the medical records.[39] Low birth weight, preterm birth, small for gestational age (SGA), respiratory distress, fetal growth restriction (FGR), and pre-eclampsia performed better with PPV greater than 70%.

3.2 | Interpretation, challenges, modifications

The authors of several publications described the specific challenges they faced in using the CDs in their respective settings and, in some cases, proposed modifications to the CDs. Stuurman et al.[37] proposed a modification to allow more flexibility in assigning LOCs. Criteria that were acceptable at higher levels of diagnostic certainty were also de facto acceptable at lower levels of diagnostic certainty in their analyses. For example, for the low birth weight (LBW) outcome (Figure 2; Table S5), if a baby met all but one of the requirements for LOC3 (they were weighed within

TABLE 3 Summary of the main findings regarding performance of the case definitions.

Pregnancy outcomes	
Hypertensive disorders	Field-tested two studies: 181 cases LOC1, 68.5%; LOC2, 13.3%; unclassifiable, 18.2% of cases (all retrospective data)
Fetal growth restriction	Field-tested one study: 132 cases (all high-income) LOC1, 64.4%; unclassifiable, 25% (retrospective data)
Non-reassuring fetal status	Field tested one study: 113 cases (all high-income) LOC3, 15%; unclassifiable, 69.9% (retrospective data)
Pathways to preterm labor	Field tested one study: 126 (all high-income) LOC1, 44.4%; unclassifiable, 51.6% (retrospective data)
Dysfunctional labor	Field tested one study: 126 (all high-income) LOC1, 33.3%; unclassifiable 41.3% (retrospective data)
Infant outcomes	
Stillbirth	Field tested three studies: 1194 cases LOC1, inter-study variability 10.8%–25.5%; LOC3, 30.4%; LOC4, 41.9%.
Preterm birth	Field tested four studies: 2192 cases LOC1, 25.2%; LOC3, 51.5%
Neonatal deaths	Field tested two studies: 813 cases LOC1, 93.5%; LOC2, 6.2%
Congenital microcephaly	Field tested two studies: 228 cases LOC2, 24.6%; LOC4, 26.8%; unclassifiable, 25.9%, (retrospective data)
Low birth weight	Field tested two studies: 2173 cases LOC2, 42%; LOC3, 41.3%
Respiratory distress	Field-tested one study: 126 cases (all high-income) LOC1, 59.5%
Small for gestational age	Field tested two studies: 1592 cases LOC1 inter-study variability 4.2%–43.2%; LOC3, 23.6%; LOC4, 45.2%; (6/21 [28.6%]) sites from one study unable to classify any cases
Neonatal infections – BSI	Field tested two studies: 846 cases LOC1 15.9%; LOC2 51.3%
Neonatal infections – respiratory	Field tested one study: 155 cases LOC3, 51.6%
Neonatal infections – meningitis	Field tested one study: 64 cases LOC3, 14.1%; LOC4, 76.6%

Abbreviations: BSI, bloodstream infection; LOC, level of diagnostic certainty.

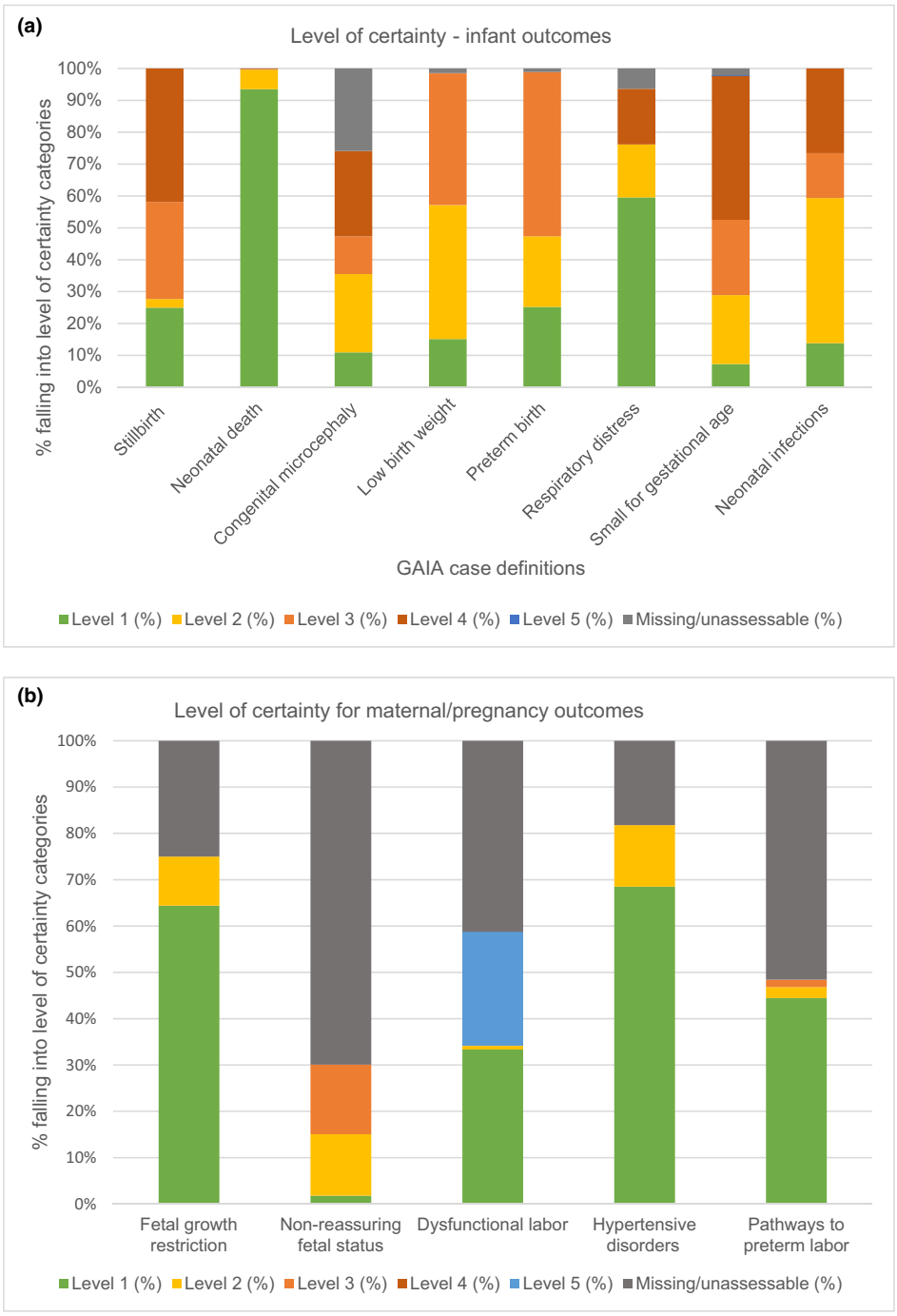

FIGURE 1 (a) Stacked bar graphs illustrating the level of diagnostic certainty (LOC) for each of the neonatal/infant outcomes assessed: LOC1–3, classifiable cases; LOC4, reported case with insufficient evidence to classify; LOC5, not a case. (b) Stacked bar graphs illustrating the LOC for each of the maternal/obstetric outcomes assessed.

48 h of birth and the documented weight was <2500 g), but the scale used was of higher precision than required at LOC3 (weight was measured using a scale with <50 g resolution, tared to zero and calibrated which is required at LOC2, rather than the less precise dial/spring/color-coded scale required for LOC3) then they accepted this higher-level (LOC2) criteria at the lower level (LOC3) to prevent the case falling between LOC2 and LOC3. So, in this case, electronic, calibrated scales required at LOC1 and 2 were also permissible when assigning LOC3 if all other essential parts of the LOC3 definition were met.[37]

This level of flexibility, although also recommended as a modification to the stillbirth definition by the investigators in the earlier Stuurman et al.[36] was not applied whilst categorizing the cases as part of this study, leading to several cases falling between two LOCs, and therefore assigned LOC4 (Table S6). Kochhar et al.[38] found that all the antepartum and intrapartum stillbirths

Level 2		Level 3	
Newborn infant weighed within 24 h of birth	✓	Newborn infant weighed within 48 h of birth	
AND		AND	
Weight using scale (electronic/spring) graduated to at least 50 g	✓	Weight measured using dial/spring/color -coded scale	
AND		AND	
Scale calibrated once per year or more often if moved.	✓	Weight recorded as <2500 g	
AND			
Scale tared to 0 g	✓		
AND			
Weight recorded as <2500 g	✓		

Meets all criteria for LOC2 – **assigned LOC2**

Level 2		Level 3	
Newborn infant weighed within 24 h of birth		Newborn infant weighed within 48 h of birth	✓
AND		AND	
Weight using scale (electronic/spring) graduated to at least 50 g		Weight measured using dial/spring/color -coded scale	✓
AND		AND	
Scale calibrated once per year or more often if moved		Weight recorded as <2500 g	✓
AND			
Scale tared to 0 g			
AND			
Weight recorded as <2500 g			

Meets all criteria for LOC3 – **assigned LOC3**

Level 2		Level 3	
Newborn infant weighed within 24 h of birth		Newborn infant weighed within 48 h of birth	✓
AND		AND	
Weight using scale (electronic/spring) graduated to at least 50 g	✓	Weight measured using dial/spring/color -coded scale	
AND		AND	
Scale calibrated once per year or more often if moved.		Weight recorded as <2500 g	✓
AND			
Scale tared to zero grams			
AND			
Weight recorded as <2500 g			

Meets some criteria for LOC3 and some for LOC2 – **variably categorized as LOC4 or LOC3 in published studies. Suggestion from three studies that these cases are categorized at LOC3**

FIGURE 2 Figure demonstrating the way that some cases fall between levels of confidence – illustrated with LOC2 and LOC3 of the low birth weight GAIA definition.

designated as LOC4 fulfilled all but one criterion for LOC2. All cases were classified as LOC3 for GA, which is insufficient for LOC2 (it requires GA LOC1 or 2). This observation highlighted the need to allow for flexibility in the utilization of GA as one of the classifying criteria. Further, they were all born in a tertiary hospital and therefore did not fulfill the 'non-attended delivery' criteria for LOC3 (the deliveries were attended). They therefore slipped between the LOCs. They were not classified as LOC2 as the GA criteria were not met, and they were not classified as LOC3, as the delivery was attended (and therefore more detailed information documented than required for LOC3). Had they also accepted the higher-level criteria (attended delivery) de facto at the lower level, all the unclassified cases would have met LOC3. The definitions presented in this review have therefore been variably applied in the field-validation studies conducted to date, with some permitting this flexibility and others not.

The investigators also highlighted some ambiguity within the CDs. As an example, the stillbirth CD requires that the baby is born with no signs of life; it specifies no spontaneous movements, no umbilical cord pulse, no heartbeat, no cry, spontaneous respirations, or chest movement. This was stringently interpreted by Stuurman et al.[36] as requiring absence of all of these signs as documented at birth; however, verbal communication from the authors of the CD later clarified that it was acceptable for one or more signs not to be recorded. This more liberal definition was therefore used in the 2021 study by the same investigators.[37]

Watson et al.[39] highlighted challenges with the LBW and SGA CDs in their retrospective study. Information regarding the type of weighing scale used and associated calibration information was not readily available, limiting the ability to classify these cases even in high-income settings. They suggested that flexibility regarding the absence of this information could be built into the CD to enable use with retrospective datasets.[39] Another solution would be to determine the standard operating procedures at the facility level, rather than on a case-by-case basis when assessing outcomes; this is already recommended in the published CD.

Stuurman et al.[37] noted that the GA and birth weight requirements were not constant across all the neonatal CDs. The GA criteria were noted to be consistent for preterm birth, stillbirth, neonatal death, and SGA but different for congenital microcephaly; for some LOCs the criteria were more lenient and for others more stringent; for example, LOC1A allows for second-trimester ultrasound scan, which is a GA LOC2 criteria and is not acceptable at LOC1 in the other definitions. They highlighted that the birth weight requirements for the LBW and SGA outcomes were also inconsistent, noting that SGA LOC3A required more stringent scale specifications (a scale with <50 g resolution, tared to zero and calibrated) than LBW LOC3 (weight measured using dial/spring/color-coded scale).[37] A full description of these inconsistencies is provided in their manuscript.[37]

4 | DISCUSSION

Development of the 26 GAIA CDs was an important undertaking that aimed to harmonize maternal vaccine safety research permitting the generation of globally comparable safety data. A significant amount of work has gone into field assessment of 13 CDs; however, 13 out of 26 (50%) have not undergone any formal assessment in published studies, including two of the 10 first definitions (maternal death and postpartum hemorrhage), prioritized based on a consultative process that deemed them the most critical for safety monitoring in maternal vaccine research. Furthermore, five of the CDs have only been assessed in a single study (albeit with data contributed from three different countries, all high-income settings).

The neonatal CDs for neonatal death, preterm birth, BSIs and LBW were assessed in more than one study and generally performed well, regardless of whether the cases classified were retrospectively or prospectively selected. By contrast, the stillbirth definition performed poorly in all three studies that assessed it because a significant proportion of cases met some of the criteria for LOC2 and some of the criteria for LOC3. This challenge was also highlighted for the LBW, SGA and neonatal meningitis definitions.[37] As a result, all of these studies identified modifications that would enhance classification, in particular, expressly accepting criteria for higher levels of diagnostic certainty at lower levels. This simple change, which would require a statement in the CD preamble, would ensure that cases that meet at least LOC3 (with some elements of LOC2) are not classified as LOC4. In the Kochhar et al. study, this change would have increased the proportion of stillbirths classifiable at LOC1-3 from 29.1% to 100%.[38] Revisions of the definitions providing corrections or allowing for flexibility based on these findings are under way.

Five outcomes have only been assessed using data from high-income settings – respiratory distress, FGR, non-reassuring fetal status, dysfunctional labor and pathways to preterm labor. The latter four CDs were unclassifiable in large numbers of cases (25%–70%) and for some require a significant amount of detailed clinical data to support classification (Tables S7 and S8). The retrospective nature of the data used in this study was likely to have contributed to this challenge. Performance of these definitions needs to be assessed using prospectively collected data to determine whether the classification challenges are due to the CDs being too specific, or due to to missing or inadequate data in these retrospective studies. These assessments need to be made in both high-, middle- and low-income settings as it is possible that the level of clinical detail required to classify these outcomes is lacking in lower-resourced settings, even in prospectively collected datasets. A feasibility assessment conducted in Uganda sought to establish whether 25 health centers of varying levels had the physical, laboratory, and human resources necessary to fulfill the criteria for each of 10 outcomes. The results were encouraging, with most facilities, in theory, able to classify to LOC3; however, they did not assess the five outcomes listed earlier in this study.[40] Application of these definitions in clinical trials and observational studies in LMICs may require improvements in data collection and documentation to enable classification. Stuurman et al. found that data for classifying antepartum and intrapartum stillbirths were frequently missing or conflicting in their retrospective study, indicating that improved documentation was required.[36]

Watson et al.[39] emphasized that review of both clinical and research records was labor-intensive, with 1–2 h spent on each record. Kochhar et al.[38] also noted that staff training on three CDs and the GA algorithm took, on average, 3 h, whilst the case final review took between 10 and 60 min per subject.[38] Application of the CDs prospectively using a standardized protocol and specially designed case report forms would likely reduce the time required for classification, as might use of alternative data extraction protocols and algorithms or case logic to classify cases. Ensuring that requirements for gestational age assessment are consistent across LOCs for neonatal outcomes is also likely to make classification more straightforward (see LBW and SGA example earlier).

Given the common exclusion of pregnant women from clinical vaccine trials, safety data in this group relies heavily on post-marketing pharmacovigilance and retrospective datasets, such as electronic health records, and billing codes on administrative data are commonly used in these study designs. The GAIA definitions were developed primarily for prospective use in clinical trials; however, CDs that can be applied to retrospective datasets and from regular clinical data are also needed. The definitions might need to be adapted for use in this context. Conducting these retrospective studies could also require improvements in data linkage from different sources, for example, maternal and infant records. The congenital microcephaly definition, published in 2019, has incorporated use of validated algorithms for diagnosing the outcome and use of ICD-9 or ICD-10 diagnostic codes into the definition, which will enhance use with retrospective electronic health records data.[15] Moll et al.[41] successfully developed a claims-based algorithm for determining pregnancy outcomes (live birth, preterm birth, stillbirth, and spontaneous abortions), achieving high-percentage agreement between the algorithm and clinician adjudication of GAIA LOCs (62.4%–100% depending on the outcome). This study supports the notion that it might be possible to translate the GAIA CDs into the language of electronic health records.

4.1 | Future studies (upcoming research)

The authors are aware of a number of upcoming studies that will undertake further work in validating the CDs. These include a large retrospective cohort study from South Africa that aims to describe the incidence of adverse pregnancy and birth outcomes. A planned sub-analysis will describe the data required to improve diagnostic certainty in the setting. Optimizing documentation and implementation of key diagnostics such as urine dipsticks and blood sugar monitors will be key to improving diagnostic certainty in these settings. Another cohort study, designed to describe background rates of adverse outcomes in a new maternal vaccine clinical trials platform in Uganda, will assess the GAIA CDs in a prospective cohort of 4000 women and their infants; the investigators aim to include all the GAIA CDs published in 2016 and 2017 (ClinicalTrials.gov identifier: NCT04653948). Watson et al.[39] plan to conduct further analyses of their dataset to describe inter-site and inter-user variability in determining LOC by medical personnel, as this may be expertise-dependent and prone to assessor bias. Inter-user variability, as well as ways of improving data quality, will also be considered in the Uganda study. An ongoing systematic review will identify maternal vaccine trials that have applied the definitions in their published safety analyses (PROSPERO CRD42021253680).

The Brighton Collaboration CDs and guidelines are meant to undergo review on a regular basis. It is important therefore that further validation work is undertaken to enable this, and that planning of these reviews is now considered.

5 | CONCLUSIONS

Harmonization of adverse event terminologies, definitions, and methods of assessment is of critical importance to allow comparability and timely assessment of vaccine safety through pooling and meta-analyses of globally generated data. Further work is required to ensure that the GAIA definitions are suitable for undertaking these assessments in both clinical trials and post-implementation studies. The 13 CDs that have not undergone any field assessment should be prioritized as well as those that have only been assessed in high-income settings. Simple modifications, such as ensuring consistency across definitions, removal of the potential for ambiguity, or variations in interpretation and modifications to ensure that higher-level criteria are de facto accepted at lowers levels of confidence, would improve performance of the CDs.

AUTHOR CONTRIBUTIONS

HGD: conceptualization, methodology, visualization, data curation, analysis and writing the original draft of the manuscript. CB: data curation, analysis, manuscript review and editing. CD and GW: data curation, manuscript review and editing. KLD and CLC: conceptualization, visualization, manuscript review and editing. PH, FM and CJ: manuscript review and editing.

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CONFLICT OF INTEREST STATEMENT

HGD is an investigator on the cited Uganda study; she has no other conflicts to report. CB has no conflicts of interest to report. PTH was a member of the GAIA working group. CLC is principal investigator for mentioned study in South Africa; she was a member of the GAIA working group and has no other COIs. KLD is principal investigator for the Ugandan study; she has no other conflicts to report. CEJ was a member of the GAIA working group and author of a GAIA case definitions; she was an author of one of the studies assessed in this manuscript (Watson et al.[39]). GW was author of one of the studies assessed in this manuscript (Watson et al.[39]). FM was the Task Force Lead for the development of all the GAIA case definitions after leading the selection of outcomes during the 2014 WHO consultation meeting, is an author or co-author of the GAIA case definitions and co-investigator of the Watson et al.[39] and Moll et al.[41] studies. FM continues to work in the development of Brighton Case definitions with support from CEPI's SPEAC project.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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