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**Applicability of the GAIA maternal and neonatal outcome case definitions for the evaluation of adverse events following vaccination in pregnancy in high-income countries**

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**ABSTRACT:**

**Background:** The Brighton Collaboration Global Alignment of Immunization Safety in Pregnancy (GAIA) project developed case definitions for the assessment of adverse events in mothers and infants following maternal immunization. This study evaluated the applicability of these definitions to data collected in routine clinical care and research trial records across seven sites in high-resource settings.

**Methods:** Data collection forms were designed and used to retrospectively abstract the key elements of the GAIA definitions from records for five neonatal and five maternal outcomes, as well as gestational age. Level of diagnostic certainty was assessed by the data abstractor and an independent clinician, then verified by Automated Brighton Case-logic. The ability to assign a level of diagnostic certainty for each outcome and the positive predictive value (PPV) for their respective ICD-10 codes were evaluated.

**Results:** Data from 1248 case records were abstracted: 624 neonatal and 622 maternal. Neonatal outcomes were most likely to be assessable and assigned by level of diagnostic certainty. PPV for preterm birth, low birth weight, small for gestational age and respiratory distress were all above 75%. Maternal outcomes for pre-eclampsia and fetal growth restriction showed PPV over 80%. However, microcephaly (neonatal outcome) and dysfunctional labor (maternal outcome) were often non-assessable, with low PPVs.

**Conclusions:** The applicability of GAIA case definitions to retrospectively ascertain and classify maternal and neonatal outcomes was variable amongst sites in high-resource settings. The implementation of the case definitions is largely dependent on the type and quality of documentation in clinical and research records in both high- and low resource settings. While designed for use in the prospective evaluation of maternal vaccine safety, the GAIA case definitions would likely need to be specifically adapted for observational studies by using alternative sources of data, linking various data sources, and allowing flexibility in the ascertainment of the elements and levels of certainty of the case definition.

**INTRODUCTION:**

Despite significant reductions in under-five mortality, neonatal mortality rates have not decreased at the same rate, thus reducing neonatal mortality is an important target of the 2030 Sustainable Development Goals([1](#_ENREF_1), [2](#_ENREF_2)). Vaccination in pregnancy is a strategy that has been shown to reduce infection in both pregnant women and neonates and is seen as a priority by the World Health Organisation (WHO) to reduce the global burden of infection in these populations([3](#_ENREF_3)). Maternal immunization programmes for tetanus are well established and have proven successful in reducing the burden of disease in mothers and neonates, with the benefits of influenza and pertussis immunization programmes being demonstrated more recently([4-6](#_ENREF_4)). Vaccines in development, such as respiratory syncytial virus and group B *Streptococcus* have specific indications for use in pregnancy and show promise for reducing the burden of these infections ([7](#_ENREF_7), [8](#_ENREF_8)). Amongst pregnant women with SARS-CoV-2, there is associated risk of hospitalisation, intensive care admissions, preterm delivery and maternal death ([9](#_ENREF_9)). The potential risk posed by SARS-CoV-2 to pregnant women indicates clinical trials and observational studies of SARS-CoV-2 vaccines in pregnant women will be necessary to demonstrate safety and efficacy in this population.

Standardised case definitions to evaluate adverse events following immunizations (AEFI) during pregnancy are essential for a globally harmonised approach to the monitoring of vaccine safety, both for vaccines progressing through clinical trials and those implemented in routine care([10](#_ENREF_10), [11](#_ENREF_11)). During the current COVID-19 pandemic, there is a pressing need for rapid up-scaled implementation of SARS-CoV-2 vaccine trials and safety assessment studies in pregnant women. This will require global collaboration, data pooling and sharing, as well as high-quality comparable data on AEFIs to ensure protection of pregnant women and their infants in a compressed time frame.

Standardised case definitions allow for comparability of data across studies and countries. Improved recording and detection of AEFI during pregnancy globally will increase vaccine confidence. The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project developed 25 case definitions for assessing AEFIs during pregnancy using the Brighton Collaboration template and levels of diagnostic certainty([10](#_ENREF_10), [12-22](#_ENREF_12)). The GAIA project was designed in response to the WHO call for global efforts to monitor the safety of vaccines in pregnancy for use in both high and low-resource settings, in line with the WHO Global Vaccine Safety Blueprint 1.0([23](#_ENREF_23)).

It is important to evaluate GAIA definitions in practice to test their applicability and feasibility in different contexts and understand their limitations. The GAIA definitions were designed for use in clinical trials of vaccines in pregnancy, however investigators may apply these definitions in retrospective or observational studies. Therefore, it is important to determine their utility in these settings as well.

The objective of this study was to evaluate the applicability of ten GAIA case definitions and one enabling term (a term upon which other case definitions rely) retrospectively to data collected in routine clinical care or in research trials across seven sites in high-resource settings; the United States of America (USA), United Kingdom (UK) and Australia.

**METHODS:**

**Study setting:**

Study sites in three different countries in high-resource settings, four in the USA, two in the UK and one in Australia, were included in the study.

**Case definitions evaluated:**

The GAIA case definitions evaluated comprised five neonatal outcomes: preterm birth, low birth weight, small for gestational age, respiratory distress and microcephaly and five maternal outcomes: preterm labor, fetal growth restriction, pre-eclampsia, non-reassuring fetal status and dysfunctional labor. Gestational age is required for most case definitions, as such this enabling term was assessed in all pertinent cases. ICD-9 and ICD-10-CM codes were created using the Codemapper tool ([24](#_ENREF_24)), and reviewed by medical experts (SB,FM).

**Data collection:**

Clinical cases were identified through individual hospital coding departments according to ICD-9 & 10 codes. Research cases were identified differently depending on the study site, either using MedDRA codes or by hand searching research records from relevant clinical trials.

Data collection forms were developed for each outcome and used uniformly across all study sites (see Appendix for data collection forms and guidance for use). All investigators were from clinical backgrounds, either paediatric or obstetric, and underwent training to abstract data from test cases prior to using the data collection forms to abstract data from clinical or research records. Inter and intra-rater comparisons were made by conducting a review of the responses from an exercise of adjudication or mock cases and scenarios.

Abstracted data was recorded on paper data collection forms. Fully anonymised data was then entered into password-protected REDcap database developed for this project([25](#_ENREF_25), [26](#_ENREF_26)). A Brighton Collaboration level of diagnostic certainty was assigned to each abstracted case according to the GAIA case definitions; the site principal investigator verified the level of diagnostic certainty assigned to each case. Where initial data abstraction was performed by the principal investigator, another investigator verified the level of diagnostic certainty. Where there were discordances, a third investigator reviewed the case.

Brighton Collaboration levels of diagnostic certainty were determined in two ways: at abstraction by the investigator, and at the analysis stage by applying an automated series of decision rules based upon the Brighton definitions and associated case logic. This was programmed using SAS (Version 9.4. Cary, NC: SAS Institute Inc; 2014), which was based on the rules from the Automated Brighton Case (ABC-tool) classification (see appendix for logic of ABC-tool). The ABC-tool was in development at the time, and not fully functional, therefore the modified tool programmed in SAS is be described as ‘ABC case logic’ here.

The Brighton Collaboration levels of diagnostic certainty:

|  |  |
| --- | --- |
|  | **Classification** |
| Level 1 | Definite case |
| Level 2 | Probable case based on resources |
| Level 3 | Possible case based on resources |
| Level 4 | Insufficient evidence to confirm |
| Level 5 | Not a case of the outcome event |

**Analysis:**

Based on the abstracted data in REDCap database, the following parameters were assessed across all sites for each of the case definitions, (analysis by site was also performed and is described in the appendix and supplementary data):

* *Ability* to assign a level of diagnostic certainty up to level 3 – both by abstractor and using ABC-logic. Where the level of certainty was not assessable, the missing components required to achieve a level 1 diagnostic certainty were identified.
* *Quality* of case description available in records, what level of diagnostic certainty was ascertainable for each outcome – both by abstractor and using ABC logic.
* *Performance* of the case definitions – the positive predictive value (PPV) for ICD-10 codes (for clinical cases only, as research cases were not selected based on ICD-10 codes).

**Ethics:**

The study protocol was reviewed and approved by the institutional review board at Cincinnati Children’s Hospital Medical Center (Ref: 00002988) and at Baylor College of Medicine and Affiliated Hospitals (H-42922). Monash Health Human Research Ethics Committee Low risk panel approved (NMA HREC Reference Number: LNR/18/MonH/405 and Monash Health Ref: RES-18-0000-280L.)

**RESULTS:**

A total of 1246 cases were identified across the seven study sites: 624 neonatal and 622 maternal. Of the neonatal records, 578 were from clinical case records and 46 from research case records. Of the maternal records, 583 were from clinical case records and 39 from research case records. Clinical case records were available at all participating sites, but research records were only available at three sites, all from interventional or observational studies of vaccines in pregnancy.

**Gestational age:**

Gestational age was non-assessable by the abstractor in 18.3% (114/624) of neonatal cases reviewed, and 2.1% (13/622) of maternal cases. In neonatal cases, of those assessable, 48% (298/624) had a level 1 level of diagnostic certainty, this was highest in sites where obstetric and neonatal records were linked. At sites where there was no maternal information in the infant records, in particular research records, assessability was low. From maternal cases, gestational age was assessable for 78% (484/622) at level 1 level of diagnostic certainty, which was consistent across all sites. Figure 1 illustrates the level of diagnostic certainty for gestational age, by study site and by abstractor or ABC case logic. Inability to assess gestational age was most often due to lack of information on ‘certain’ last menstrual period and missing information on first trimester ultrasound.

**Neonatal Case definitions**

Preterm Birth:

Preterm birth was non-assessable by the abstractor in 17.6% (25/142) of cases, and 27.5% (39/142) by ABC-case-logic. Where it was assessable, the majority of cases were level 1 level of diagnostic certainty (Figure 2). Where there was difficulty in assigning level 1, this was due to missing data on last menstrual periods and first trimester ultrasound. The PPV was very high in most sites (Table 1), except two sites where neonatal records often did not include information on timing of first ultrasound or ‘certain’ last menstrual period.

Low birth weight:

Low birth weight was non-assessable by the abstractor in 26.0% (32/123) of cases and 30.1% (37/123) by ABC-case-logic, the most frequent reason for this was missing information on calibration of scales. Three sites classified all cases as level 1 level of diagnostic certainty (Figure 2). The mean PPV across all sites was high (Table 1).

Small for gestational age:

Small for gestational age was mostly assigned level 3B level of diagnostic certainty by abstractors (Figure 2), except three sites where mothers last menstrual period was recorded in the neonatal records and level 1 diagnostic level of certainty was high. 27.2% (34/125) were non-assessable by abstractor and 57.6% (72/125) by ABC-case-logic. The main difficulty for assessing small for gestational age related to the definition depending on a gestational age assessment and proper weight measurement, one hospital was not able to ascertain standard scale calibration required for the case definition. The mean PPV across all sites was good (Table 1).

Respiratory distress:

Almost all cases were assessable, with only 6.3% (8/126) of cases non-assessable by abstractor, and 33.6% not assessable using the ABC case logic. The majority of cases were classified as level 1 level of diagnostic certainty (Figure 2). The mean PPV was high (Table 1).

Microcephaly:

30.6% (33/108) were non-assessable by abstractor and 66.7% (72/108) by ABC-case-logic. Where cases were identified, it was based on post-natal diagnosis from neonatal records. The PPV was very low (Table 1), and varied across sites, dependent on whether maternal or neonatal records were used. The difficulties in classifying microcephaly were due to missing data, as it was often made as a post neonatal period diagnosis and making it impossible to look back to neonatal case records. The difficulties in assigning a level of diagnostic certainty were due to poor documentation of head circumference centile.

**Maternal case definitions**

Preterm Labor:

There was significant variability across sites for preterm labor, with almost half non-assessable, 51.6% (65/126) were non-assessable by abstractor and 48.4% (61/126) by ABC-case-logic. One site was able to classify all cases, across other sites the majority were non-assessable due to missing recorded information on the number of contractions and change in cervix (Figure 3).

Fetal growth restriction:

Fetal growth restriction was mainly assessable at level 1 level of diagnostic certainty (Figure 3). Only 30.5% (33/132) were non-assessable by abstractor and 33.3% (44/132) in ABC-case logic. When cases were non-assessable this was due to missing information on weight. The PPV was good (Table 1).

Pre-eclampsia:

Only 26.4% (33/125) were non-assessable by abstractor, and 37.8% were non-assessable by the ABC tool, with most cases from the UK classified as level 1 level of diagnostic certainty (Figure 3). The PPV was high across all sites (Table 1).

Non-reassuring fetal status:

The majority of these cases were non-assessable, 69.9% (79/113) by abstractor and 69% (78/113) by ABC-case-logic, this was due to fetal heart rate not being captured on the data collection forms, as likely not recorded in the medical or research records. As a result the PPV was very low (Table 1).

Dysfunctional Labor:

On abstraction, 41.2% (52/126) cases were non-assessable and on ABC- case logic all cases were non-assessable as details on cervical dilation were missing in all cases (Figure 3). The PPV was very low (Table 1).

*Table 1: Summary of results; total numbers of medical and research records reviewed, percentage of outcomes non-assessable, mean positive predictive values for neonatal and maternal outcomes for ICD-10 codes and ranges across all sites.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Medical and research records** | **Records reviewed** | **Non-assessable by abstractor**  **n (%)** | **Non-assessable by ABC-case-logic**  **n (%)** | **Mean % PPV for ICD-10 code across all sites, from medical records (95% CI)** | **Range in % PPV estimates across sites** |
| Gestational age | Medical Records  Research records  Total | 1161  85  1246 | 113 (9.7)  14 (16.5)  127 (10.2) | 243 (20.9)  17 (20.0)  260 (20.9) | -  -  - | -  -  - |
| **Neonatal outcomes** | | | | | | |
| Preterm Birth | Medical Records  Research records  Total | 123  19  142 | 25 (20.3)  0 (0)  25 (17.6) | 38 (30.9)  1 (5.3)  39 (27.5) | P07: PPV 76.4 (67.6-85.2)  -  - | 52.9-100%  -  - |
| Low Birth Weight | Medical Records  Research records  Total | 110  13  123 | 31 (28.2)  1 (7.7)  32 (26.0) | 36 (32.7)  1 (7.7)  37 (30.1) | P07: PPV 88.0 (80.6-95.4)  -  - | 0-100%  -  - |
| Small for gestational age | Medical Records  Research records  Total | 118  7  125 | 32 (27.1)  2 (28.6)  34 (27.2) | 65 (55.1)  7 (100)  72 (57.6) | P05: PPV 70.4 (62.1-78.8)  -  - | 20-100%  -  - |
| Respiratory Distress | Medical Records  Research records  Total | 119  7  126 | 4 (3.4)  4. (57.1)  8 (6.3) | 40 (33.6)  5 (71.4)  45 (35.7) | P22: PPV 76.7 (67.8-85.7)  -  - | 30-100%  -  - |
| Microcephaly | Medical Records  Research records  Total | 108  -  108 | 33 (30.6)  -  33 (30.6) | 72 (66.7)  -  72 (66.7) | Q02: PPV 40.0 (29.0-50.0)  -  - | 0-100%  -  - |
| **Maternal outcomes** | | | | | | |
| Preterm Labor | Medical Records  Research records  Total | 121  5  126 | 60 (49.6)  5 (100)  65 (51.6) | 58 (47.9)  3 (60.0)  61 (48.4) | O60. PPV: 56.8 (47.7-65.8)  -  - | 0-100%  -  - |
| Fetal growth restriction | Medical Records  Research records  Total | 120  12  132 | 32 (26.7)  1 (8.3)  33 (30.5) | 43 (5.0)  1 (8.3)  44 (33.3) | O36. PPV: 80.9 (72.9-88.8)  -  - | 55-100%  -  - |
| Pre-eclampsia | Medical Records  Research records  Total | 111  14  125 | 28 (25.2)  5 (35.7)  33 (26.4) | 42 (37.8)  9 (64.3)  51 (40.8) | O14: PPV 81.2 (72.9-89.5)  -  - | 33-100%  -  - |
| Non-reassuring fetal status | Medical Records  Research records  Total | 108  5  113 | 75 (64.4)  4 (80.0)  79 (69.9) | 74 (68.5)  4 (80.0)  78 (69.0) | O68: PPV 38.3(24.4-52.2)  O76: PPV 15.0(0-30.7)  O77: PPV 57.9(35.7-80.1)  -  - | 0-64%  -  - |
| Dysfunctional labor | Medical Records  Research records  Total | 123  3  126 | 50 (40.7)  2 (66.7)  52 (41.2) | 123 (100)  3 (100)  126 (100) | O62: PPV 34.0(21.1-46.7)  O66: PPV 55.0(33.2-76.8)  -  - | 11.1-50%  -  - |

**DISCUSSION:**

Neonatal outcomes were most likely to be assessable and able to be assigned a level of diagnostic certainty. Positive predictive values for preterm birth, low birth weight, small for gestational age and respiratory distress were all above 75%. Maternal outcomes for pre-eclampsia and fetal growth restriction also showed a high assessability with PPV over 80%. However neonatal outcomes for microcephaly were often non-assessable, with a very low PPV. Maternal outcomes for preterm labor, non-reassuring fetal status and dysfunctional labor were also often non-assessable with poor PPV. The range of PPV was large for all definitions across sites and could not be extrapolated from one site to another, indicating the utility of some GAIA case definitions in this setting and the limitations of others, depending on the data recorded in clinical or research records. Missing data was one of the most important reasons a case could not be assigned a GAIA level of diagnostic certainty. A key observation derived from this study is that the quality of documentation in clinical and research records directly impacts the applicability of the GAIA case definitions, even in high resource settings.

Correct identification of gestational age is fundamental for maternal immunization programmes. Timing of immunization during pregnancy is an important factor in vaccine immunogenicity and a consideration in vaccine safety. Many other outcomes also rely on accurate gestational age identification. As such, accurate identification of this enabling factor is essential for maternal vaccine studies. Gestational age had excellent assessability from maternal records and was good from neonatal records. This was best where maternal and neonatal records were linked, however assessability was poor where data were missing or incomplete and maternal and neonatal records were not linked. This highlights the importance of linking maternal and neonatal records within health facilities, and during clinical trials documenting key maternal information in neonatal records. Gestational age assessment should also include flexibility of options, for example, certain or uncertain last menstrual period with third trimester ultrasound.

Neonatal outcomes were most likely to be assessed and classified to a level of diagnostic certainty. Low birth weight and small for gestational age were not classified as frequently; this was due to weight not being recorded or information on the calibration of weighing machines not being specified or available. Some flexibility on requirements for machine calibration could be considered in the GAIA case definitions. Microcephaly was also less likely to be classified, with a very low PPV. The difficulties in classifying microcephaly were due to missing data, as it was often made as a post neonatal period diagnosis and making it impossible to look back to neonatal case records. The difficulties in assigning a level of diagnostic certainty were due to poor documentation of head circumference centile.

Maternal outcomes varied in their assessability. Pre-eclampsia and fetal growth restriction had good assessability, however non-reassuring fetal status and dysfunctional labor had low assessability due to discrepancies in the data collection forms and what is documented in the medical or research records, making it difficult to classify outcome by level of diagnostic certainty. Preterm labor had low assessability due to missing records. The data collection forms for non-reassuring fetal status and dysfunction labor should be reviewed and revised. Additionally, it could be relevant to assess whether abstractors who provide obstetric care were more frequently able to complete these forms for the obstetric definitions than abstractors who do not provide obstetrics care. Again, missing or incomplete data presents a large problem.

Previous evaluation of GAIA case definitions in low-resource settings showed outcomes for preterm birth and hypertension were sensitive in both retrospective and prospective studies and reliable and feasible to use; however the stillbirth definition was not as sensitive and would need further modification of gestational age assessment parameters to be useful in the setting([27](#_ENREF_27)). A recent study in the USA demonstrated successful application of GAIA case definition in retrospectively collected electronic medical records for pregnancy outcomes (Moll K. et al. abstract and presentation at ICPE conference, 2020).

Case identification in retrospective studies is usually based on ICD codes; however, coding alone does not allow for verification of cases, and codes do not allow for the case classification into level of diagnostic certainty. Research documentation has changed over time with different documentation requirements, and MedDRA codes are not used globally and were not necessarily reported appropriately. Therefore, a retrospective review presented challenges to determine applicability of the GAIA case definitions, or to validate them against MedDRA codes. It is important to understand the GAIA case definitions were primarily designed for prospective research data collection, rather than retrospective. Applicability of GAIA case definitions to retrospectively classify outcomes varied across sites and countries. For use in retrospective studies, the GAIA case definitions would need to be reviewed and adapted. Study findings highlight the priority for adapting and revising some of these definitions.

The investigators noted that review of both clinical and research records was labor intensive, with between one to two hours spent on each record. To use the GAIA case definitions properly, investigators need to fully understand the background and rationale for each case definition, be familiar with the terminology and documentation in clinical or research situations, and utilize data collection forms and guidance documents specifically developed for the project.

Investigator bias in assigning level of diagnostic certainty and classification needs to be considered; it is expertise-dependent, and there will likely be inter-site and inter-user variability. This topic will be addressed further in a complimentary paper on abstractors’ variability.

**Strengths and limitations:**

This is the first study to evaluate GAIA case definitions in high income settings. A large number of cases were evaluated across multiple different sites and countries ensuring their usability in different contexts and settings. The data collection forms developed can be used as a blueprint for application of the GAIA case definitions globally.

Individual abstractor expertise could have influenced decisions on level of diagnostic certainty, with the potential for bias with inter-user and inter-site variability. In some cases the design of the data collection forms presented issues with appropriate data collection to complete the level of diagnostic certainty. Data collection was often limited by incomplete or missing notes. We were able to assess few research records due to the relatively low numbers of women enrolled in intervention studies in pregnancy compared to those receiving clinical care and the low frequency of adverse events in this selected population of women, who were often at low risk of complications.

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| **Lessons learned:** |
| * A priori development of source documents and data collection forms based on the GAIA case definitions is necessary to ensure that all elements of the definition are included * Training of personnel responsible for data abstraction/extraction is crucial to ensure consistency and comparability of data collection |
| * Case review can be labor-intensive |
| * There is difficulty in retrospectivity ascertaining cases from clinical records * Missing data and lack of clarity on data documentation led to difficulties assigning level of diagnostic certainty |
| * Importance of full understanding of background, methodology and rationale for all GAIA case definitions before assigning levels of diagnostic certainty |
| * GAIA case definitions were designed to be applied prospectively and this must be taken into consideration when applying retrospectively |
| * GAIA case definitions could be applied in retrospective case ascertainment by adapting them using alternative sources of data, linkage of various data sources, and allowing flexibility in the ascertainment of the elements and levels of certainty of the case definition. * International variations in case documentation and practice make standardisation challenging |
| * Some GAIA case definitions with low PPV might need to be updated to ensure relevance in clinical observational studies |

**CONCLUSION:**

The applicability of the GAIA case definitions to retrospectively identify and classify maternal and neonatal outcomes reported in either clinical or research records was variable in sites in high-resource settings. Even though the case definitions include various levels of diagnostic certainty to be applicable to various resource settings based on diagnostic capabilities, the implementation of the case definitions is largely dependent on the type and quality of documentation in clinical and research records in both high- and low resource settings. Furthermore, while originally designed for use in the prospective evaluation of maternal vaccine safety, the GAIA case definitions would likely need to be specifically adapted for observational studies by using alternative sources of data, linking various data sources, and allowing flexibility in the ascertainment of the elements and levels of certainty of the case definition.

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**FIGURES:**

*Figure 1: Stacked bar graphs to illustrate level of diagnostic certainty by gestational age by abstractor and ABC case logic across all study sites.*



LOC = level of diagnostic certainty, AU\_1 = Australian study site 1, UK\_1 = UK study site 1, UK\_2 = UK study site 2, US\_1 = USA study site 1, US\_2 = USA study site 2, US\_3 = USA study site 3

*Figure 2: Stacked bar graphs to illustrate level of diagnostic certainty for neonatal outcomes by abstractor and ABC-case-logic across all study sites.*



LOC = level of diagnostic certainty, AU\_1 = Australian study site 1, UK\_1 = UK study site 1, UK\_2 = UK study site 2, US\_1 = USA study site 1, US\_2 = USA study site 2, US\_3 = USA study site 3

*Figure 3: Stacked bar graphs to illustrate level of diagnostic certainty for maternal outcomes by abstractor and ABC-case-logic across all study sites.*



LOC = level of diagnostic certainty, AU\_1 = Australian study site 1, UK\_1 = UK study site 1, UK\_2 = UK study site 2, US\_1 = USA study site 1, US\_2 = USA study site 2, US\_3 = USA study site 3