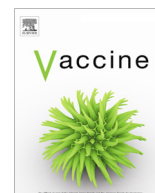Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immunization in pregnancy safety surveillance in low and middle-income countries- field performance and validation of novel case definitions

Sonali Kochhar [a,b,c,*], Ed Clarke [d], Alane Izu [e], Kebonethebe Emmanuel Kekane – Mochwari [e], Clare L. Cutland [e,f]

[a] Global Healthcare Consulting, New Delhi, India
[b] Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[c] Department of Global Health, University of Washington, Seattle, USA
[d] Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, Banjul, Gambia
[e] Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[f] African Leadership in Vaccinology Expertise (ALIVE), Faculty of Health Science, University of the Witwatersrand, South Africa

ARTICLE INFO

ABSTRACT

Background: A globally standardized approach in high and low and middle-income countries (LMIC) to actively monitor the safety of vaccines for pregnant women during development and implementation phases is critical. Brighton Collaboration's (BC) Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project has developed globally standardized case definitions (CDs) of key obstetric and neonatal terms for the assessment of safety of vaccines in pregnancy. CDs are categorized into levels of diagnostic certainty, facilitating their use in varied settings. This study evaluates the field performance of CDs in LMIC.
Methods: Data from pregnant participants of RCTs for trivalent inactivated influenza vaccine conducted at Chris Hani Baragwanath Academic Hospital, South Africa (SA) between 2011 and 2013 were reviewed retrospectively for preterm birth, stillbirth and hypertension CDs and the Gestational age assessment (GA) algorithm. Data from an ongoing pneumococcal vaccine trial (conducted at MRC Unit, The Gambia) were collected prospectively for GA.
Results: For GA, 600 mother-infant dyads from Gambia and 155 mother-infant dyads from SA were reviewed. Level 2B (unsure LMP and US in 2nd trimester) was the most common level seen in Gambia (63%) and level 3B1 (unsure LMP with physical examination) in SA (43%). Preterm deliveries had similar results in SA. The pregnancy-induced hypertension definition performed well, with 96% (54/56) of cases fulfilling 'level 1' for 'preeclampsia with severe features'. 24 stillbirths were identified and 21 records were reviewed; 73.3% (11/15) of the stillbirths classified as antepartum by attending physicians and 83.3% (5/6) of the intrapartum stillbirths did not fulfil the criteria for any level of certainty.
Conclusion: BC CDs for neonatal and maternal outcomes (preterm and hypertension) and GA were sensitive, reliable and feasible to use in RCTs in SA and Gambia. Modifications to the stillbirth CD are required to improve its usefulness in varied settings.

1. Introduction

Immunization in pregnancy is a well-established and effective public health strategy utilized to prevent maternal and neonatal tetanus in low- and middle-income countries (LMIC) [1]. Vaccines for pregnant women against influenza and pertussis infection are currently recommended, predominantly in high-income countries (HIC) [1,2]. Meningococcal vaccines have been used widely in the meningitis belt in Sub-Saharan Africa, including in pregnant women. Immunization of pregnant women may provide protection against infectious diseases for the pregnant women, the fetus

* Corresponding author at: Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.
E-mail address: sonalikochhar@yaahoo.co.in (S. Kochhar).

(through the placental transport of IgG antibodies) and infants too young to receive routine childhood immunization (through passively immunizing infants, via the colostrum and breast milk and indirectly through herd immunity) [1–5]. By preventing infection in the mother, there is also an indirect protective effect of preventing transmission of infection to the infant (cocooning) [5]. This strategy holds enormous promise to reduce vaccine-preventable disease-related morbidity and mortality among pregnant women and young infants [2–5]. This is particularly true in LMIC, where the burden of vaccine-preventable infectious diseases is high and health services access is limited [3,5]. Pregnant women are at increased risk of morbidity and mortality associated with certain infectious diseases e.g. influenza [2]. Pregnancies complicated by infection are at higher risk of adverse pregnancy outcomes, including stillbirth, spontaneous abortion, low birth weight and preterm birth [2–5].

Promising new vaccines are being developed for use during pregnancy including for respiratory syncytial virus, Group B streptococcus, cytomegalovirus and monovalent pertussis [1,3,5]. Despite the potential benefits of immunization in pregnancy, there is still reluctance by some health professionals to offer vaccines, and by pregnant women to receive vaccines [3,6]. The safety of vaccines administered to pregnant women is a key consideration for the women, their families, communities, healthcare providers, researchers, vaccine manufacturers, regulatory bodies and ethics committees [3,5]. A globally harmonized approach to actively monitoring the safety of vaccines used in pregnancy both during the vaccine development and implementation phases is critical [3,7,8]. The sensitive phase immediately post-vaccine licensure, where safety concerns are likely to be seen, while effectiveness data is becoming available [3,8], is a vital time to conduct active safety monitoring, beyond passive surveillance. Harmonized data collection ensures that safety data is comparable, whether it is collected in clinical trials, observational studies or in pharmacovigilance programs in HIC and LMIC. Combining multi-location data sets would enhance the detection of important AEs associated with pregnancy (e.g. preterm birth, stillbirth, neonatal infections, fetal distress, congenital anomalies etc.) [3,5,7]. This will assist in increasing confidence in and the uptake of immunization in pregnant women.

Safety assessment of vaccines for pregnant women requires a real-time assessment of benefit versus risk [3,7]. Knowledge of baseline outcome rates is essential for such assessments. While progress is being made, knowledge of baseline rates of maternal and neonatal outcomes in LMIC remain limited including stillbirth, neonatal death and premature birth [3,8–10]. For example, even if a vaccine decreases premature births by decreasing infections that lead to this AE, these will still occur in pregnancies and may be incorrectly reported as being related to the immunization in pregnancy. This makes early benefit-risk-analyses difficult and may adversely impact an immunization in pregnant women program regardless of whether there is any causal relationship between outcome and immunization. Vaccine manufacturers and regulators need the confidence that adverse events can be identified and documented consistently to determine the safety of vaccines in pregnancy [3,8–10].

Historically, case definitions (CDs) (i.e., a globally harmonized set of criteria for the identification and assessment) of Adverse Events Following Immunisation (AEFI) have not been standardized, which resulted in poor comparability of safety data across vaccine clinical trials and studies in the pre-and post-licensure periods [3,7,8]. In vaccine safety, standardized CDs (which are reliable, and practically implementable in different resource settings) and guidelines for data collection, analysis, and presentation are needed to further improve vaccine safety management, the quality of vaccines and for a comparison and assessment with other vaccines of the frequency and extent of AEFI [11]. This is especially true as new vaccines are developed and introduced to large populations. Reporting details may vary depending upon available resources, and diagnostic facilities in a geographic region, and whether the information is from a clinical trial, epidemiologic study, an individual case report of an AEFI or post-marketing surveillance [7,11,12]. Therefore, CDs and guidelines, if developed for global use, need to accommodate the varying quality of information from different resource settings, given the widely differing availability of tools, trained personnel and data collected to explore an AE and make a diagnosis. Most AEs following pregnancy occur within 48 hours of delivery [13], however, as many as 24% of all births globally and 44% of births in sub-Saharan Africa are not facility-based [14]. Data from delivery-related events, including labor progress, delivery, possible complications and their precipitating events are limited in unattended deliveries.

Global standardization would enable comparability of vaccine safety data collected from HIC and LMIC (including from clinical trials, epidemiologic studies, individual case reports, and surveillance systems). Harmonized vaccine safety research will allow the development of knowledge on the risks of immunization, and enhance trust in immunization programs [7,11,12,15,16]. It is also important to use the harmonized and applicable methodologies (including case definitions and measurement of gestational age) for studying health interventions in pregnancy and monitoring pregnancy outcomes [3].

The Brighton Collaboration (BC) was formed in the year 2000 to help overcome these shortcomings (see https://www.brightoncollaboration.org/). The BC case definitions (CDs) include criteria for the verification of clinical events as "cases", independent from causality assessment of the AEFI [7,12]. BC CDs are evidence-based tools which help to assign diagnostic certainty levels to clinical events in the pre-and post-marketing surveillance of vaccines, in the determination of background rates of particular events in a given population and in measuring safety outcomes both prospectively in randomized clinical trials and also retrospectively through chart or other source document reviews [7,12,15]. BC CDs are designed for diagnosis, monitoring, evaluation and surveillance. They are not intended to guide patient care. The CDs are independent from presumed causality assessment. Based on the availability of personnel, clinical and diagnostic facilities, the diagnoses may be established with a different degree of confidence according to the resources available in different settings [16]. These differences are accounted for in the BC Levels of Diagnostic Certainty which allow for consistent comparisons to be made irrespective of the resources and diagnostics available [7]. Of importance, BC definitions are recommended for use by the World Health Organization (WHO), the United State Food and Drug Administration (US FDA), the US Centers for Disease Control and Prevention (CDC), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and other normative bodies [10].

Ideally, newly developed CDs should be evaluated for their applicability, reliability, specificity and sensitivity in their settings of use. Where CD's evaluation was done, researchers found that small changes in the CD can have a large impact on its sensitivity, the completeness and timeliness of reporting data accurately in clinical trials and surveillance systems, and the CD's appropriateness for use in different resource settings [10,16,17]. There might be concerns that collection of data required for the BC CDs may add additional burden on investigators, and that the CDs may require data not routinely available in routine care or randomized controlled trials (RCTs) in low resource settings. The CDs need to be applicable to both HIC and LMIC, and to achieve the stated purpose,

the CDs need to be shared with the intended stakeholders and implemented in the respective research, surveillance, and country settings [11,12,17,18].

The Bill and Melinda Gates Foundation-funded Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project, was established in response to the WHO call for a globally standardized approach to actively monitor the safety of immunization for pregnant women programs with a specific focus on LMIC needs [3,8]. GAIA project partners have developed a set of 25 globally harmonized CDs of key obstetric and neonatal terms for the assessment of safety of vaccines in pregnant women [3]. Each CD is categorized into multiple diagnostic certainty levels, facilitating their use irrespective of the diagnostic resources available. Enabling terms critical for the obstetric and neonatal CDs were also developed to support investigators using the definitions (e.g. gestational age (GA) assessment algorithm).

WHO's Global Advisory Committee on Vaccine Safety (GACVS) recommended the evaluation and validation of the BC GAIA CDs, guidelines and tools in the context of "real-world" clinical research and observational studies to establish their applicability in LMIC, where they need to be applied [19]. The GAIA CDs have undergone limited field testing, particularly in LMIC [20]. The availability of large data sets through completed and ongoing clinical trials conducted by members of the Immunizing Pregnant women and Infants network (IMPRINT) network provided an ideal platform to assess their field applicability and evaluate and validate them.

This study aimed to evaluate the field performance of novel BC GAIA CDs designed to harmonize safety monitoring for Immunization in Pregnant Women in LMIC. Three BC CDs (preterm birth, stillbirth and hypertension) [21–23] and one enabling term (the GA algorithm) [21] were assessed.

These outcomes were chosen as they are common adverse pregnancy outcomes in low resource settings [24], there was a high incidence of the outcomes in the RCTs, they required GA assessment (a key feature of many of the CDs), or occurred within one month of birth (were more likely to be captured in LMIC settings). Intrapartum and antepartum stillbirth CDs were assessed. The objectives of the study were to assess the applicability (what levels of diagnostic certainty (levels 1–5) can be ascertained in these settings), applicability utilizing the data routinely collected in RCT, feasibility (practicality) of implementation, reliability (specific aspects of the CDs and GA Algorithm are repeatedly interpreted in the same way by different study staff in LMIC), and to systematically analyze discordant cases and to describe issues identified by the clinical staff in applying the BC CDs and GA Algorithm in LMIC research settings in SA and The Gambia.

The results of this study were used to propose edits and suggestions for the improvement of the BC CDs for incorporation in the regular BC review of the CDs as well as recommendations for evidence-based clinical practice.

2. Methods

2.1. Study participants and setting

Participants for this study were pregnant women participating in randomized controlled clinical trials (RCTs) of vaccines during pregnancy in two African countries, South Africa (SA) and The Gambia.

The cohort of South African women utilized as the population from which participants were selected has been described previously [25]. Briefly, HIV-uninfected and HIV-infected pregnant women who were enrolled into RCTs for trivalent inactivated influenza vaccine (NCT01306669, NCT01306682) conducted at the Respiratory and Meningeal Pathogens Research Unit at the Chris Hani

Baragwanath Academic Hospital (CHBAH), Soweto, between 2011 and 2013, were eligible for this study. Medical records and study-specific notes of mother-infant dyads that had at least one of the outcomes of interest were reviewed retrospectively by medical officers or clinical associates.

Women from The Gambia who were participants in an ongoing maternal and neonatal pneumococcal vaccination trial (NCT02628886, start date March 11, 2016) being conducted at MRC Unit, The Gambia at the London School of Hygiene and Tropical Medicine were eligible for the study. Data on gestational age assessment were collected prospectively based on the GA algorithm.

2.2. Study design and case selection

In SA, de-identified data from maternal/ fetal/ neonatal participants of the maternal influenza trials with the specific serious adverse events (preterm birth, stillbirth and hypertension) were extracted by local data managers in the database. Additional variables required for the BC CDs were abstracted from medical notes onto specifically prepared clinical report forms and a REDCap database.

During the clinical trials conducted in Respiratory and Meningeal Pathogens Research Unit, SA, the AE were classified by the medical personnel who attended the delivery, according to standards used in the Obstetrics department. Selected cases in which preterm birth, stillbirth and hypertension were considered to be the final diagnosis were analyzed for sensitivity against the BC GAIA CDs. In the RCTs conducted in SA, gestational age was assessed using an algorithm which included symphysis-fundal height (SFH), last menstrual period (LMP) and if available, ultrasound GA assessment. Ultrasound assessment of gestational age was not offered routinely in SA due to resource constraints. Gestational age was determined at the time of enrollment into the vaccine trial and was used to determine the fetal gestational age in order to assess the pregnant women's eligibility for the RCT (as vaccination is administered up to 34 weeks of gestation) and specific outcomes, such as preterm birth. Original trial databases were utilized to identify participants who were diagnosed with at least one of the three outcomes of interest, as recorded by attending health care workers in medical records.

Utilizing the search methods, eligible clinical cases were pooled and verified. Duplicate cases were removed. Only cases with written documentation of a suspected or definite diagnosis were considered eligible for the study.

In The Gambia, data related to the GA algorithm were collected prospectively from the cohort of expectant mothers enrolled in the trial. Ultrasound facilities to determine gestational age were established for the trial within a newly established platform for maternal immunization studies in The Gambia. This aimed to maximise the level of certainty achieved. There are limited ultrasound facilities in the country. Although increasing, such assessments have not routinely been available in public health centres and there is limited availability in private health centres. Symphyseal-Fundal height (SFH) determination is generally done for GA assessment. 600 pregnant women were recruited for the Prevenar 13 maternal vaccination trial (PROPEL) and GA assessment was done for them. Although vaccination was not undertaken until between 28 and 34 weeks gestation, the trial aimed to recruit expectant mothers as early in pregnancy as possible based on the time they initially booked at the government antenatal clinic. Early recruitment aimed to enhance the accuracy and hence level of certainty of the ultrasound-based assessment. Data on SFH both at initial screening and also at the time of vaccination were also collected by trial clinicians. When available, information on LMP was also recorded. Anonymized data related to the GA algorithm collected

by the trial clinical team in The Gambia were double-entered into a validated clinical trial database for analysis.

2.3. Applying the Brighton Collaboration CDs

The databases contained reviewed cases with their unique participant identification numbers (PID) and the respective information on the symptoms and signs of the CDs and the GA algorithm. No personal identifying information of the RCT participants was entered in the databases. The databases were password protected, and access was limited to data entry and analysis personnel only. The data abstraction from medical records for assessment of the level of diagnostic certainty for the CDs and GA algorithm utilizing the BC definitions was done by the researchers (clinical associates, professional nurses, investigators, medical officers) at each site, who had not previously been involved in the routine care of the participants. Independent of each other, they reviewed the medical records in a blinded manner using the structured paper case report form (CRF).

In case of queries, they approached the study investigator at the sites for clarification. The databases were checked for accuracy and completeness with respect to the information on the criteria of the CDs and GA algorithm by the site data manager and statistician.

For quality control purposes, an audit of 5 percent of the files was randomly conducted by the medical officer or clinical associate. The study statistician analyzed the data to ascertain the highest level of certainty achieved by each participant for the relevant definition(s).

In The Gambia, fields required for the determination of the level of certainty of the gestational age assessment were extracted from the clinical trial database and the proportion of participants in whom a given level of certainty had been established determined by the study statistician.

The BC event classification in 5 categories was done as follows
Event meets CD

(1). Level 1: Criteria as specified in the CD
(2). Level 2: Criteria as specified in the CD
(3). Level 3: Criteria as specified in the CD
  Event does not meet CD
(4). Reported case with insufficient evidence to meet the CD
(5). Not a case

2.4. Statistical analysis

In SA, the descriptive statistical analysis of participant demographics included examinations of means, ranges, frequencies, standard deviations, interquartile ranges, and percentages. The statistical packages Stata and R were used.

In The Gambia, the level of certainty related to the assessment of GA, based on the data collected prospectively, was determined for all participants enrolled in the trial. This was compared to the level of certainty which would otherwise have been available to the trial team had data available on the government antenatal card held by the expectant mother been used. The analysis was descriptive and based on the percentage of all participants falling into each category.

2.5. Ethics

The study/trial protocols were reviewed and approved by the applicable institutional review boards/ethics committees (Human Research Ethics Committee (human) of the University of the Witwatersrand, Johannesburg, SA and the Gambia Government/MRC Joint Ethics Committee, The Gambia).

3. Results

In SA, 2 310 maternal participants were enrolled into the maternal influenza trials, 2118 were HIV-uninfected and 194 were HIV-infected. The baseline demographic characteristics and clinical features of South African participants are provided in Table 1. The study results are shown in Tables 2 and 3 and Fig. 1.

For GA assessment, 600 mother-infant dyads from The Gambia and 155 mother-infant dyads from SA were reviewed and level 2B (unsure LMP and US in 2nd trimester) was the most common level seen in The Gambia (63%) and level 3B1 (unsure LMP with physical examination) in SA (43%). Sixty-four premature deliveries were reviewed in SA, 48.6% (31/64) fulfilled GAIA level 3B1 for gestational age assessment (Table 3). Demographic data were reviewed for 89% (57/64) of the premature deliveries (Table 1) as some files were not available for review (as they had been archived off-site or were out of filing room for another study).

In SA, only one mother had a first-trimester ultrasound, which is required for Gestational age assessment Level 1. Second-trimester ultrasounds or first-trimester physical examinations were available for 20.6% (32/155) participants, who fulfilled level 2. Three of these participants were downgraded from Level 2A-1 to Level 2B as the LMP and US did not correlate (≥14 days discrepancy), so 'certain LMP' was amended to 'uncertain LMP'. The majority of cases met criteria according to level 3 (78.7%; 122/155) as there was a lack of access to ultrasound examination in public health care facilities during the Maternal Influenza trial recruitment period and poor patient recall of LMP.

Prospectively collected data related to the assessment of GA were available for 600 participants enrolled in the trial in The Gambia. Based on having a first-trimester ultrasound, 8 of 600 (1.3%) participants had their gestational age assessed in the trial with the highest level of certainty (Level 1). 379 of 600 (63.2%) of participants had a second trimester (14 weeks to < 28 weeks) ultrasound. However, all were assigned a 2B level of certainty in the absence of the certain LMP data required for the higher level 2A level. The remaining 213 participants (35.5%) attained only the lowest level (Level 3B) of certainty based on the defined GA algorithm. While they all had a third-trimester ultrasound, the absence of a certain LMP prevented them from being ascribed the higher 3A certainty level. Classifying the level of certainty achieved based on review of the antenatal card, 517/600 (86.2%) achieved the lowest level of certainty (Level 3B) based on an uncertain LMP and SFH, 71/600 (11.8%) achieved level 3A based on a first trimester physical examination and 12/600 did not have data available to allow classification (Level 4).

Medical records of 56 South African women with 'pregnancy-induced hypertension' were reviewed. Of these women, 96% (54/56) were classified as having 'preeclampsia with severe features, level 1'. The remaining 2 women had 'gestational hypertension level 2'.

There were 24 stillbirths (>28 weeks GA) identified in the participants of the maternal influenza trials [25]. Of these, 87.5% (21/24) files were reviewed for classification using the BC stillbirth definition. Seventy-one percent (15/21) of the stillbirths had evidence of maceration and intrauterine fetal death prior to the onset of labor and were classified as antepartum stillbirths by attending physicians. Of these, 73.3% (11/15) did not fulfil the criteria for any level of certainty and were, therefore 'unclassified antepartum stillbirths'. There were six intrapartum stillbirths, one of whom (16.7%) fulfilled any level of certainty.

All of the 'unclassified' antepartum and intrapartum stillbirths fulfilled all but one criteria for the 'level 2' of certainty. Level 2 required gestational age of stillbirth to fulfil level 1 or 2 for the gestational age requirement; however, all cases were classified as

Table 1
Demographics and baseline clinical features of South African women.

Mother characteristic				
Number of women	Overall HIV- negative N = 2118	Overall HIV- positive N = 194	Hypertension cohort N = 56	Premature delivery cohort N = 57
Mean age (Standard Deviation); years	26.1 (5.3)	28.1 (5.0)	25.5 (5.5)	25.2 (5.2)
Median body mass index (IQR)	27.6 (24.3, 31.7)	27.9 (24.9, 32.0)	29.0 (25.6, 32.6)	26.3 (23.2, 29.6)
Mean gestational age at enrolment (Standard Deviation); weeks	27.0 (23.3, 31.0)	27.6 (24.9, 30.7)	27.0 (22.7, 30.7)	26.9 (22.4, 31.0)
Median gravidity (IQR)	2.0 (1.0, 3.0)	2.0 (2.0, 3.0)	2.0 (1.0, 2.2)	2.0 (1.0, 2.0)
Median parity (IQR)	1.0 (0.0, 1.0)	1.0 (1.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
Number of twin pregnancies (%)	55 (2.6)	5 (2.6)	NA (NA)	1 (1.8)
Fetal outcomes and newborn characteristics				
Number of fetal outcomes known	N = 2027	N = 183	N = 56	N = 57
Number of normal vaginal deliveries (%)	1399 (69.0)	111 (60.7)	39 (69.6)	39 (68.4)
Number of caesarian section deliveries (%)	628 (31.0)	72 (39.3)	17 (30.4)	18 (31.6)
Number of preterm birth < $37^{0/7}$ (%)	205 (10.1)	25 (13.7)	11 (19.6)	49 (86.0)
Overall median birth weight (range); kilograms	3.1 (2.8, 3.4)	3.0 (2.7, 3.3)	3.0 (2.6, 3.2)	2.1 (1.5, 2.6)
Overall number of low birth weight newborns (%)	255 (12.5)	29 (15.6)	Information not available	Information not available
Number of newborns died after delivery (%)	13 (8.2)	4 (30.8)	0(0)	2 (8.3)
Number of newborns admitted to neonatal nursery (%)	129 (81.6)	9 (69.2)	5 (50.0)	16 (64.0)

Table 2
Gestational age assessment classification using the GAIA definition of mothers enrolled in the Immunisation in Pregnant Women trials in South Africa and The Gambia.

	The Gambia n (%) N = 600	South Africa n (%) N = 155	Overall n (%) N = 755
Level 1–1	0 (0)	0 (0)	0
Level 1–2	8 (1.3)	1 (0.7)	9 (1.2)
Level 2A-1	0	12 (7.7)	12 (1.6)
Level 2A-2	0	5 (3.2)	5 (0.7)
Level 2B	379 (63.2)	15 (9.7)[#]	394 (52.2)
Level 3A-1	0	7 (4.5)	7 (0.9)
Level 3A-2	0	37 (23.9)	37 (4.9)
Level 3A-3	0	3 (1.9)	3 (0.4)
Level 3A-4	0	4 (2.6)[*]	4 (0.5)
Level 3B-1	213 (35.5)	67 (43.2)[$]	280 (37.1)
Level 3B-2	0	0 (0)	0
Level 3B-3	0	4 (2.6)	4 (0.5)

GA assessment levels amended:

[#] 3 moved from Level 2A-1 to Level 2B as there was a discrepancy of >10 days between the EDD calculated using the LMP and EDD calculated using second-trimester ultrasound. 'Certain' LMP amended to 'Uncertain' LMP.

[*] 3 moved from Level 2A-2 to Level 3A-4 as the difference between EDD from LMP and physical examination was >7 days.

[$] 11 moved from 3A to 2 to 3B-1 as the difference between EDD from LMP and 2nd-trimester physical examination was >14 days.

level 3 for GA. All of the unclassified stillbirths were born in a tertiary hospital and therefore did not fulfil the 'non-attended delivery' criteria in level 3 of certainty.

If level 3 of the BC stillbirth CD was modified to allow for attended deliveries, all the 'unclassified' antepartum and intrapartum stillbirths would fulfil level 3 (see Table 4).

3.1. Feasibility and reliability of the CDs

Data variables utilized in the CDs reviewed are routinely recorded by attending medical staff in records from attended deliveries in LMICs, therefore the collection of data for classification of adverse events using the GAIA CDs is feasible and not resource-intensive.

Implementation of the CDs and GA algorithm in Pharmacovigilance reporting in SA and The Gambia, would be feasible, however, the data reporting tools utilized in SA and The Gambia would require some minor modifications to ensure that all required variables are collected. Training of personnel involved in routine PV reporting would ensure that data review and collection are standardized.

There were high levels of reliability and agreement between the clinician's diagnoses and the categorizations according to the BC CD for preterm and hypertension and GA assessment but stillbirths could not be classified easily with the current definition.

3.2. Resources required and CRF completion

The case identification at the sites was primarily done by clinical associate/ clinical officers, physicians, nurses and researchers.
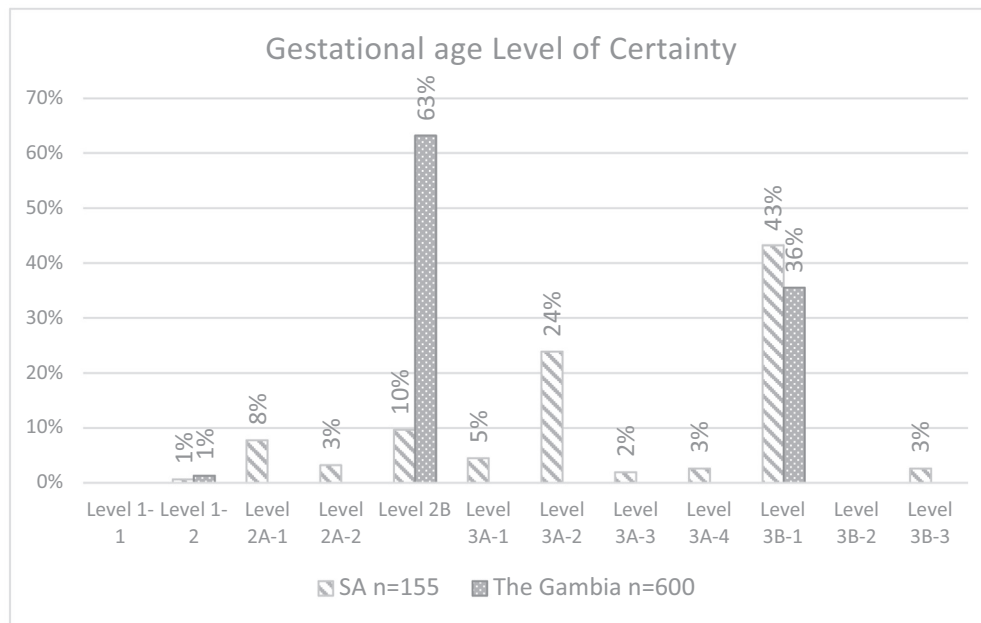
Table 3
Level of certainty for Gestational age attained in preterm infants in South Africa.

Level of certainty achieved	Overall N (%) N = 64	<28 weeks N = 11	28–33 weeks N = 19	34–36 weeks N = 34
Level 1–1	0	0	0	0
Level 1–2	0	0	0	0
Level 2A-1	5 (7.8)	3 (27.2)	2 (10.5)	0
Level 2A-2	1 (1.6)	0	0	1 (2.9)
Level 2B	10 (15.6)	2 (18.2)	5 (26.3)	3 (8.8)
Level 3A-1	2 (3.1)	0	0	2 (5.9)
Level 3A-2	13 (20.3)	3 (27.3)	1 (5.3)	9 (26.5)
Level 3A-3	0	0	0	0
Level 3A-4	2 (3.1)	0	1 (5.3)	1 (2.9)
Level 3B-1	31 (48.4)	3 (27.3)	10 (52.6)	18 (52.9)
Level 3B-2	0	0	0	0
Level 3B-3	0	0	0	0

Fig. 1. Level of certainty distribution for gestational age for pregnant women included in maternal immunisation trials in The Gambia (n = 600) and South Africa (n = 155).

Table 4
Level of certainty for stillbirths from South African Maternal influenza immunisation cohort.

	Antepartum n (%) N = 18	Intrapartum n (%) N = 6	Modified Antepartum #1[*] n (%) N = 18	Modified Intrapartum #1[*] n (%) n = 6	Modified Antepartum #2[$] n (%) N = 18	Modified Intrapartum #2[$] n (%) n = 6
Level 1	5 (27.8)	0	5 (27.8)	0	5 (27.8)	0
Level 2	2 (11.1)	0	2 (11.1)	0	2 (11.1)	0
Level 2A					0	0
Level 2B					11 (61.1)	6 (100)
Level 3	0	0	11 (61.1)	6 (1 0 0)	0	0
Unclassified	11 (61.1)	6 (100)	0	0	0	0

[*] Attended delivery accepted in level 3 of certainty.
[$] Level 2A remains identical to current level 2, Level 2B is identical to current level 2, except GA level 3 is allowed.

The staff needed training on an average for 3 h to be able to understand and utilize the CDs and GA algorithm. Time taken to review the medical records was dependent on the clinical course of disease progression and care of the mother and/ or foetus/ neonate. Once the complete file had been reviewed (10–60 min), completion of the case report form took less than 10 min.

All study staff at the SA and Gambian research centers found the CRFs easy to complete.

4. Discussion

The consistent determination of GA during clinical trials of maternal vaccines as well as within post-implementation pharmacovigilance programmes is essential. The timing of vaccine administration during pregnancy is by definition dependent on having knowledge of the gestational age of the expectant mother. The time window within which the administration of newly licensed maternal vaccines is recommended in the future is likely to be narrow – being based on safety data generated in the tightly regulated clinical trial setting. For this reason, the ability to determine gestational age accurately will become increasingly key to program implementation. Furthermore, the detection of post-implementation safety signals, such as the occurrence of preterm delivery and infants

borne small for gestational age is absolutely dependent on the robustness with which gestational age is initially assessed. The prospective collection of data related to the GA algorithm in a clinical trial in The Gambia highlighted a number of challenges in determining gestational age with the highest degree of certainty, even prospectively. While we aimed to recruit early in pregnancy in order to undertake a first-trimester ultrasound, few women in the trial presented to government antenatal services in the first trimester. Consequently, only a little over 1% of participants had the first-trimester ultrasound required to achieve the highest level of certainty. Of the remaining participants, nearly two-thirds had a second-trimester ultrasound. In The Gambia, it was found that certainty regarding LMP date was uncommon thus reducing the level of certainty otherwise achieved based on the second-trimester ultrasound. In the remaining third of participants, the lowest level of certainty was achieved based on the reliance on the SFH in the third trimester. This is the current primary mechanism of determining gestational age in The Gambia although ultrasound is being gradually phased in. Consequently, the ultrasound markedly enhanced the level of certainty related to gestational age achieved compared to that which would normally be available.

Retrospective case identification required a search through the archived study files, as electronic health records are not commonly available in LMIC. ICD coding, if used, was accurate in identifying

the adverse event, but a manual review of medical records was required to abstract all variables required for CD completion.

The study design showed strengths: several methods (including ICD-10 codes and electronic search with pre-defined terms of the discharge summaries) were used to identify cases. The investigators involved in case ascertainment were independent of those providing clinical care to the study participants and during the data entry and case evaluation were blinded to the discharge diagnosis. The study utilized both prospective and retrospective review of the GA algorithm in clinical trials in LMIC and showed similar sensitivity, reliability and feasibility. The simple study design can be replicated, allowing comparison of clinical data across different settings and countries.

The study limitations include the fact that in a retrospective review of study participants charts, it is not possible to have a complete understanding of the clinician's decision making. Incomplete documentation of data in the records can lead to underreporting of cases.

There were no major issues identified in utilizing the preterm birth and hypertension CDs and the GA algorithm in the retrospective analysis in the RCTs in SA and for the GA algorithm in the prospective analysis in the ongoing RCT in The Gambia.

Seventy-one percent of the identified stillbirths (including antepartum and intrapartum) could not be classified, due to limitations in the CD. The main reason for not classifying stillbirths was that data for a participant did not fit into a level of diagnostic certainty. Although facility-based deliveries have increased in LMICs, resources are still limited to accurately assess GA. The current stillbirth definition does not adequately allow for the classification of facility-based deliveries with level 3 GA. The BC GAIA CD for stillbirth could be improved in order to adequately capture cases with diagnostic certainty, especially in LMIC, where identification of potential immunization in pregnancy-related safety outcomes can be challenging. These CDs could be utilized to determine the background rates of the outcomes of interest in the study population and the sample size of studies for active surveillance. It would also be useful to assess the applicability of the case definitions for observational studies.

A recent publication demonstrated that it was feasible to implement BC GAIA CDs (ten obstetric and neonatal CDs) at sites with very limited resources (one government-funded district hospital and 15 government-accredited health centers at the Health and Demographic Surveillance Site (IMHDSS) in Uganda. IMHDSS consists of 65 villages located 120 km from Kampala). Higher level facilities were able to diagnose higher levels of certainty. Most sites were able to classify cases with at least one level of certainty [26].

5. Conclusion

The diagnosis of preterm birth, hypertension and the enabling term (Gestational Age (GA) Assessment Algorithm) could be made using the BC GAIA CDs in LMICs with high reliability, minimum selection bias and utilizing the data routinely collected in the RCTs in LMIC. The BC GAIA stillbirth definition requires modification to address the issues encountered. A suggestion is to either split level 2 into 2A and 2B, where 2A is identical to current level 2, and level 2B allows for GA level 3; or include attended deliveries in level 3. The second option underestimates the certainty and option 2A/2B is recommended. The BC GAIA CDs are a plausible standard, are easily applicable and useful for capturing a majority of cases of preterm birth, hypertension and Gestational Age (GA) Assessment in clinical trials conducted in LMIC settings in SA and The Gambia. The CDs utilization is an evidence-based method for the ascertainment of cases and can help to improve data quality, comparability, pooling and standardization.

Conflict of interest

None.

References

[1] Giles ML, Krishnaswamy S, Wallace EM. Maternal immunisation: What have been the gains? Where are the gaps? What does the future hold? F1000Res. 2018 1;7. pii: F1000 Faculty Rev-1733. doi: 10.12688/f1000research.15475.1
[2] Swamy Geeta K, Phillips Heine R. Vaccinations for pregnant women. Obstet Gynecol. 2015;125(1):212–26. https://doi.org/10.1097/AOG.0000000000000581.
[3] Kochhar S, Bonhoeffer J, Jones CE, Muñoz FM, Honrado A, Bauwens J, et al. Imunization in pregnancy clinical research in low- and middle-income countries - Study design, regulatory and safety considerations. Vaccine 2017;35:6575–81. https://doi.org/10.1016/j.vaccine.2017.03.103 (48 Pt A).
[4] Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006;12(11):1638–43. https://doi.org/10.3201/eid1211.060152.
[5] Kochhar S, Edwards KM, Ropero-Álvarez AM, Moro PL, Ortiz JR. Introduction of new vaccines for immunization in pregnancy- programmatic, regulatory, safety and ethical considerations. Vaccine 2018. In print.
[6] Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: a literature review. Vaccine 2015;33(47):6420–9. https://doi.org/10.1016/j.vaccine.2015.08.046.
[7] Kochhar S, Bauwens J, Bonhoeffer J. Safety assessment of immunization in pregnancy. Vaccine 2017;35(48):6469–71. https://doi.org/10.1016/j.vaccine.2017.09.033.
[8] Bonhoeffer J, Kochhar S, Hirschfeld S, Heath PT, Jones CE, Bauwens J, et al. Global alignment of immunization safety assessment in pregnancy - The GAIA project. Vaccine 2016;34(49):5993–7. https://doi.org/10.1016/j.vaccine.2016.07.006.
[9] Divala TH, Mungwira RG, Laufer MK. Moving targets: The challenges of studying infectious diseases among pregnant women in resource limited settings. Vaccine 2015;33(47):6401–5. https://doi.org/10.1016/j.vaccine.2015.08.042.
[10] Chen RT, Moro PL, Bauwens J, Bonhoeffer J. Obstetrical and neonatal case definitions for immunization safety data. Vaccine 2016;34(49):5991–2. https://doi.org/10.1016/j.vaccine.2016.08.026.
[11] Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H et al. The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Henriksen K, Battles JB, Marks ES, et al. editors. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005.
[12] Kohl KS, Gidudu J, Bonhoeffer J, Braun MM, Buettcher M, Chen RT, et al. The development of standardized case definitions and guidelines for adverse events following immunization. Vaccine 2007;25(31):5671–4. https://doi.org/10.1016/j.vaccine.2007.02.063.
[13] Regan AK, Tracey L, Blyth CC, Mak DB, Richmond PC, Shellam G, et al. A prospective cohort study comparing the reactogenicity of trivalent influenza vaccine in pregnant and non-pregnant women. BMC Pregnancy Childbirth 2015;15:61. https://doi.org/10.1186/s12884-015-0495-2.
[14] Delivery care. UNICEF Data, June 2018. Accessed on Dec 4th 2018 at https://data.unicef.org/topic/maternal-health/delivery-care/

[15] Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiol Drug Saf 2003;12(4):335–40. https://doi.org/10.1002/pds.851.

[16] Rath B, Magnus M, Heininger U. Evaluating the Brighton Collaboration case definitions, aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis, by systematic analysis of 255 clinical cases. Vaccine 2010;28(19):3488–95. https://doi.org/10.1016/j.vaccine.2010.02.053.

[17] Bates DW, Buchwad D, Lee J, Kith P, Doolittle TH, Umali P, et al. A comparison of case definitions of chronic fatigue syndrome. Clin Infect Dis 1994;18(Suppl 1):S11–5. PMID: 8148436.

[18] Kamaroff AL, Fagioli LR, Geiger AM, Doolittle TH, Lee J, Kornish RJ, et al. An examination of the working case definition of chronic fatigue syndrome. Am J Med 1996;100(56–64):18.

[19] Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project. WHO Global Vaccine Safety. Accessed at https://www.who.int/vaccine_safety/committee/topics/pregnancy/Jul_2016_gaia_project/en/ on December 4th, 2018 at http://www.who.int/vaccine_safety/committee/topics/pregnancy/Jul_2016_gaia_project/en/

[20] Maternal Immunization Safety Monitoring in Low- and Middle-Income Countries: A Roadmap for Program Development. Accessed on December 8th 2018 at https://www.gapps.org/PDF/MaternalImmunizationSafetyMonitoringInLMICs.pdf

[21] Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine 2016;34(49):6047–56. https://doi.org/10.1016/j.vaccine.2016.03.045.

[22] Tavares Da Silva F, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, et al. definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine 2016;34(49):6057–68. https://doi.org/10.1016/j.vaccine.2016.03.044.

[23] Rouse CE, Eckert LO, Wylie BJ, Lyell DJ, Jeyabalan A, Kochhar S, et al. Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016;34(49):6069–76. https://doi.org/10.1016/j.vaccine.2016.03.038.

[24] Padhi BK, Baker KK, Dutta A, Cumming O, Freeman MC, Satpathy R, et al. Risk of adverse pregnancy outcomes among women practicing poor sanitation in rural india: a population-based prospective cohort study. PLoS Med 2015;12(7):e1001851. https://doi.org/10.1371/journal.pmed.1001851.

[25] Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(10):918–31. https://doi.org/10.1056/NEJMoa1401480.

[26] Stark JH, Wool E, Tran L, Robinson E, Chemelski M, Weibel D, et al. Assessing feasibility of resources at health facilities in Uganda to diagnose pregnancy and neonatal outcomes. Int Health 2018. https://doi.org/10.1093/inthealth/ihy066.