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Vaccine safety surveillance in pregnancy in low- and middle-income countries using GAIA case definitions: A feasibility assessment

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ABSTRACT

Background: Global efforts to adequately monitor safety of new vaccines for pregnant women in low and middle-income countries (LMICs) are needed. The Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) project recently published case definitions based on levels of diagnostic certainty for pregnancy- and neonatal outcomes and maternal vaccination. As a preliminary step to assessing the applicability of these definitions in LMICs, WHO selected sites and conducted a feasibility assessment to evaluate their ability to identify and classify selected outcomes (preterm birth, neonatal death, neonatal invasive bloodstream infection (NI-BSI), stillbirth) and maternal vaccination.

Methods: Candidate sites were initially screened using a questionnaire. For each outcome, eligible sites were asked to retrospectively identify and collect information for three individuals born in 2016. Subsequently, outcomes were classified by level of diagnostic certainty.

Results: Fifty-one sites (15 countries) were screened; 32 of them (9 countries) participated in the assessment and identified 315 subjects with the outcomes of interest. Twenty-four sites (8 countries) identified at least one subject per outcome and agreed to continue participating. The majority (80%) of preterm births, neonatal deaths, and NI-BSI subjects, but only 50% of stillbirths, could be assessed for diagnostic certainty. The main reasons for not classifying stillbirths were insufficient information to distinguish between antepartum and intrapartum stillbirth (29%); or that not all data for one subject fit into a single level of diagnostic certainty (35%). Forty-nine percent of mothers were considered vaccinated, 6% not-vaccinated, and vaccination status could not be assessed in 44% of them.

Discussion: GAIA case definitions for four neonatal outcomes and maternal vaccination were successfully piloted in 24 sentinel sites across four WHO regions. Our assessment found that modification of the stillbirth definition could help avoid potential misclassification. Vaccine safety monitoring in LMICs will benefit from systematic recording of all vaccinations during pregnancy.

1. Introduction

The goal of maternal vaccination is to transfer protective immunity to infants too young to benefit directly from primary immunization, and to protect the fetus from the effects of maternal or early life infection [1]. Tetanus, pertussis and influenza vaccines are already recommended by the World Health Organization (WHO) [2–4]; whilst new vaccines against hepatitis E, Zika virus, respiratory syncytial virus (RSV) and Group B Streptococcus (GBS) are under clinical evaluation. Low and middle-income countries (LMICs), where perinatal and infant mortality rates are higher, would particularly benefit from maternal vaccination with these new vaccines. A potential threat to maternal vaccination programs, however, is the fear of a perceived association between vaccination and common antenatal complications such as spontaneous abortion and stillbirth. It is critical that those countries that may benefit the most from new vaccines develop pregnancy intervention safety monitoring beyond passive surveillance.

The Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) project, funded by the Bill and Melinda Gates Foundation, has recently proposed standard definitions of key obstetric and neonatal terms, maternal immunization and

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gestational age using the Brighton Collaboration method [5–8]. Each case definition is stratified into multiple levels of diagnostic certainty, where Level 1 is the highest attainable level (maximum specificity), and Level 2 and 3 have a stepwise increase in sensitivity, while retaining an acceptable level of specificity [9]. Diagnostic certainty of level 4 or above is considered insufficient to confirm the case definition [10]. These attempts at standardizing case definitions may help enable meaningful comparisons across studies [11]. The Global Advisory Committee on Vaccine Safety (GACVS) and Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) highlighted the need for field validation and assessment of the applicability of the GAIA case definitions in high-, middle- and low-income settings [12].

WHO is planning to conduct a pregnancy multi-country collaborative (MCC) study to assess the applicability of GAIA definitions in LMICs. The long-term goal of this work is to assess the feasibility of conducting well-designed collaborative observational studies to monitor the safety of new vaccines targeted for use in pregnant women in LMICs as part of the WHO Global Vaccine Safety Initiative (GVSI) [13–15]. A first multi-center international proof-of-concept study investigated the association between Guillain-Barre Syndrome and the 2009 H1N1 pandemic influenza vaccine using a network of hospital-based sentinel sites in high- and middle-income countries. This study successfully demonstrated its political and scientific feasibility [16]. A subsequent proof-of-concept study [17], aimed at addressing the WHO's Global Vaccine Safety Blueprint's [14] strategic goal of enhanced pharmacovigilance capacity, was performed under the umbrella of the GVSI [18]. This study further demonstrated that a global hospital-based network with participation of LMICs, could effectively evaluate rare and serious vaccine adverse events, and could even potentially be used to characterize risk differences between vaccine strains [17].

As a preliminary step to select eligible sites for the pregnancy MCC study, we conducted a feasibility assessment to identify sites able to access data of acceptable quality to detect and classify selected neonatal outcomes and maternal vaccination by GAIA levels of diagnostic certainty.

2. Methods

Selection of primary, secondary and tertiary care centers was a multi-step process: (1) Preliminary site identification was followed by (2) a screening questionnaire to select sites for the feasibility assessment, and a (3) feasibility assessment to select sites for the pregnancy MCC study (Fig. 1).

2.1. Step 1: preliminary site identification

We selected as potential sites those that participated in the previous MCC project [17], including sites in two high income countries in order to facilitate data quality control. We also included additional sites from LMICs identified through WHO regional and country offices and Ministries of Health. The inclusion criteria included the existence of a functional national vaccine pharmacovigilance system willing to strengthen its capacity to monitor vaccine safety during pregnancy, an obstetrics department with $\geq$1000 deliveries per year, a pediatric ward, patient records (paper/electronic), and a clinician willing to serve as focal point for the project (Suppl_1 First step in selection).

2.2. Step 2: screening questionnaire

Sites were asked to complete screening questions on hospital characteristics (including whether it is a primary, secondary or tertiary care center), patient records and operational aspects (Suppl_2 Screening questionnaire). Exclusion criteria included lack of access to individual patient charts, computers, or internet.

2.3. Step 3: feasibility assessment

Diagnostic capacity and data access were further assessed in screened sites through the conduct of a simulation exercise.

The following four GAIA case definitions were selected: preterm birth [9], neonatal death [19], neonatal invasive bloodstream infection (BSI) [20], and stillbirth [10] (Suppl_3 GAIA case definitions). For this feasibility assessment, these outcomes were selected for their relatively high incidence; necessity to have a mother-baby linkage; occurrence within one month of birth (more likely to be recorded in hospital records); requiring gestational age assessment (a key component for case definition of several pregnancy-related outcomes); or requiring laboratory data. Among neonatal infections, only the case definition for neonatal invasive BSI was assessed; meningitis and respiratory infections were not [20]. Both the antepartum and intrapartum stillbirth case definitions were assessed. For neonatal death, no distinction was made based on 'type' of neonatal death (extremely preterm, preterm, term) in this assessment. However, the ability to collect gestational age was assessed.

The GAIA definition for maternal immunization was also selected, [19] given the need to ascertain vaccine exposures for vaccine safety monitoring (Suppl_3 GAIA case definitions). Tetanus-containing vaccines were chosen as the preferred exposure of interest, as they are widely used in pregnant women in LMICs [21].

Between May and July 2017, sites were requested to complete case report forms (CRFs) in predesigned Epi Info™ or Microsoft Excel™ data entry screens for at least one, but preferably three retrospectively identified subjects for each of the four pregnancy outcomes (leading to a maximum of twelve subjects per site) (Suppl_4 CRFs). Sites were instructed to select the first three recorded cases in 2016 among neonates born in 2016 from their archives or databases. ICD codes were provided for sites using ICD codes (Suppl_4 CRFs). Data collection on subjects was restricted to the data items part of the GAIA case definitions; therefore, additional data (such as singleton versus multiple deliveries) were not collected. Details on the data sources used for subject identification were collected.

Sites were first sent the CRFs in Epi Info™ format, and only if problems in correctly installing the software were encountered they were sent the CRFs in Excel™ format. Instructions on how to complete the CRFs were provided, without formal training (Suppl_4 CRFs). Cases were then automatically classified by level of diagnostic certainty, using a case classification algorithm designed by the research team and programmed in SAS ® v9.4 [22].

To inform future study preparation, including training and resources, sites were also asked to indicate the level of difficulty in completing the CRFs (ranging from very easy to very difficult), staff's qualification, and time required to identify cases and complete CRFs.

Our analysis was based on a convenience sample size. The choice to request three subjects per outcome per site was a pragmatic one and was not based on any statistical sample size considerations.

Descriptive statistics were calculated in Excel™.

2.4. Outcome assessment measures and site eligibility criteria used in the feasibility assessment

An 'identified subject' was defined as a subject for whom any information had been completed in the CRF for one of the four selected pregnancy-related outcomes. A 'classified case' was

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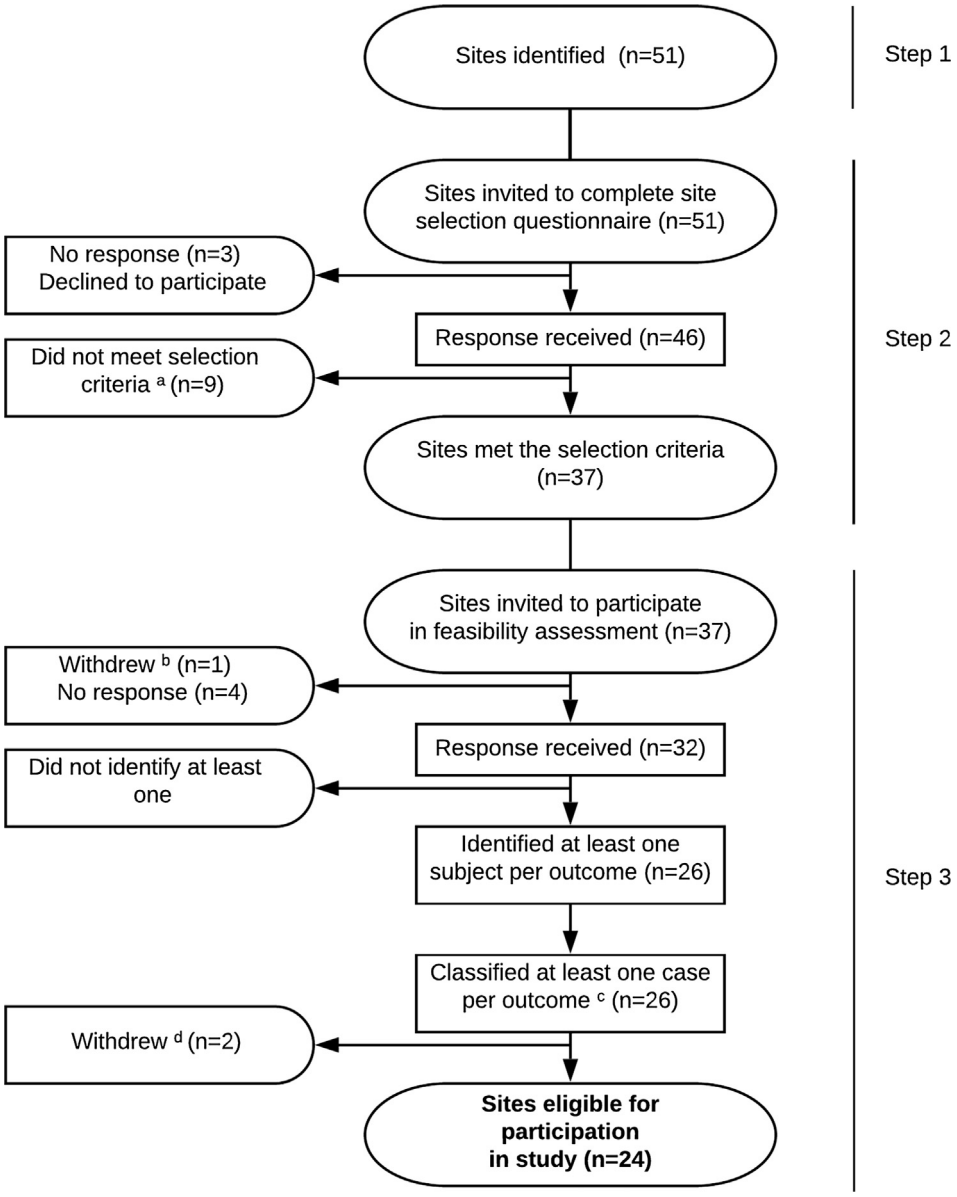

Fig. 1. Flow of site selection. [a]Did not meet selection criteria: Lack of access to patient charts (n = 7), to computers (n = 2), to internet (n = 6). There may be multiple exclusion criteria for one site. [b]Withdrew because of a very low rate of vaccination during pregnancy. [c]For the outcomes neonatal death, neonatal invasive bloodstream infection and preterm birth only; stillbirth not used as a selection criterion. Withdrew after selection. [d]Withdrew as they experienced difficulties reaching the minimum required diagnostic capacity and data access.

defined as an identified subject for whom sufficient information was provided to apply a level of diagnostic certainty listed in the respective GAIA case definition.

Sites were considered eligible for participation in the pregnancy MCC study if at least one case was classifiable for each selected outcome, demonstrating minimum diagnostic capacity and data access.

2.5. Post hoc sensitivity analysis

The stillbirth case definition reads "Delivery of an infant reported to have no signs of life at birth (no spontaneous movements, no umbilical cord pulse, no heartbeat, no cry or spontaneous respirations, no chest movement)" [10]. We interpreted this to mean that information on the absence of each sign of life should be reported. We subsequently learned from the authors of this case definition that information is not required for all signs (i.e. it is acceptable if one or more signs are not recorded). Therefore, a post hoc sensitivity analysis with a less strict definition was performed, requiring absence of at least one sign of life (instead of all).

2.6. Ethics

Data were collected from existing records by the clinician in charge of the patients and identified as focal point for the pregnancy MCC project. No identifying information was collected, and patients were not contacted. Therefore, the feasibility assessment was considered exempted from ethical clearance.

3. Results

3.1. Site selection

Initially, 51 sites in 15 countries were identified (Albania, Australia, Burkina Faso, China, Ghana, India, Iran, Nepal, Rwanda,

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Singapore, South Africa, Spain, Tanzania, Togo and Zimbabwe) and invited to complete the screening questionnaire. Thirty-seven sites in 12 countries met the screening criteria and were invited to participate in the assessment. Thirty-two out of these 37 sites, in nine countries, returned data (response rate 86%, Fig. 1). Of these, six sites did not identify at least one subject per outcome and were excluded. For the remaining 26 sites, at least one case could be classified for neonatal death, neonatal invasive BSI and preterm birth; for six sites of these 26 sites, none of the stillbirth subjects could be classified. After identifying some limitations to the stillbirth case definition (described below), classification of at least one stillbirth case was no longer used as a selection criterion. Two more sites withdrew after completing the feasibility assessment, leaving 24 sites from 8 countries eligible to participate in any future study, including one primary care center, four secondary hospitals, 18 tertiary hospitals and one regional health institution. Site characteristics are listed in Table 1 and Suppl_5 (Methods and sources of data for subject identification). Sources cited for subject identification include: admissions and discharge books, delivery register, clinic report book, medical record department register, and hospital records,

3.2. Piloting selected GAIA outcome definitions

3.2.1. Subject identification and case classification by level of diagnostic certainty

Overall, a total of 72–87 subjects per outcome were identified (Table 2). Twenty-six of 32 sites participating in the feasibility assessment identified at least one subject per pregnancy outcome. Eighty-four percent of the identified neonatal death subjects could be classified as well as 83% of the preterm birth and 77% of the neonatal invasive BSI subjects, whereas only 51% of the identified stillbirth subjects could be classified (in the main analysis). The most frequent levels of diagnostic certainty were Level 2 for neonatal death (81%) and neonatal invasive BSI (51%), and Level 3 for preterm birth (69%) and stillbirth (41%).

3.2.2. Classification issues

Stillbirth was the case definition with the highest number of non-classified subjects. There were three main reasons for non-classification of stillbirths (Table 3). First, sometimes it was questionable whether the identified subject was indeed stillborn (8%; e.g. Apgar score not 0). Second, it was not always clear whether a stillbirth was an antepartum or an intrapartum stillbirth (29%). However, as there are separate case definitions for these two events, this distinction is required for classification. Third, sometimes evidence on level of diagnostic certainty was not the same across all the data elements provided (35%). The stillbirth case definition consisted of a combination of data elements on absence of signs of life, prenatal (lack of) fetal cardiac activity and movement, delivery (attended, non-attended), physical examination of the stillborn and gestational age [10] (Suppl_3 GAIA case definitions). The way these data elements must be ascertained differs between levels of diagnostic certainty. Combinations of elements that reflect different levels of diagnostic certainty prohibited classification.

Table 1
Description of the eligible sites.

WHO region country	Type of facility	Nr of beds	Nr of annual deliveries	Discharge diagnosis stored electronically
African Region				
Ghana				
GH-A	Secondary	193	1700	NR
GH-B	Secondary	80	1200	NR
GH-C	Secondary	326	8600	NR
GH-D	Secondary	352	5000	NR
South Africa				
SA-A	Tertiary	3000	21,500–22,000	NR
Tanzania				
TA-A	Tertiary	250	NR	Yes
TA-B	Tertiary	163	3000–4000	Yes
TA-C	Tertiary	156	10,000–11,000	Yes
TA-D	Tertiary	350	4500	No
Zimbabwe				
ZI-A	Primary	32	5000	NR
ZI-B	Tertiary	210	1700	NR
European Region				
Spain				
SP-A	Regional health institution	NR	NR	Yes
South-East Asian Region				
India				
IN-A	Tertiary	1800	5800	Yes
IN-B	Tertiary	1500	3300	Yes
IN-C	Tertiary	1237	6100	No
IN-D	Tertiary	1023	3500	No
IN-E	Tertiary	2032	2500	Yes
IN-F	Tertiary	1390	8500	No
IN-G	Tertiary	766	3000	Yes
Nepal				
NE-A	Tertiary	580	8000	Yes
NE-B	Tertiary	763	10,000	In process
Eastern Mediterranean Region				
Iran				
IR-A	Tertiary	122	6000	NR
IR-B	Tertiary	380	1500	NR
IR-C	Tertiary	230	9900	No

NR: not reported by the site.

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Table 2
Subjects identified and cases classified in the feasibility assessment.

	Preterm birth n(%)	Neonatal deaths n(%)	Neonatal invasive BSI n(%)	Stillbirth n(%)	Stillbirth (SA) n(%)	Maternal immunization n(%)
Total subjects identified	87	74	82	72	72	144*
Cases classified among subjects identified**	72 (83)	62 (84)	63 (77)	37 (51)	38 (53)	144 (1 0 0)
GAIA Level 1 (highest)	8 (11)	12 (19)	26 (41)	4 (11)	5 (13)	8 (6)
GAIA Level 2	14 (19)	50 (81)	32 (51)	5 (14)	5 (13)	37 (26)
GAIA Level 3	50 (69)	0 (0)	5 (8)	15 (41)	15 (39)	99 (69)
GAIA Level 4 (lowest)	NA	NA	NA	13 (35)	13 (34)	NA

GAIA: Global Alignment of Immunization Safety Assessment in pregnancy; NA: not applicable; SA: sensitivity analysis.
* Maternal immunization status was assessed for all 315 subjects (100%); 144 (46%) were identified by the sites as exposed to maternal immunization (i.e. question on maternal immunization exposure was answered with "Yes").
** Total may not tally to 100% due to rounding.

Table 3
Examples of reasons why subjects identified as stillborn in the assessment could not be classified according to the GAIA case definition [21] *.

	Examples from the assessment
Unclear if there was a stillbirth	
Signs of life at birth(n = 6)	• Sign of life at birth (n = 1) • Spontaneous movements present at birth (n = 1) • Apgar score not 0 (n = 5)
Missing information on at least one sign of life(n = 13)	• Signs of life at birth unknown (n = 3) • Spontaneous movement unknown (n = 5) • Umbilical cord pulse unknown (n = 6) • Heartbeat unknown (n = 4) • Respiration unknown (n = 4) • Crying unknown (n = 5) • Apgar score unknown (n = 5)
Sensitivity analysis	
Missing information on all signs of life (n = 3)	• Missing information on all signs of life (n = 3)
Unclear if the stillbirth was ante- or intrapartum	
Lack of prenatal data (n = 10)	• On foetal movement (through prenatal ultrasound, maternal report, physical exam of mother, radiology) (n = 7) • On foetal cardiac activity (through prenatal ultrasound, auscultation or Doppler) (n = 7)
Lack of information on whether physical exam was consistent with intrapartum vs. antepartum death (n = 15)	• Unknown whether physical exam was consistent with intrapartum or antepartum death (N = 9) • Physical exam was consistent with both intrapartum and antepartum death (N = 5) • Physical exam consistent with neither intrapartum nor antepartum death (n = 1)
Mixed information (n = 7)	• Physical exam consistent with antepartum death, but with foetal cardiac activity (n = 3) • Physical exam consistent with antepartum death, but with radiology findings not consistent with intrauterine death (n = 3) • Physical exam consistent with intrapartum death, but with no foetal cardiac activity and movement (n = 2)
Evidence accepted at higher levels of diagnostic certainty not accepted at lower levels	
L3: Attended delivery and GA L3 (n = 25)	• All deliveries reported in the feasibility assessment were attended. For stillbirth L3, only non-attended deliveries with verbal report are eligible; therefore, none of the subjects fulfil the criteria for L3. Consequently, none of the subjects with gestational age L3 (only eligible for stillbirth L3) could be classified.
L4: Physical exam and GA (n = 25)	• Subjects reported as stillborn but where the foetus was "not available for physical examination after birth", or subjects where "maternal information [was] insufficient to assess gestational age" can qualify for L4. In our study, certain subjects could not be classified as Level 1–3 (for example subjects with no signs of life at birth but for whom it was unclear if the stillbirth was ante- or intrapartum). However, for most of these subjects a physical examination was performed after birth and gestational age could be assessed. Consequently, these subjects were not eligible for L4.

GA: gestational age; Lx: Level x.
* More than one reason may apply.

The sensitivity analysis with a less strict interpretation of the 'signs of life' section of the stillbirth case definition resulted in the classification of one additional stillbirth case, leading to a minor increase in the percentage of classified cases (from 51% to 53%) (Table 2).

Reasons for non-classification of neonatal death, neonatal invasive BSI and preterm birth were illogical dates (n = 17), insufficient information (n = 6), missing date of birth (n = 8), or not meeting the case definition (e.g. gestational age >37 weeks for preterm (n = 3), age at death (n = 5) or age at infection onset >28 days (n = 7)). No issues with the applicability of these three case definitions were identified.

3.2.3. Maternal vaccination status

For each identified subject, sites were requested to report whether the mother received any vaccination during pregnancy. This question could be answered with 'Yes' (49%), 'No' (6%), or 'Unknown' (44%); sites were explicitly instructed to only answer 'No' if there was documented evidence of no vaccination. Among vaccinated women from whom vaccination information was retrieved, 99 (68%) of the cases were classified as Level 3 (report of vaccination during pregnancy, but no formal recording available), 37 (27%) as Level 2 (date of immunization recorded in medical record, details of disease against which was vaccinated), and eight (6%) reached Level 1 (data of immunization recorded in

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Table 4
Level of difficulty of completing CRFs in Excel™, and range and median of average time reported by sites participating in feasibility assessment to identify one subject and to complete one CRF.

	Outcome			
	Preterm birth	Neonatal death	Neonatal invasive BSI	Stillbirth
Difficulty of completing CRFs in Excel				
N sites	11	9	10	10
Very easy	1	1	2	1
Easy	3	2	2	2
NEND	2	1	0	1
Difficult	5	5	6	4
Very difficult	0	0	0	2
Average time to identify one subject (codes)				
N sites	10	7	9	10
Range*	30 min to 5 h	25 min to 1 day	20 min to 2 days	1 min to 5 h
Median	1 h 15 min	2 h	1 h 15 min	1 h
Average time to identify one subject (no codes)				
N sites	13	15	14	13
Range	2 min to >1 working day	2 min to >1 working day	2 min to 2 days	5 min to >1 working day
Median	<2 h	<2 h	<2 h	<2 h
Average time to complete one CRF				
N sites	23	22	22	23
Range	5 min to 1 day	5 min to 1 day	5 min to 1 day	5 min to 1 day
Median	1 h	50 min	1 h	1 h

BSI: bloodstream infection; CRF: case report form; h: hour; min: minute; N: neonatal.

medical record, details of vaccine, including lot number) (Suppl_3 GAIA case definitions).

3.3. Feedback on CRF completion

CRFs were completed in Epi Info™ (n = 14) or Excel™ (n = 18). Among 32 sites that completed the feasibility assessment, 23 sites (72%) provided feedback. Among 12 sites that used Epi Info™, 11 sites indicated that the CRFs were 'easy' to complete, and one site that they were 'very easy'. For sites that used Excel™, data was collected by outcome; sites reported more difficulties in completing the CRFs, but no major difference between outcomes were observed (Table 4).

3.4. Resources

Among the 32 sites that completed the feasibility assessment, 23 sites (72%) provided information on resources required for subject identification and CRF completion. In these sites, the identification of subjects was mostly done by physicians (n = 19 sites), nurses (n = 12) and researchers (n = 7). The type of staff reported required for CRF completion was very similar.

Table 4 shows the time reported required to identify one subject and to complete one CRF. No important differences were seen in time needed between sites that reported identifying subjects through codes (e.g. ICD codes) and those that did not use codes. Large variations were observed in the time required to identify a subject, ranging from minutes to several hours, and occasionally 1–2 working days. The median average time required to complete one CRF was approximately one hour.

4. Discussion

We conducted a pilot assessment of GAIA case definitions for four neonatal outcomes and maternal vaccination as part of a study site selection process. Out of 51 contacted sites, 24 sites were judged eligible for participation in a future study after successfully demonstrating their ability to access and produce data of acceptable quality to identify and classify pregnancy-related outcomes and maternal vaccination exposure using the GAIA case definitions.

We found a relatively low level of ascertainment of the vaccination status of the mothers that may have been related to the retrospective nature of the study and the limited resources available. A frequent reason for absence of vaccination records was because receipt of a vaccine during pregnancy is routinely written on mothers' antenatal records or take-home antenatal card, which were not always available in this retrospective assessment that relied on medical records, and in which no contact with the mother was sought. Better mother-baby linkage or additional follow-up during the study would likely increase the number of mothers with a verified vaccination status.

Furthermore, most maternal vaccination cases were classified as Level 3 (68%), i.e. "receipt of vaccination during pregnancy, but no formal recording of immunization available" [19]. Thus, the level of recording needs to be improved considerably. The issue of retrospective vaccination status ascertainment has been previously recognized in vaccine safety investigations. One proposed solution was to prepare a list of events of interest for vaccine safety investigations and routinely ascertain exposure status during hospitalization for patients with a diagnosis that matches this list [23].

We learned that retrospective subject identification required a labor-intensive manual search of archives at most sites, as electronic records were not widely available. In addition, multiple sites indicated that if ICD coding was used, this was often incomplete or inaccurate. Consequently, in this study, ICD codes were not necessarily helpful for subject identification and archives still needed to be searched.

No major problems with interpreting the GAIA case definitions other than those described for stillbirth were identified. Almost half the identified stillbirths could not be classified, due to limitations to the collected data or the case definition. Frequently, information to distinguish between antepartum and intrapartum stillbirth was insufficient (or conflicting). Additionally, some stillbirths could not be classified because not all data for one subject fit into a single level of diagnostic certainty. The GAIA classification of diagnostic certainty for stillbirth could be improved by accepting 'higher level' evidence (e.g. attended deliveries; prenatal ultrasound to detect fetal cardiac activity) at lower levels of diagnostic certainty (that currently require e.g. non-attended deliveries; auscultation to detect fetal cardiac activity). Moreover, the stillbirth case definition requires clarity on how to read the "OR"/"AND"

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combinations within each level of diagnostic certainty, and the part on signs of life. The sensitivity analysis resulted in the classification of only one additional case.

We noted that a mismatch in levels of evidence of different data elements can also arise with the maternal immunization definition, where different levels of evidence of pregnancy are matched with different levels of vaccination evidence.

We are aware of two other studies implementing the GAIA case definitions. A study at a Health and Demographic Surveillance System (HDSS) site in Uganda piloted five maternal and five neonatal GAIA definitions (hypertensive disorders, maternal death, pathways to preterm birth, postpartum hemorrhage and non-reassuring fetal status; congenital anomalies, neonatal death, neonatal infection, preterm birth and stillbirth). From this study, it was concluded that capacity to use the GAIA definitions exists even in settings with very limited resources, although heterogeneity by type of health facility existed [24,25]. Results were presented at a conference, so details were limited [24]. Another study evaluating whether cases from routine care and clinical trials can be classified according to 10 GAIA definitions in high income settings is ongoing [24].

Our feasibility assessment presents several limitations. Due to time constraints, no automated logical checks were included in the CRFs, which may have affected data quality and, indirectly, the proportion of identified classifiable cases. Similarly, only a few sites were contacted for data clarification and cleaning purposes when illogical data entries were found. Logical checks will be essential in future studies, to ensure data quality. Furthermore, as this was a feasibility assessment, a maximum of three subjects per pregnancy outcome per site were included, therefore, caution is needed when drawing conclusions, e.g. on the percentage of cases classified at each level, especially at site level. In addition, sites may have selected subjects with maximum information for inclusion in the exercise. When the actual study will be conducted and all cases collected during a given period are included, we will have a better reflection of the level of diagnostic certainty to be expected in situations of real-world surveillance. Preliminary sites were not selected to be representative for each country, but were initially chosen based on the criteria described in Suppl_1 (First step in selection). Further site selection following the feasibility assessment was based on data quality (access to sufficiently detailed clinical records); which comes at a cost of reduced generalizability and possibly biasing future surveillance activities to sites with better quality data.

The feasibility assessment was a first step towards identifying sites that could participate in a larger international collaborative study aimed at fully assessing the applicability of the GAIA case definitions in the real-world setting of LMICs and estimating the minimum detectable risk of selected neonatal outcomes in relation to the maternal vaccination status.

To investigate future potential safety signals in a timely manner, adverse events following immunization would need to be resolved with additional studies, and if verified, further prioritized, so that infrastructure can be developed accordingly [12]. This should be done in the context of both pharmacovigilance systems development and maternal, newborn and child health surveillance [12]. The GAIA case definitions, once field tested and validated, can form an integral part of improving data quality and standardization [11]. Field testing and validation of the GAIA case definitions in the real-world setting of LMICs will be important in evaluating their applicability and generalizability in settings where linkage of the necessary information to identify a potential maternal immunization-related safety outcome can be particularly challenging. Such data will also inform about the occurrence rates of those conditions of interest and will allow estimating the required sample size of future active surveillance studies.

5. Conclusion

In this feasibility assessment, the GAIA case definitions for four neonatal outcomes and maternal immunization were successfully piloted in 24 sentinel sites across four WHO regions. These sites have been selected for the pregnancy MCC study. Modification of the GAIA stillbirth definition could help avoid potential misclassification. Retrospective subject identification is resource-intensive, as archives must be searched manually at most of the selected sites. Given the state of most institutions' record-keeping systems in our study, a retrospective study was deemed to be less capable of providing complete case assessments. Also, a retrospective design would limit opportunities to build institutional capacities. In this context, a prospective approach may provide better opportunities to improve institutional data collection and recording systems, including mother-baby data linkage and systematic recording of all vaccinations administered during pregnancy, hence strengthening capacities for public health surveillance activities and research.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the World Health Organization or the US Food and Drug Administration.

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Declarations of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.09.033.

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