Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide

Preterm Birth and Assessment of Gestational Age

V1.0 – 27 October 2022

Authors: Sonali Kochhar

Nature: Report | Diss. level: Public

TABLE OF CONTENTS

DOCUMENT INFORMATION 2

DOCUMENT HISTORY 3

DEFINITIONS & ACRONYMS 4

1. BACKGROUND 5
3. METHODS 5
4. RESULTS 6
5. RECOMMENDATIONS & DISCUSSION 7
6. REFERENCES 7

APPENDIXES:

APPENDIX 1 15
APPENDIX 2 21
APPENDIX 3 24
APPENDIX 4 29
APPENDIX 5 36
APPENDIX 6 45

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DOCUMENT INFORMATION

Main Author(s)	Sonali Kochhar Barbara Law	E-mail: sonalikochhar@yahoo.co.in E-mail: barbara.law@cepi.net
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Description of the deliverable	This deliverable collates into a single document the SPEAC Preterm Birth resources (risk factors, background rates, ICD9/10-CM, MedDRA and SNOMED codes), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess Gestational Age at birth and the occurrence of Preterm Birth in several settings including as an adverse event following immunization.
Key words	Preterm Birth, Gestational age, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, SNOMED, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.5.2.2 Preterm Birth and assessment of gestational age Companion Guide	25 October 2022	1.0	Sonali Kochhar	

DEFINITIONS & ACRONYMS

AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
ART	Assisted reproductive technology
BC	Brighton Collaboration
CD	Case Definition
CDCP	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence Interval
CT	Computed Tomography
CUI	Concept Unique Identifier
FH	Fundal height
GA	Gestational Age
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
LMIC	Lower- or Middle-Income Country
LMP	Last Menstrual Period
LOC	Level of Certainty
MedDRA	Medical Dictionary for Regulatory Activities
SPEAC	Safety Platform for Emergency Vaccines
UI	Uncertainty interval/ confidence interval
UMLS	Unified Medical Language System
US	Ultrasound scan
VAERS	Vaccine Adverse Event Reporting System

INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.

All tools and resources noted above are compiled together into a companion guide for each Brighton AESI case definition. That is the purpose of this deliverable, which focuses on Preterm Birth.

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for Preterm Birth.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Preterm Birth Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Preterm Birth Background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Preterm Birth and Assessment of Gestational Age Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Preterm Birth and Assessment of Gestational Age Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. A new feature of this and future Companion Guides is that a systematic search was done for risk factors and background rates. The methods section in Appendix 6 has been amended to include the new approach and specific search strategy used.

4. Results

4.1 Systematic Search for Background incidence and Risk Factors

A total of 1015 articles were retrieved as per the search strategy mentioned, reviewing references of shortlisted articles and articles identified after expert consultation, of which 868 articles were screened out as they were non-contributory to risk factors or general population background incidence, focused on treatment, diagnosis or prevention, and duplicates. Of 147 articles screened in for full text review, further screening eliminated 49 publications that either didn't provide incidence data or risk factors. 98 articles provided original source data, all of which were included.

The preterm birth background rates determined from Chawanpaiboon S *et al*[7] and Global and Country-Level Preterm Birth Estimate[8] were found to be the most comprehensive references (identified after expert consultation) for preterm birth background rates.

The search strategy for the Chawanpaiboon S *et al* paper was as follows-

A systematic review was done for data on preterm birth for 194 WHO Member States from 1990 to 2014 in databases of national civil registration and vital statistics (CRVS). A search was also done for population-representative surveys and research studies for countries with no or limited CRVS data. A systematic review was also done, searching MEDLINE, Embase, Popline, Global Index Medicus, CINAHL, PsychInfo, and the Cochrane Central Register of Controlled Trials for articles with data for preterm birth. Given the large population in China (where national data on preterm birth are not reported), Sinomed, a Chinese language database was also searched, restricted to the six most highly cited medical journals. All searches were done without language restrictions.

For 38 countries with high-quality data for preterm births in 2014, data are reported directly. For countries with at least three data points between 1990 and 2014, a linear mixed regression model was used to estimate preterm birth rates. The regional and global estimates of preterm birth for 2014 were also estimated. 1241 data points across 107 countries were identified. Additional details of the search strategy are available at https://www.thelancet.com/cms/10.1016/S2214-109X(18)30451-0/attachment/3b7a79c8-b16f-410c-a7c7-3b3039631e52/mmc1.pdf

All outputs are provided in separate appendices as shown below:

1. Preterm Birth Diagnostic Codes: ICD-9-CM, ICD-10-CM, MedDRA, and SNOMEDCT-US
2. Preterm Birth background rates
3. Preterm Birth Risk Factors
4. Preterm Birth and assessment of gestational age case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
5. Preterm Birth and assessment of gestational age data abstraction and interpretation forms with algorithms for assessing level of certainty.
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Preterm Birth including: ICD-9/10-CM, SNOMED and MedDRA codes for data entry or database searching; background rates; risk factors; guidance for real time investigation; and tools for collecting and interpreting clinical data to apply the Brighton Preterm Birth case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used to assign level of certainty for all identified AEFI with features of Preterm Birth. This standard, harmonized approach will facilitate signal detection and assessment, epidemiologic studies of background incidence, hypothesis testing for causality and capacity to combine data across trials for meta-analyses.

6. References

1. Quinn J-A, Munoz FM, Gonik B et al. Preterm Birth: Case definition & guidelines for data collection, analysis and presentation of immunization safety data. Vaccine 2016; 34:6047-6056. http://dx.doi.org/10.1016/j.vaccine.2016.03.045
2. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. Doi:10.1002/pds.4245
3. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic types for reducing conceptual complexity. Studies Health Technology Information, 2001 84(Pt 1): 216-20. PMID: 11604736; PMCID: PMC4300099.
4. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
5. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. Doi: 10.2165/00002018-199920020-00002.
6. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second Biocreative Challenge Evaluation Workshop., 2007. 131–133.
7. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, Landoulsi S, Jampathong N, Kongwattanakul K, Laopaiboon M, Lewis C, Rattanakanokchai S, Teng DN, Thinkhamrop J, Watananirun K, Zhang J, Zhou W, Gülmezoglu AM. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019 Jan;7(1):e37-e46. doi: 10.1016/S2214-109X(18)30451-0. PMCID: PMC6293055.
8. Global and Country-Level Preterm Birth Estimate. Accessed on 30 July 2022 at https://www.efcni.org/wp-content/uploads/2018/11/WPD2018-Annex-B-PTB-Estimates-FINAL-2Nov2018.pdf
9. Laelago T, Yohannes T, Tsige G. Determinants of preterm birth among mothers who gave birth in East Africa: systematic review and meta-analysis. Ital J Pediatr. 2020;46(1):10. doi: 10.1186/s13052-020-0772-1. PMID: 31992346; PMCID: PMC6988288.
10. Chang YK, Tseng YT, Chen KT. The epidemiologic characteristics and associated risk factors of preterm birth from 2004 to 2013 in Taiwan. BMC Pregnancy Childbirth. 2020;20(1):201. doi: 10.1186/s12884-020-02903-1. PMID: 32252663; PMCID: PMC7137208.
11. Keiser AM, Salinas YD, DeWan AT, Hawley NL, Donohue PK, Strobino DM. Risks of preterm birth among non-Hispanic black and non-Hispanic white women: Effect modification by maternal age. Paediatr

Perinat Epidemiol. 2019;33(5):346-356. doi: 10.1111/ppe.12572. PMID: 31365156; PMCID: PMC6993282.

12 Zini ME, Omo-Aghoja LO. Clinical and sociodemographic correlates of preterm deliveries in two tertiary hospitals in southern Nigeria. Ghana Med J. 2019;53(1):20-28. doi: 10.4314/gmj.v53i1.4. PMID: 31138940; PMCID: PMC6527821

13. Hassoune S, Tsoumbou Bakana G, Boussouf N, Nani S. Magnitude of prematurity in the countries of the Great Maghreb. Tunis Med. 2018;96(10-11):628-635. PMID: 30746655

14.Stylianou-Riga P, Kouis P, Kinni P, Rigas A, Papadouri T, Yiallouros PK, Theodorou M. Maternal socioeconomic factors and the risk of premature birth and low birth weight in Cyprus: a case-control study. Reprod Health. 2018;15(1):157. doi: 10.1186/s12978-018-0603-7. PMID: 30231873; PMCID: PMC6146509

15. Kahveci B, Melekoglu R, Evruke IC, Cetin C. The effect of advanced maternal age on perinatal outcomes in nulliparous singleton pregnancies. BMC Pregnancy Childbirth. 2018;18(1):343. doi: 10.1186/s12884-018-1984-x. PMID: 30134873; PMCID: PMC6106883.

16. Sendeku FW, Beyene FY, Tesfu AA, Bante SA, Azeze GG. Preterm birth and its associated factors in Ethiopia: a systematic review and meta-analysis. Afr Health Sci. 2021;21(3):1321-1333. doi: 10.4314/ahs.v21i3.43. PMID: 35222597; PMCID: PMC8843273.

17. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84. doi: 10.1016/S0140-6736(08)60074-4. PMID: 18177778; PMCID: PMC7134569

18. Pusdekar YV, Patel AB, Kurhe KG, Bhargav SR, Thorsten V, Garces A, Goldenberg RL, Goudar SS, Saleem S, Esamai F, Chomba E, Bauserman M, Bose CL, Liechty EA, Krebs NF, Derman RJ, Carlo WA, Koso-Thomas M, Nolen TL, McClure EM, Hibberd PL. Rates and risk factors for preterm birth and low birthweight in the global network sites in six low- and low middle-income countries. Reprod Health. 2020;17(Suppl 3):187. doi: 10.1186/s12978-020-01029-z. PMID: 33334356; PMCID: PMC7745351.

19. Baldewsingh GK, Jubitana BC, van Eer ED, Shankar A, Hindori-Mohangoo AD, Covert HH, Shi L, Lichtveld MY, Zijlmans CWR. Adequate antenatal care and ethnicity affect preterm birth in pregnant women living in the tropical rainforest of Suriname. BMC Pregnancy Childbirth. 2020;20(1):683. doi: 10.1186/s12884-020-03364-2. PMID: 33176728; PMCID: PMC7656737

20. Koullali, B., van Zijl, M.D., Kazemier, B.M. *et al.* The association between parity and spontaneous preterm birth: a population-based study. *BMC Pregnancy Childbirth* 20, 233 (2020). https://doi.org/10.1186/s12884-020-02940-w

21. Shaikh K, Premji SS, Lalani S, Forcheh N, Dosani A, Yim IS, Samia P, Naugler C, Letourneau N; Maternal Infant Global Health Team (MiGHT) Collaborators in Research. Ethnic disparity and exposure to supplements rather than adverse childhood experiences linked to preterm birth in Pakistani women. J Affect Disord. 2020; 267:49-56. doi: 10.1016/j.jad.2020.01.180. PMID: 32063572

22. Blondel B, Kogan MD, Alexander GR, Dattani N, Kramer MS, Macfarlane A et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. Am J Public Health 2002;92:1323–30.

23. Fetene G, Tesfaye T, Negesse Y, Dulla D. Factors associated with preterm birth among mothers who gave birth at public Hospitals in Sidama regional state, Southeast Ethiopia: Unmatched case-control study. PLoS One. 2022;17(4):e0265594. doi: 10.1371/journal.pone.0265594. PMID: 35442955; PMCID: PMC9020679

24. Murray SR, Stock SJ, Cowan S, Cooper ES, Norman JE. Spontaneous preterm birth prevention in multiple pregnancy. Obstet Gynaecol. 2018 Jan;20(1):57-63. doi: 10.1111/tog.12460. Epub 2018 Jan 28. PMID: 30008614; PMCID: PMC6034359.

25. Berger R, Rath W, Abele H, Garnier Y, Kuon RJ, Maul H. Reducing the Risk of Preterm Birth by Ambulatory Risk Factor Management. Dtsch Arztebl Int. 2019; 116(50):858-864. doi: 10.3238/arztebl.2019.0858. PMID: 31931955; PMCID: PMC6970314.

26. Lee KJ, Yoo J, Kim YH, Kim SH, Kim SC, Kim YH, Kwak DW, Kil K, Park MH, Park H, Shim JY, Son GH, Lee KA, Oh SY, Oh KJ, Cho GJ, Shim SY, Cho SJ, Cho HY, Cha HH, Choi SK, Hwang JY, Hwang HS, Kwon EJ, Kim YJ; KOrean Preterm collaboratE Network (KOPEN) Working Group. The Clinical Usefulness of Predictive Models for Preterm Birth with Potential Benefits: A KOrean Preterm collaboratE Network (KOPEN) Registry-Linked Data-Based Cohort Study. Int J Med Sci. 2020;17(1):1-12. doi: 10.7150/ijms.37626. PMID: 31929733; PMCID: PMC6945556.
27. Grétarsdóttir ÁS, Aspelund T, Steingrímsdóttir Þ, Bjarnadóttir RI, Einarsdóttir K. Preterm births in Iceland 1997-2016: Preterm birth rates by gestational age groups and type of preterm birth. Birth. 2020 Mar;47(1):105-114. doi: 10.1111/birt.12467. PMID: 31746027.
28. Lyndon A, Baer RJ, Gay CL, El Ayadi AM, Lee HC, Jelliffe-Pawlowski L. A population-based study to identify the prevalence and correlates of the dual burden of severe maternal morbidity and preterm birth in California. J Matern Fetal Neonatal Med. 2021;34(8):1198-1206. doi: 10.1080/14767058.2019.1628941. PMID: 31170837.
29. Stock S, Norman J. Preterm and term labour in multiple pregnancies. Semin Fetal Neonatal Med. 2010 Dec;15(6):336-41. doi: 10.1016/j.siny.2010.06.006. PMID: 20643592.
30. Goldenberg RL, Andrews WW, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006 Sep;195(3):792-6. doi: 10.1016/j.ajog.2006.05.050. PMID: 16846583.
31. Regasa MT, Hinkosa L, Besho M, Bekele T, Bekuma TT, Tsegaye R, Hirko GF, Markos J, Wakgari A. Predictors of preterm birth in Western Ethiopia: A case control study. PLoS One. 2021;16(4):e0247927. doi: 10.1371/journal.pone.0247927. PMID: 33826631; PMCID: PMC8026033.
32. Hiersch L, Pasternak Y, Melamed N, Meshulam M, Shashar R, Hadar E, Aviram A, Yogev Y, Ashwal E. The Risk of Preterm Birth in Women with Three Consecutive Deliveries-The Effect of Number and Type of Prior Preterm Births. J Clin Med. 2020;9(12):3933. doi: 10.3390/jcm9123933. PMID: 33291626; PMCID: PMC7761894
33. Kalengo NH, Sanga LA, Philemon RN, Obure J, Mahande MJ. Recurrence rate of preterm birth and associated factors among women who delivered at Kilimanjaro Christian Medical Centre in Northern Tanzania: A registry-based cohort study. PLoS One. 2020 Sep 14;15(9):e0239037. doi: 10.1371/journal.pone.0239037. PMID: 32925974; PMCID: PMC7489548.
34. Tingleff T, Vikanes Å, Räisänen S, Sandvik L, Murzakanova G, Laine K. Risk of preterm birth in relation to history of preterm birth: a population-based registry study of 213335 women in Norway. BJOG. 2022;129(6):900-907. doi: 10.1111/1471-0528.17013. PMID: 34775676.
35. Seyama R, Makino S, Nojiri S, Takeda J, Suzuki T, Maruyama Y, Takeda S, Itakura A. Retrospective study of the recurrence risk of preterm birth in Japan. J Matern Fetal Neonatal Med. 2022 ;35(3):515-519. doi: 10.1080/14767058.2020.1727435. Epub 2020 Feb 18. PMID: 32068466.
36. Williams TC, Drake AJ. Preterm birth in evolutionary context: a predictive adaptive response? Philos Trans R Soc Lond B Biol Sci. 2019;374(1770):20180121. doi: 10.1098/rstb.2018.0121. PMID: 30966892; PMCID: PMC6460087.
37. Wolnicki BG, von Wedel F, Mouzakiti N, Al Naimi A, Herzeg A, Bahlmann F, Kyvernitakis I. Combined treatment of McDonald cerclage and Arabin-pessary: a chance in the prevention of spontaneous preterm birth? J Matern Fetal Neonatal Med. 2020;33(19):3249-3257. doi: 10.1080/14767058.2019.1570123. PMID: 30700183.
38. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, Caritis SN, Miodovnik M, Menard MK, Thurnau GR, Dombrowski MP, Roberts JM, McNellis D. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999;181(5 Pt 1):1216-21. doi: 10.1016/s0002-9378(99)70111-0. PMID: 10561648.
39. Brhane M, Hagos B, Abrha MW, Weldearegay HG. Does short inter-pregnancy interval predicts the risk of preterm birth in Northern Ethiopia? BMC Res Notes. 2019;12(1):405. doi: 10.1186/s13104-019-4439-1. PMID: 31307529; PMCID: PMC6631733.

40. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA. 2006;295(15):1809-23. doi: 10.1001/jama.295.15.1809. PMID: 16622143.
41. Abadiga M, Wakuma B, Oluma A, Fekadu G, Hiko N, Mosisa G. Determinants of preterm birth among women delivered in public hospitals of Western Ethiopia, 2020: Unmatched case-control study. PLoS One. 2021;16(1):e0245825. doi: 10.1371/journal.pone.0245825. PMID: 33493193; PMCID: PMC7833256
42. Marinovich ML, Regan AK, Gissler M, Magnus MC, Håberg SE, Mayo JA, Shaw GM, Bell J, Nassar N, Ball S, Gebremedhin AT, Marston C, de Klerk N, Betrán AP, Padula AM, Pereira G. Associations between interpregnancy interval and preterm birth by previous preterm birth status in four high-income countries: a cohort study. BJOG. 2021;128(7):1134-1143. doi: 10.1111/1471-0528.16606. PMID: 33232573.
43. Williams C, Fong R, Murray SM, Stock SJ. Caesarean birth and risk of subsequent preterm birth: a retrospective cohort study. BJOG. 2021;128(6):1020-1028. doi: 10.1111/1471-0528.16566. PMID: 33043563.
44. Pervin J, Rahman SM, Rahman M, Aktar S, Rahman A. Association between antenatal care visit and preterm birth: a cohort study in rural Bangladesh. BMJ Open. 2020;10(7):e036699. doi: 10.1136/bmjopen-2019-036699. PMID: 32709651; PMCID: PMC7380851
45. Vintzileos AM, Ananth CV, Smulian JC, Scorza WE, Knuppel RA. The impact of prenatal care in the United States on preterm births in the presence and absence of antenatal high-risk conditions. Am J Obstet Gynecol. 2002;187(5):1254-7. doi: 10.1067/mob.2002.127140. PMID: 12439515.
46. Gurung A, Wrammert J, Sunny AK, Gurung R, Rana N, Basaula YN, Paudel P, Pokhrel A, Kc A. Incidence, risk factors and consequences of preterm birth - findings from a multi-centric observational study for 14 months in Nepal. Arch Public Health. 2020; 78:64. doi: 10.1186/s13690-020-00446-7. PMID: 32695337; PMCID: PMC7368758.
47. Debiec KE, Paul KJ, Mitchell CM, Hitti JE. Inadequate prenatal care and risk of preterm delivery among adolescents: a retrospective study over 10 years. Am J Obstet Gynecol. 2010;203(2):122.e1-6. doi: 10.1016/j.ajog.2010.03.001.
48. Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, Ramsey R, Cotroneo P, Collins BA, Johnson F, Jones P, Meier AM. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1996;175(5):1286-92. doi: 10.1016/s0002-9378(96)70042-x. PMID: 8942502.
49. Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol. 1992;11(1):32-40. doi: 10.1037//0278-6133.11.1.32. PMID: 1559532.
50. Yaya, S., Odusina, E.K., Adjei, N.K. *et al.* Association between intimate partner violence during pregnancy and risk of preterm birth. *BMC Public Health* 21, 1610 (2021). https://doi.org/10.1186/s12889-021-11625-8
51. Barbero P, Mugüerza L, Herraiz I, García Burguillo A, San Juan R, Forcén L, Mejía I, Batllori E, Montañez MD, Vallejo P, Villar O, García Alcazar D, Galindo A. SARS-CoV-2 in pregnancy: characteristics and outcomes of hospitalized and non-hospitalized women due to COVID-19. J Matern Fetal Neonatal Med. 2022;35(14):2648-2654. doi: 10.1080/14767058.2020.1793320. Epub 2020 Jul 20. PMID: 32689846.
52. Dagklis T, Tsakiridis I, Mamopoulos A, Dardavessis T, Athanasiadis A. Modifiable risk factors for spontaneous preterm birth in nulliparous women: a prospective study. J Perinat Med. 2020;48(2):96-101. doi: 10.1515/jpm-2019-0362. PMID: 31851617.
53. Ekwo E, Moawad A. The risk for recurrence of premature births to African-American and white women. J Assoc Acad Minor Phys. 1998;9(1):16-21. PMID: 9585671.

54. Manuck TA. Racial and ethnic differences in preterm birth: A complex, multifactorial problem. Semin Perinatol. 2017;41(8):511-518. doi: 10.1053/j.semperi.2017.08.010. Epub 2017 Sep 21. PMID: 28941962; PMCID: PMC6381592.
55. Smith LK, Draper ES, Manktelow BN, Dorling JS, Field DJ. Socioeconomic inequalities in very preterm birth rates. Arch Dis Child Fetal Neonatal Ed. 2007; 92(1):F11-4. doi: 10.1136/adc.2005.090308. PMID: 16595590; PMCID: PMC2675287.
56. Thompson JM, Irgens LM, Rasmussen S, Daltveit AK. Secular trends in socio-economic status and the implications for preterm birth. Paediatr Perinat Epidemiol. 2006;20(3):182-7. doi: 10.1111/j.1365-3016.2006.00711.x. PMID: 16629692.
57. Farley TA, Mason K, Rice J, Habel JD, Scribner R, Cohen DA. The relationship between the neighbourhood environment and adverse birth outcomes. Paediatr Perinat Epidemiol. 2006;20(3):188-200. doi: 10.1111/j.1365-3016.2006.00719.x. PMID: 16629693.
58. Janevic T, Lieb W, Ibroci E, Lynch J, Lieber M, Molenaar NM, Rommel AS, de Witte L, Ohrn S, Carreño JM, Krammer F, Zapata LB, Snead MC, Brody RI, Jessel RH, Sestito S, Adler A, Afzal O, Gigase F, Missall R, Carrión D, Stone J, Bergink V, Dolan SM, Howell EA; Krammer Serology Core Study Group. The influence of structural racism, pandemic stress, and SARS-CoV-2 infection during pregnancy with adverse birth outcomes. Am J Obstet Gynecol MFM. 2022;4(4):100649. doi: 10.1016/j.ajogmf.2022.100649. PMID: 35462058; PMCID: PMC9022447.
59. Margerison CE, Luo Z, Li Y. Economic conditions during pregnancy and preterm birth: A maternal fixed-effects analysis. Paediatr Perinat Epidemiol. 2019;33(2):154-161. doi: 10.1111/ppe.12534. PMID: 30675915
60. Beyerlein A, Lack N, Maier W. Associations of area-level deprivation with adverse obstetric and perinatal outcomes in Bavaria, Germany: Results from a cross-sectional study. PLoS One. 2020 ;15(7):e0236020. doi: 10.1371/journal.pone.0236020. PMID: 32687491; PMCID: PMC7371156.
61. Mehra R, Shebl FM, Cunningham SD, Magriples U, Barrette E, Herrera C, Kozhimannil KB, Ickovics JR. Area-level deprivation and preterm birth: results from a national, commercially-insured population. BMC Public Health. 2019;19(1):236. doi: 10.1186/s12889-019-6533-7. PMID: 30813938; PMCID: PMC6391769.
62. Cushing L, Morello-Frosch R, Hubbard A. Extreme heat and its association with social disparities in the risk of spontaneous preterm birth. Paediatr Perinat Epidemiol. 2022;36(1):13-22. doi: 10.1111/ppe.12834. PMID: 34951022.
63. Krieger N, Huynh M, Li W, Waterman PD, Van Wye G. Severe sociopolitical stressors and preterm births in New York City: 1 September 2015 to 31 August 2017. J Epidemiol Community Health. 2018 Dec;72(12):1147-1152. doi: 10.1136/jech-2018-211077. PMID: 30327451; PMCID: PMC6252370
64. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. Clin Perinatol. 2011;38(3):351-84. doi: 10.1016/j.clp.2011.06.007. PMID: 21890014; PMCID: PMC3179976.
65. Hidalgo-Lopezosa P, Jiménez-Ruz A, Carmona-Torres JM, Hidalgo-Maestre M, Rodríguez-Borrego MA, López-Soto PJ. Sociodemographic factors associated with preterm birth and low birth weight: A cross-sectional study. Women Birth. 2019;32(6):e538-e543. doi: 10.1016/j.wombi.2019.03.014. PMID: 30979615.
66. Brett KM, Strogatz DS, Savitz DA. Employment, job strain, and preterm delivery among women in North Carolina. Am J Public Health. 1997;87(2):199-204. doi: 10.2105/ajph.87.2.199. PMID: 9103097; PMCID: PMC1380794.
67. Li J, Qiu J, Lv L, Mao B, Huang L, Yang T, Wang C, Liu Q. Paternal factors and adverse birth outcomes in Lanzhou, China. BMC Pregnancy Childbirth. 2021;21(1):19. doi: 10.1186/s12884-020-03492-9. PMID: 33407234; PMCID: PMC7789361
68. Simmons LE, Rubens CE, Darmstadt GL, Gravett MG. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. Semin Perinatol 2010;34:408–15

69. Hamadneh S, Hamadneh J. Active and Passive Maternal Smoking During Pregnancy and Birth Outcomes: A Study From a Developing Country. Ann Glob Health. 2021;87(1):122. doi: 10.5334/aogh.3384. PMID: 34900622; PMCID: PMC8641528.
70. Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin Neonatol. 2000 Aug;5(3):231-41. doi: 10.1053/siny.2000.0025. PMID: 10956448.
71. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res. 2004 Apr;6 Suppl 2:S125-40. doi: 10.1080/14622200410001669187. PMID: 15203816.
72. Lee H, Okunev I, Tranby E, Monopoli M. Different levels of associations between medical co-morbidities and preterm birth outcomes among racial/ethnic women enrolled in Medicaid 2014-2015: retrospective analysis. BMC Pregnancy Childbirth. 2020;20(1):33. doi: 10.1186/s12884-020-2722-8. PMID: 31931778; PMCID: PMC6958731.
73. Nsereko E, Uwase A, Mukabutera A, Muvunyi CM, Rulisa S, Ntirushwa D, Moreland P, Corwin EJ, Santos N, Nzayirambaho M, Wojcicki JM. Maternal genitourinary infections and poor nutritional status increase risk of preterm birth in Gasabo District, Rwanda: a prospective, longitudinal, cohort study. BMC Pregnancy Childbirth. 2020;20(1):345. doi: 10.1186/s12884-020-03037-0. PMID: 32493304; PMCID: PMC7268654.
74. Gete DG, Waller M, Mishra GD. Effects of maternal diets on preterm birth and low birth weight: a systematic review. Br J Nutr. 2020 Feb 28;123(4):446-461. doi: 10.1017/S0007114519002897. Epub 2019 Nov 12. PMID: 31711550.
75. Batura R, Colbourn T. A stitch in time: narrative review of interventions to reduce preterm births in Malawi. Int Health. 2020;12(3):213-221. doi: 10.1093/inthealth/ihz101. PMID: 31867622; PMCID: PMC7320425
76. Tsuji M, Shibata E, Morokuma S, Tanaka R, Senju A, Araki S, Sanefuji M, Koriyama C, Yamamoto M, Ishihara Y, Kusuhara K, Kawamoto T; Japan Environment & Children's Study Group. The association between whole blood concentrations of heavy metals in pregnant women and premature births: The Japan Environment and Children's Study (JECS). Environ Res. 2018;166:562-569. doi: 10.1016/j.envres.2018.06.025. PMID: 29966876.
77. Ciesielski TH, Bartlett J, Williams SM. Omega-3 polyunsaturated fatty acid intake norms and preterm birth rate: a cross-sectional analysis of 184 countries. BMJ Open. 2019;9(4):e027249. doi: 10.1136/bmjopen-2018-027249. PMID: 31005937; PMCID: PMC6527982
78. Gao R, Liu B, Yang W, Wu Y, Snetselaar LG, Santillan MK, Bao W. Association between maternal prepregnancy body mass index and risk of preterm birth in more than 1 million Asian American mothers. J Diabetes. 2020:10.1111/1753-0407.13124. doi: 10.1111/1753-0407.13124. PMID: 33073932; PMCID: PMC8955936.
79. Karasneh RA, Migdady FH, Alzoubi KH, Al-Azzam SI, Khader YS, Nusair MB. Trends in maternal characteristics, and maternal and neonatal outcomes of women with gestational diabetes: A study from Jordan. Ann Med Surg (Lond). 2021 ;67:102469. doi: 10.1016/j.amsu.2021.102469. PMID: 34178318; PMCID: PMC8213882.
80. Fox HK, Callander EJ. Health service use and health system costs associated with diabetes during pregnancy in Australia. Nutr Metab Cardiovasc Dis. 2021;31(5):1427-1433. doi: 10.1016/j.numecd.2021.02.009. Epub 2021 Feb 17. PMID: 33846005
81. Seah JM, Kam NM, Wong L, Tanner C, Shub A, Houlihan C, Ekinci EI. Risk factors for pregnancy outcomes in Type 1 and Type 2 diabetes. Intern Med J. 2021;51(1):78-86. doi: 10.1111/imj.14840. PMID: 32237194.
82. López-de-Andrés A, Perez-Farinos N, Hernández-Barrera V, Palomar-Gallego MA, Carabantes-Alarcón D, Zamorano-León JJ, de Miguel-Diez J, Jimenez-Garcia R. A Population-Based Study of Diabetes During Pregnancy in Spain (2009-2015): Trends in Incidence, Obstetric Interventions, and Pregnancy

Outcomes. J Clin Med. 2020;9(2):582. doi: 10.3390/jcm9020582. PMID: 32098048; PMCID: PMC7074053.
83. Wiles K, Webster P, Seed PT, Bennett-Richards K, Bramham K, Brunskill N, Carr S, Hall M, Khan R, Nelson-Piercy C, Webster LM, Chappell LC, Lightstone L. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. Nephrol Dial Transplant. 2021;36(11):2008-2017. doi: 10.1093/ndt/gfaa247. PMID: 33313680; PMCID: PMC8577624.
84. Miranda-Hernández D, Sánchez A, Sánchez-Briones RE, Rivas-Ruiz R, Cruz-Reynoso L, Cruz-Domínguez P, Jara LJ, Saavedra MÁ. Impact of Systemic Lupus Erythematosus on Pregnancy: Analysis of a Large 10-Year Longitudinal Mexican Cohort. J Clin Rheumatol. 2021;27(6S):S217-S223. doi: 10.1097/RHU.0000000000001626. PMID: 33264243.
85. Abdo RA, Halil HM, Muhammed MA, Karebo MS. Magnitude of Preterm Birth and Its Associated Factors: A Cross-Sectional Study at Butajira Hospital, Southern Nations, Nationalities, and People's Region, Ethiopia. Int J Pediatr. 2020 ;2020:6303062. doi: 10.1155/2020/6303062. PMID: 32577120; PMCID: PMC7305533.
86. Giurgescu C, Fahmy L, Slaughter-Acey J, Nowak A, Caldwell C, Misra DP. Can support from the father of the baby buffer the adverse effects of depressive symptoms on risk of preterm birth in Black families? AIMS Public Health. 2018;5(1):89-98. doi: 10.3934/publichealth.2018.1.89. PMID: 30083571; PMCID: PMC6070463.
87. Mochache K, Mathai M, Gachuno O, Vander Stoep A, Kumar M. Depression during pregnancy and preterm delivery: a prospective cohort study among women attending antenatal clinic at Pumwani Maternity Hospital. Ann Gen Psychiatry. 2018;17:31. doi: 10.1186/s12991-018-0202-6. Erratum in: Ann Gen Psychiatry. 2018;17:41. PMID: 30061917; PMCID: PMC6058385.
88. Orr ST, Miller CA. Maternal depressive symptoms and the risk of poor pregnancy outcome. Review of the literature and preliminary findings. Epidemiol Rev. 1995;17(1):165-71. doi: 10.1093/oxfordjournals.epirev.a036172. PMID: 8521934.
89. Hoffman S, Hatch MC. Stress, social support and pregnancy outcome: a reassessment based on recent research. Paediatr Perinat Epidemiol. 1996 Oct;10(4):380-405. doi: 10.1111/j.1365-3016.1996.tb00063.x. PMID: 8931053.
90. Elenga N, Djossou FÉL, Nacher M. Association between maternal human immunodeficiency virus infection and preterm birth: A matched case-control study from a pregnancy outcome registry. Medicine (Baltimore). 2021;100(4):e22670. doi: 10.1097/MD.0000000000022670. PMID: 33530154; PMCID: PMC7850744.
91. Traisathit P, Mary JY, Le Coeur S, Thantanarat S, Jungpichanvanich S, Pornkitprasarn W, Gomutbutra V, Matanasarawut W, Wannapira W, Lallemant M. Risk factors of preterm delivery in HIV-infected pregnant women receiving zidovudine for the prevention of perinatal HIV. J Obstet Gynaecol Res. 2009;35(2):225-33. doi: 10.1111/j.1447-0756.2008.00925.x. PMID: 19708170.
92. Hurt K, Kodym P, Stejskal D, Zikan M, Mojhova M, Rakovic J. Toxoplasmosis impact on prematurity and low birth weight. PLoS One. 2022;17(1):e0262593. doi: 10.1371/journal.pone.0262593. PMID: 35025961; PMCID: PMC8758008.
93. Young MR, Wall KM, Dude CM, Burdette ER, Jamieson DJ, Ofotokun I, Haddad LB. Trichomonas vaginalis and spontaneous preterm birth in a high-risk obstetric cohort in Atlanta, Georgia. Sex Transm Dis. 2022. doi: 10.1097/OLQ.0000000000001654.
94. Cotch MF, Pastorek JG 2nd, Nugent RP, Hillier SL, Gibbs RS, Martin DH, Eschenbach DA, Edelman R, Carey JC, Regan JA, Krohn MA, Klebanoff MA, Rao AV, Rhoads GG. Trichomonas vaginalis associated with low birth weight and preterm delivery. The Vaginal Infections and Prematurity Study Group. Sex Transm Dis. 1997;24(6):353-60. doi: 10.1097/00007435-199707000-00008. PMID: 9243743.
95. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000;342(20):1500-7. doi: 10.1056/NEJM200005183422007. PMID: 10816189.
96. Mueller-Heubach E, Rubinstein DN, Schwarz SS. Histologic chorioamnionitis and preterm delivery in different patient populations. Obstet Gynecol. 1990 ;75(4):622-6. PMID: 2314782.

97. Doyle TJ, Kiros GE, Schmitt-Matzen EN, Propper R, Thompson A, Phillips-Bell GS. Maternal and perinatal outcomes associated with SARS-CoV-2 infection during pregnancy, Florida, 2020-2021: A retrospective cohort study. Clin Infect Dis. 2022:ciac441. doi: 10.1093/cid/ciac441. Epub ahead of print. PMID: 35675310
98. Carrasco I, Muñoz-Chapuli M, Vigil-Vázquez S, Aguilera-Alonso D, Hernández C, Sánchez-Sánchez C, Oliver C, Riaza M, Pareja M, Sanz O, Pérez-Seoane B, López J, Márquez E, Domínguez-Rodríguez S, Hernanz-Lobo A, De León-Luis JA, Sánchez-Luna M, Navarro ML. SARS-COV-2 infection in pregnant women and newborns in a Spanish cohort (GESNEO-COVID) during the first wave. BMC Pregnancy Childbirth. 2021;21(1):326. doi: 10.1186/s12884-021-03784-8. PMID: 33902483; PMCID: PMC8072086.
99. Marcu EA, Dinescu SN, Pădureanu V, Dumitrescu F, Diaconu R. Perinatal Exposure to HIV Infection: The Experience of Craiova Regional Centre, Romania. Healthcare (Basel). 2022 Feb 6;10(2):308. doi: 10.3390/healthcare10020308. PMID: 35206923; PMCID: PMC8871740.
100. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. PLoS One. 2014 Mar 26;9(3):e92778. doi: 10.1371/journal.pone.0092778. PMID: 24671232; PMCID: PMC3966829.
101. Sujan AC, Rickert ME, Öberg AS, Quinn PD, Hernández-Díaz S, Almqvist C, Lichtenstein P, Larsson H, D'Onofrio BM. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA. 2017;317(15):1553-1562. doi: 10.1001/jama.2017.3413. PMID: 28418479; PMCID: PMC5875187.
102. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. Am J Obstet Gynecol. 2009;201(6):579.e1-8. doi: 10.1016/j.ajog.2009.06.061. PMCID: PMC2881461.
103. Nguyen MH, Fornes R, Kamau N, Danielsson H, Callens S, Fransson E, Engstrand L, Bruyndonckx R, Brusselaers N. Antibiotic use during pregnancy and the risk of preterm birth: a population-based Swedish cohort study. J Antimicrob Chemother. 2022;77(5):1461-1467. doi: 10.1093/jac/dkac053. PMID: 35233608; PMCID: PMC9047673
104. Quantin C, Yamdjieu Ngadeu C, Cottenet J, Escolano S, Bechraoui-Quantin S, Rozenberg P, Tubert-Bitter P, Gouyon JB. Early exposure of pregnant women to non-steroidal anti-inflammatory drugs delivered outside hospitals and preterm birth risk: nationwide cohort study. BJOG. 2021;128(10):1575-1584. doi: 10.1111/1471-0528.16670. PMID: 33590634; PMCID: PMC8451913.

APPENDIX 1

Preterm Birth Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMED

1.1 Preterm Birth Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMEDCT

TABLE 1. NARROW TERMS FOR PRETERM BIRTH

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0270078	Extreme immaturity		10015873	765.0	P07.2	206170008 276658003 47243004
C2909141	Preterm labor with preterm delivery	Preterm labor with preterm delivery Preterm labor with delivery NOS			O60.1 O60.10	10761241000119104
C3264531	Extreme immaturity of newborn, gestational age less than 23 completed weeks				P07.21	
C3264533	Extreme immaturity of newborn, gestational age 23 completed weeks				P07.22	
C2909943	Extreme immaturity of newborn, gestational age 24 completed weeks				P07.23	
C3264536	Extreme immaturity of newborn, gestational age 25 completed weeks				P07.24	
C3264538	Extreme immaturity of newborn, gestational age 26 completed weeks				P07.25	
C3264540	Extreme immaturity of newborn, gestational age 27 completed weeks				P07.26	
C2909940	Extreme immaturity of newborn, unspecified weeks of gestation				P07.20	
C1135244	29-30 weeks of gestation completed			765.25		
C1135245	31-32 weeks of gestation completed			765.26		
C1135246	33-34 weeks of gestation completed			765.27		
C1135247	35-36 weeks of gestation completed			765.28		
C0156718	Early onset of delivery, unspecified as to episode of care or not applicable	Early onset of delivery, unspecified as to episode of care	10014051	644.20		
C0156719	Early onset of delivery, delivered, with or without mention of antepartum condition		10014050	644.21		
C4302273	Baby premature at delivery less than 23 weeks					722839000

C4302272	Baby premature at delivery 23 completed weeks				722840003
C4076153	Baby premature 24 weeks				15887011000119107
C4076156	Baby premature 25 weeks				15887051000119108
C4076147	Baby premature 26 weeks				15887091000119103
C0588032	Baby premature 24-26 weeks				147086007 169854002 310523002
C1328472	Premature baby less than 26 weeks	10062694			890097003
C4076148	Baby premature 27 weeks				15887131000119101
C4076145	Baby premature 28 weeks				15750001000119103
C0236153	Baby 28 weeks plus under 2.5 kg	10003967			
C1096450	Premature baby 26 to 32 weeks	10053593			
C0560306	Baby premature 26-28 weeks				147085006 169853008 310548004
C0411095	Very premature - less than 1000g or less than 28 weeks				268817004
C4076124	Baby premature 29 weeks				15750041000119101
C4076129	Baby premature 30 weeks				15750081000119106
C0419395	Baby extremely premature 28-32 weeks				147082009 169851005
C4039527	Baby premature 28-32 weeks				710235005
C4076108	Baby premature 31 weeks				15635451000119107
C4076107	Baby premature 32 weeks				15635411000119106
C4076122	Baby premature 33 weeks				15635371000119105
C4076114	Baby premature 34 weeks				15635331000119107
C4075960	Baby premature 35 weeks				15635291000119101
C0419394	Baby very premature 32-36 weeks				147081002 169850006
C4039390	Baby premature 32-36 weeks				710068006

C1096451	Premature baby 33 -36 weeks		10053594			
C3494730	Baby premature 35-36 weeks					429151000124100
C0419393	Baby premature 36-38 weeks					147080001 169849006
C0588039	Baby premature 36 weeks					147090009 169858004 310530008
C0588038	Baby premature 37 weeks					147089000 169857009 310529003
C0588225	Premature infant 28-37 weeks					206177006 310661005
C0411096	Premature - weight 1000g-2499g or gestation of 28-37weeks					206169007
C0588037	Baby premature 38 weeks					147088008 169856000 310528006
C0588036	Baby premature 39 weeks					147087003 169855001 310527001
C0411097	Born premature NOS	Born premature (non-specific)				157082002 206178001
C0411094	Short gestation and unspecified low birth weight problems					268816008
C0565824	Born very premature	Very preterm maturity of infant				157081009 268868001
C0029713	Other preterm infants	Other preterm Infants Other preterm infants, unspecified [weight]	10032405 10032415	765.1 765.10	P07.3	206621008
C0158905	Other preterm infants, less than 500 grams		10032414	765.11		
C4749941	Moderate to late prematurity of infant					77150700

C0405150	Early onset of delivery - delivered				199058005
C0405151	Early onset of delivery unspecified				199057000
C0233317	Premature birth of newborn female				59403008
C0233316	Premature birth of newborn male				4886009
C4510690	Preterm delivery following Cesarean section				724489002
C4510830	Preterm delivery following induction of labor				724488005

TABLE 2. TERMS RELATED TO CASE DEFINATION

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0151526	Preterm delivery Delivery: [early onset] or [premature] Early onset of delivery NOS Early onset of delivery Premature delivery Premature pregnancy delivered	Premature Birth	10004953 10014049 10036594 10036595	644.2	O60	 199056009 199059002 270496001 282020008 49550006
C2909931	Other low birth weight new born				P07.1	
C2909939	Extreme immaturity of new born				P07.2	
C0021294	Premature baby Preterm infant	Infant, Premature	10003969 10021410 10021734 10036590		P07.3	147079004 169848003 157080005

	Baby born premature Immature baby Premature infant Prematurity of infant		10036615			206167009 206168004 395507008 771299009
C0233315	Premature birth of newborn					367494004 65588006
C0728731	Prematurity	Prematurity of fetus				44247006

APPENDIX 2

Preterm Birth Background Rates

TABLE 2.1 Top ten countries for number of preterm births[@] in 2014[7,8]

	Estimated number of preterm births (UI)[$]	Estimated number of livebirths	Estimated proportion of global livebirths (%)	Preterm birth rate (%, UI) [#]	Proportion of global preterm births (%)
India[*]	3 519 947 (2 872 618–4 165 975)	25 860 462	18·5%	13·6 (11·1–16·1)	23·4%
China[*]	1 168 126 (978 578–1 333 121)	16 826 493	12·0%	6·9 (5·8–7·9)	7·8%
Nigeria[*]	803 178 (563 907–1 107 550)	7 033 430	5·0%	11·4 (8·0–15·7)	5·3%
Bangladesh[*]	603 698 (416 079–825 413)	3 152 549	2·3%	19·1 (13·2–26·2)	4·0%
Indonesia[†]	527 672 (442 389–604 295)	5 072 689	3·6%	10·4 (8·7–11·9)	3·5%
Pakistan[*]	454 104 (300 768–645 911)	5 415 657	3·9%	8·4 (5·6–11·9)	3·0%
USA[‡]	383 257 (NA–NA)	4 008 329	2·9%	9·6 (NA–NA)	2·6%
Ethiopia[†]	376 730 (269 757–525 862)	3 148 388	2·2%	12·0 (8·6–16·7)	2·5%
Brazil[‡]	339 239 (NA–NA)	3 035 148	2·2%	11·2 (NA–NA)	2·3%
Tanzania[*]	336 025 (131 167–676 648)	2 025 593	1·4%	16·6 (6·5–33·4)	2·2%

[@]All births before 37 completed weeks of gestation, or fewer than 259 days from the first date of a woman's last menstrual period (WHO definition)
$ UI= uncertainty interval (also known as confidence interval)
# Preterm births per 100 livebirths
* Preterm births based on modelled national estimates.
† Preterm births based on modelled regional estimates.
‡ Preterm births based on directly reported data.

TABLE 2.2 Estimated preterm birth[@] rates and numbers of preterm births in 2014 by region [7,8]

	Estimated preterm birth rate* (%, UI)	UNDP estimated number of livebirths	Proportion of global livebirths (%)	Estimated number of preterm births (n, UI)	Proportion of global preterm births (%)
Asia	10·4% (8·7–11·9)	75 441 991	53·9%	7 847 643 (6 579 297–8 987 184)	52·9%
Europe	8·7% (6·3–13·3)	7 927 034	5·7%	690 931 (497 738–1 051 737)	4·7%
Latin America and the Caribbean	9·8% (8·6–11·3)	10 814 139	7·7%	1 062 800 (931 611–1 220 105)	7·2%
North America	11·2% (9·5–13·2)	4 394 185	3·1%	491 297 (416 479–578 367)	3·3%
North Africa	13·4% (6·3–30·9)	5 771 560	4·1%	773 687 (365 845–1 782 375)	5·2%
Oceania	10·0% (7·9–12·7)	643 749	0·5%	64 227 (50 706–81 961)	0·4%
Sub-Saharan Africa	12·0% (8·6–16·7)	34 953 292	25·0%	4 182 440 (2 994 834–5 838 104)	28·2%
Global	10·6% (9·0–12·0)	139 945 950	100·0%	14 835 606 (12 654 938–16 728 926)	100·0%

[@]All births before 37 completed weeks of gestation, or fewer than 259 days from the first date of a woman's last menstrual period (WHO definition)

*Preterm births per 100 livebirths

TABLE 2.3 National preterm birth rates [7,8]

Countries	2014	
	Preterm births as a percentage of all live births	# pretermbirths
Argentina	8.7	**65522**
Australia	8.1	**25700**
Austria	8.4	**6840**
Bahrain	4.3	**855**
Belarus	10.1	**11257**
Belgium	11.6	**15070**
Brazil	8.2	**247413**
Canada	10.1	**38959**
Chile	14.5	**34154**
Colombia	8.5	**64283**
Croatia	5.0	**2042**
Cuba	5.8	**6796**
Czechia	8.6	**9259**
Denmark	9.0	**5265**
Estonia	7.2	**1023**
Finland	7.2	**4180**
Germany	5.4	**36602**
Greece	5.5	**5180**
Hungary	13.2	**12190**
Ireland	9.8	**6858**
Japan	6.0	**62653**
Latvia	9.6	**1933**
Lithuania	6.4	**1920**
Luxembourg	6.5	**407**
Malta	7.4	**276**
Netherlands	6.2	**10995**
New Zealand	5.9	**3559**
Norway	7.3	**4401**
Poland	6.0	**23675**
Portugal	8.3	**7081**
Republic of Korea	6.8	**31136**
Saudi Arabia	8.1	**50065**
Slovenia	4.3	**932**
Spain	7.0	**29684**
Sweden	7.7	**9026**
United Kingdom	6.3	**51110**
United States of America	9.9	**398717**
Uruguay	**12.0**	**5860**

APPENDIX 3

Preterm Birth Risk Factors

3.1 Preterm Birth Risk Factors and Etiologies

TABLE 1. Preterm birth risk factors

Age	• Maternal age less than 20 years[1] ◦ AOR* 1.76, 95% CI: 1.33–2.32[9] • Advanced maternal age (≥35 years)[10,11,12,13,14,15]
Maternal History	• Multiple pregnancy (pregnant with more than one fetus) [12,17,20, 22, 23, 24, 25,26,27,28,29] ◦ AOR 3.44,95% CI: 3.02-3.91[9] ◦ AOR: 3.60 95%CI:2.49-5.19[16] • Single marital status[17] • Nulliparity (RR - 1.27, 95% CI 1.21-1.33)[18,19,20,21] • History of preterm birth [30-38] ◦ AOR 3.45, 95% CI: 2.72-4.38[9] • History of abortion ◦ AOR 3.93, 95% CI: 2.70–5.70[9] ◦ AOR: 2.92, 95%CI: 1.91- 4.47[16] • Birth space less than 2 years [39,40,41,42] ◦ AOR 2.03, 95% CI 1.57–2.62[9] • Prior Caesarean birth [28,43] • Absence of ANC / <4 antenatal visits during pregnancy [23,44,45,46,47] ◦ AOR 5.77, 95% CI: 4.27–7.79 [9] • High levels of maternal psychological or social stress [48,49] • Emotional stress[14] • Physical intimate violence [33,50,51] • Following assisted reproductive technology (ART) [52]

Ethnicity	• Black (African-American, Afro-Caribbean) [17,21,28, 53,54]
Social status	• Low socioeconomic and educational status[17,46, 55,56] • Use of polluted cooking fuel [46] • Housing instability and severe material hardship[57] • Structural racism [58] • Community unemployment [58, 59] • Racial-economic segregation[58] • Living in deprived areas [12,60, 61,62] • Acute exposure to extreme heat [63] • Severe sociopolitical stressors [23,63,64] • Rural residence [65] ◦ AOR: 2.35, 95%CI: 1.56-3.55 [16] • Living in large cities [66] • Immigrant woman[66] • Educational level ≤ secondary studies [46,66]
Occupation	• Working > 40 hours per week [14, 17,25] • Hard physical labour under stressful condition[17,25]
Paternal Factors	• Low education (high school or less) [67] • Race/ethnicity (hispanic or non-hispanic others)[67]
Behavior	• Active smokers [25,28,46,68,69, 70, 71,72] • Maternal drug abuse/dependence [10,73]
Nutrition	• Low pre-pregnancy BMI [17, 28] • Inadequate dietary diversity for women [74]

	• No dietary supplementation during the current pregnancy [75,76] • High maternal blood cadmium [77] • Omega-3 PUFA deficiency [78] • Low mid-upper arm circumference [74]
Comorbidities	• Anemia during pregnancy [12, 41, 46,74, 76] ◦ AOR: 3.41, 95%CI: 2.1-5.56[16] ◦ AOR 4.58, 95% CI: 2.63–7.96[9] • Asthma[17] • Obesity [78] • Gestational diabetes mellitus [79, 80] • Pre-existing diabetes[1,28,81,82] • Chronic hypertension[1,27, 28, 72,83] • Pregnancy-induced hypertension [18,23] ◦ AOR: 5.11, 95%CI: 3.73-7.01[16] ◦ AOR 3.10, 95% CI: 2.34–4.09[9] • Proteinuria in early pregnancy [84] • Preeclampsia [11,12,28,33,84, 85] • Premature rupture of membrane[12,26,27,35,41,85] ◦ AOR 5.90, 95% CI: 4.39–7.93[9] ◦ AOR: 5.36, 95%CI: 3.76, 7.64[16] • Antepartum hemorrhage[12,18] ◦ AOR 4.90, 95% CI: 3.48-6.89[16] • Obstetric complications[31] • Chronic medical problem during pregnancy[10,23] • Short uterine cervix (<25 mm in the second trimester)[25,37]

	• Depression [86,87,88,89] • Thyroid disease [17] • Anomalies of the uterus (e.g. presence of a uterine septum)[17]
Infection	• HIV infection [90,91] ○ AOR: 4.74; 95%CI: 2.79- 8.05[16] ○ AOR 2.59, 95% CI: 1.84-3.66[9] • Urinary tract infection [73] • AOR 5.27, 95% CI: 2.98-9.31[9] • Vaginal discharge • AOR 5.33, 95% CI: 3.19-8.92[9] • Chlamydia [73] • Toxoplasmosis [92] • Trichomonas vaginalis[93,94] • Malaria[12] ○ AOR 3.08, 95% CI: 2.32–4.10[9] • Persistent or recurrent intrauterine infections [30,95,96] • Viral infections including SARS-CoV-2 [51,97,98], HIV [16,99] • Reproductive tract infections [13,31,75]
Medication during pregnancy	• Antidepressants[100, 101] • Benzodiazepines[102] • Selective serotonin receptor inhibitors[102] • Antibiotics [103] ○ Macrolides, lincosamides and streptogramins ○ Quinolones ○ Other antibacterials ○ Penicillins

	• NSAIDs[104] ○ Ketoprofen ○ Flurbiprofen ○ Nabumetone ○ Etodolac ◦ Indomethacin
Vaccines	• No correlation with Maternal immunization found

*AOR- Adjusted odds ratio

APPENDIX 4

Preterm Birth and Assessment of Gestational Age Key Caveats for Real Time Investigation and Case Definition Working Group Guidance for Data Analysis and Presentation

4. Preterm Birth and assessment of gestational age Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1 Key elements of Case Definition (CD) [1]

- In the case definition, there is a focus on Gestational Age (GA) assessment. Accurate assessment of GA at birth is the most important element for the identification and classification of preterm birth
- GA is typically discussed in terms of completed weeks
- The ability to accurately determine the completed weeks of gestation varies widely between pregnancies, with the most precise assessment methods not uniformly available across different settings
- Preterm birth is reported only for live born infants. It is commonly defined as any birth before 37 weeks completed weeks of gestation, term birth as 37-41 weeks and Post term birth as 42 weeks or more
- WHO further subdivides preterm birth (any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period (LMP)) based on the gestational age as -
    - extremely preterm (<28 weeks)
    - very preterm (28–<32 weeks)
    - moderate or late preterm (32–<37 completed weeks of gestation)
- There are **3 levels of certainty** for preterm birth and assessment of GA: 1 (Definite case), 2 (Probable case) and 3 (Possible case).
- The levels of certainty can be determined based on maternal history (certain date of LMP , uncertain date of LMP or date of assisted reproductive technology (ART) (including intrauterine insemination or embryo transfer); ultrasound scan (of greatest value if done in the 1st Trimester), maternal physical examination (1st trimester confirmation of an enlarged uterus via bimanual examination); fundal height in centimeters done preferably in 1st trimester or 2nd trimester; newborn birthweight, or newborn physical examination to determine physical and neuromuscular maturity
- The most accurate methods of GA assessment are included in Level 1 of diagnostic certainty. For level 1, history of one of the following: a certain LMP or ART (intrauterine insemination or embryo transfer) date along with a confirmatory 1st trimester ultrasound scan; or only a 1st trimester ultrasound scan (without the certain LMP or ART date) are needed

- Of critical importance to meet level 2 or 3 is documentation of a certain or uncertain date of LMP along with an ultrasound scan in the 2nd or 3rd trimester, physical examination of the mother, fundal height measurement in cm, newborn birth weight or the newborn physical assessment.

- Fundal height is the distance between the top of the symphysis pubis (pubic bone) and the top of the uterus during pregnancy. It's measured in centimeters with a measuring tape. After about 20 weeks of pregnancy, the fundal height in centimeters should be close to the fetus's gestational age. To measure the fundal height, with the woman lying on the examination table the healthcare provider extends a paper or plastic tape measure from the top of the symphysis pubis (pubic bone) to the top of the uterus. The distance between these two spots is the fundal height.

- For determination of the **maternal fundal height**, the Gestation Related Average Weight (GRAW) tool should be used (figure 4.1 below). A standardized method for serial fundal height measurement is explained and recommendations for referral are mentioned. The customized antenatal growth chart is used to improve detection of fetal growth issues while reducing unnecessary interventions. Fundal height growth curves of the underweight and overweight and obese pregnant women were different from the normal weight.

- For the **newborn physical assessment**, the New Ballard Score sheet for neuromuscular and physical maturity should be used (Figure 4.2 below). This characterizes the gestational maturity of the neonate by determining the neuromuscular and physical maturity scores.

- **Factors that are not part of either case definition:** Brighton case definitions are designed for use in epidemiologic settings and are not intended to guide management or assign causality. Accordingly, neither response to treatment nor defined risk intervals from vaccination to event onset are included as criteria in the case definitions. The Brighton case definitions are a key first step in causality assessment but are not designed to assign causality. They also support determination of background incidence as well as case incidence among non-exposed controls.

A standardized method for serial fundal height measurement is explained and recommendations for referral are mentioned. The customized antenatal growth chart is used to improve detection of fetal growth issues while reducing unnecessary interventions (Gaillard R, Jaddoe VW. Assessment of fetal growth by customized growth charts. Ann Nutr Metab. 2014;65(2-3):149-55. doi: 10.1159/000361055.Gestation Related Average Weight (GRAW) tool - Antenatal Growth Chart, accessed on 30 July 2022 at https://www.gestation.net/fetal_growth/graw/)

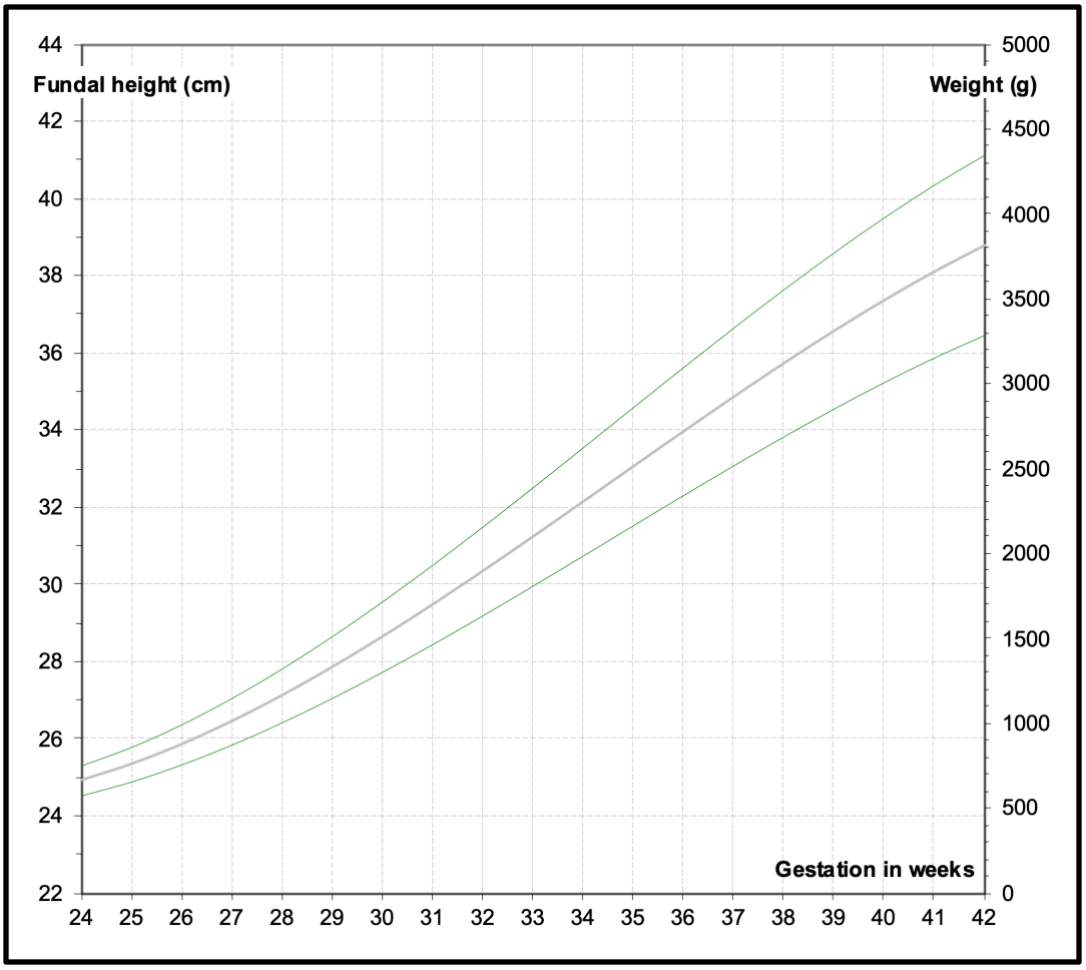


FIGURE 4.1. Gestation Related Average Weight (GRAW) tool – for fundal height assessment

Characterizing the gestational maturity of the neonate by determining the neuromuscular and physical maturity scores. (Ballard JL, Khoury JC, Wedig K, et al: New Ballard Score, expanded to include extremely premature infants. J Pediatrics 1991; 119:417-423. Accessed on 30 July 2022 at https://www.ballardscore.com/ScoreSheet/ScoreSheet)

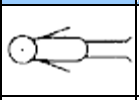
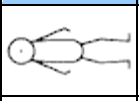
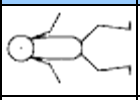
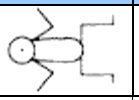
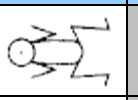
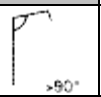
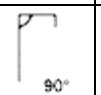
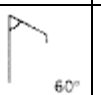
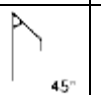
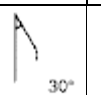
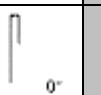
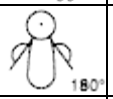
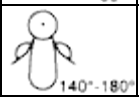
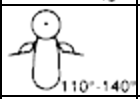
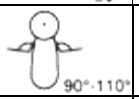
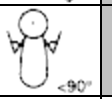
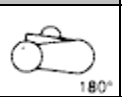
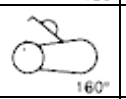
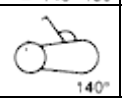
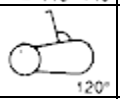
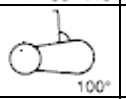
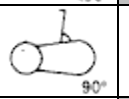
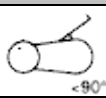
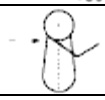
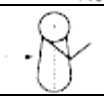
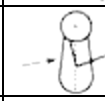
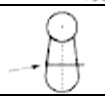
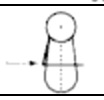
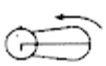
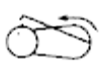
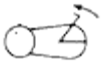
Sign	Score							Sign Score
	-1	0	1	2	3	4	5	
Posture								
Square Window								
Arm Recoil								
Popliteal Angle								
Scarf Sign								
Heel To Ear								
Total Neuromuscular Score								

FIGURE 4.2 Characterizing the gestational maturity of the neonate and assessment of fetal growth by customized Antenatal Growth Chart [1]

TABLE 4.2B Physical Maturity

Sign	Score							Sign Score
	-1	0	1	2	3	4	5	
Skin	Sticky, friable, transparent	gelatinous, red, translucent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking, pale areas, rare veins	parchment, deep cracking, no vessels	leathery, cracked, wrinkled	
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald		
Plantar Surface	heel-toe 40-50mm: -1 <40mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2 mm bud	raised areola 3-4 mm bud	full areola 5-10 mm bud		
Eye / Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff		
Genitals (Male)	scrotum flat, smooth	scrotum empty, faint rugae	testes in upper canal, rare rugae	testes descending, few rugae	testes down, good rugae	testes pendulous, deep rugae		
Genitals (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large, minora small	majora cover clitoris & minora		

TABLE 4.2C Total Physical Maturity Score

Total Score (Neuromuscular + Physical)	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

4.2 Duration of Surveillance[1]:

This should be till the pregnancy has been completed, but specific surveillance may be further predefined based on biologic characteristics of the:

- Vaccine and vaccine platform
- Vaccine targeted disease
- Preterm birth (e.g. patterns identified in previous trials)
- Vaccinee (e.g. age, nutrition, underlying disease, immunosuppression).

Similarly, the duration of follow-up for individual cases should be predefined, and at a minimum should continue until the resolution of the event.

4.3 Data Collection Guidelines: the following should be documented:

1. Clinical description of signs & symptoms and whether there was medical health professional confirmation
2. Date and time of onset, first observation, definitive diagnosis, end of episode
3. Final outcome or outcome at last observation (including spontaneous resolution or response to therapeutic intervention; return to baseline health prior to illness onset or event persistence, sequelae or fatality)
4. Concurrent signs, symptoms, and diseases in immunized woman and newborn
5. Test measurement(s):
   - 5.1 Values and units of routinely measured parameters (e.g. dates, gestational age,)- especially those indicating the severity of the event
   - 5.2 Methods of measurements (e.g. fundal height, maturity score, antenatal US, date and duration of measurement, etc.)
   - 5.3 Results of laboratory/imaging investigations, surgical and/or pathological findings and diagnoses, if present

5.4 If multiple ultrasound scans and/or maternal and newborn clinical examinations are done, record all dates and results

5.5 If multiple measurements of a particular criterion are done record all dates and results. The value corresponding to the greatest magnitude of the criterion should be taken as the basis of the analysis

6 Treatment given for:

6.1 Preterm birth to mother and/or newborn, especially medicine and dosing, or specific intervention

6.2 Outcome at last observation

7 Objective clinical evidence supporting classification of the event as 'serious'

8 Exposures, other than the immunization, 24 hours before and after immunization considered potentially relevant to the reported event (e.g. food, infections, environmental)

Most of the above go beyond the criteria needed to meet the case definition of preterm birth, which are the focus of the data abstraction forms in Appendix 5. Accordingly, separate forms will be required to capture the data outlined in the bullets.

4.4 Data Analysis Guidelines[1]

All reported preterm birth should be classified in one of five categories (see algorithms in appendix 5):

- Levels 1, 2 or 3 of the case definitions for preterm birth
- Level 4: reported preterm birth with insufficient evidence to meet the case definition
- Level 5: not a case of preterm birth

The interval between immunization and reported preterm birth can be defined as date/time of immunization to the date/time of onset of newborn delivery. If only a few cases are reported, the actual time course should be presented for each. If a large number of cases are reported or found as part of a study, data can be analyzed as the number (%) of cases occurring in intervals of: <1 week, 1- <2 weeks, 2- <4 weeks, 4- <6 weeks and 4-week increments following that.

The duration of possible preterm birth can be analyzed as the interval from the date/time of onset of the first symptoms and/or signs consistent with the definition to the end of the episode (defined as the time when the event no longer meets the lowest level of the case definition (level 3) or the final outcome. Whichever is used should be used consistently within and across study groups.

If more than one measurement of a particular criterion is taken and recorded, the highest measured value could be the basis for analysis.

APPENDIX 5

Preterm Birth and Assessment of Gestational Age Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty

5.1 Preterm Birth and Assessment of Gestational Age Data Abstraction and Interpretation Form for Medical Chart Review

This appendix provides tools that can be used to gather data pertinent to Preterm Birth and to use the data to assess the level of certainty based on the published Brighton case definition.[1] These tools can be used in a variety of settings including: medical chart review to validate Preterm Birth cases; summarize known case information from an AEFI report and guide what supplemental information would be needed to assign a level of certainty; guide data collection and case investigation during a clinical vaccine trial or as part of active surveillance; and to guide data collection for epidemiologic studies of background incidence or to assess causality.

Five tables and 1 figure are included in this appendix:

- **Table 5.1** lists all Brighton case definition[1] criteria for Preterm Birth and identifies likely sources of information for each.
- **Table 5.2** is the main data abstraction form that can be used to record data pertinent to Preterm Birth
- **Table 5.3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each case definition criterion based on data entered into table 5.2.
- **Table 5.4** is a brief summary of the final value for each criterion. As per table 5.3
- **Table 5.5** provides the formulae used to assign level of certainty for Preterm Birth based on criterion values summarized in Table 5.4.
- **Figures 5.1** shows a pictorial algorithm for determining level of certainty for Preterm Birth.

Brief instructions are provided with each table.

TABLE 5.1. PRETERM BIRTH AND ASSESSMENT OF GESTATIONAL AGE KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A 1	Certain LMP	For pregnant woman • Antenatal card • Antenatal care visit progress notes • consultation reports • Admitting history/exam • imaging report • Delivery records (maternal/infant) • Pediatric progress notes • Emergency report • Discharge summary • Billing codes • Diagnostic and procedure codes	
A2	Uncertain LMP		
B	Intrauterine insemination date or embryo transfer date		
C	Ultrasound scan		
D	Physical examination of mother in the 1st trimester		
E	Fundal Height measurement		
F	Birth weight		
G	Newborn physical assessment		

TABLE 5.2. Preterm Birth and Gestational Age (GA) Assessment DATA ABSTRACTION FORM: Record specific information, to the extent possible, for all rows in the table below. The red font identifies specific criteria related to the Preterm Birth and assessment of GA case definition. Check all the boxes that are applicable

1. Date of event onset	
2. Hospital admission?	
3. Admitting diagnosis:	
4. Discharge diagnosis:	
5. Criterion A-1: Certain LMP and correlation between GA calculated from LMP and ultrasound (US) (pregnant women is certain of her date of LMP and correlation exists between GA calculated from 1st day of LMP and US GA assessment)	☐ 1. Certain LMP and correlation between GA calculation from LMP and 1st trimester US assessment (correlation is within 7 days at ≤ 14 weeks) ☐ 2. Certain LMP and correlation between GA calculation from LMP and 2nd trimester US assessment (correlation is within 14 days at ≤ 26 weeks) ☐ 3. Certain LMP and correlation between GA calculation from LMP and 3rd trimester US assessment (correlation is within 21 days beyond 26 weeks) ☐ 4. None of the above ☐ 5. Unknown
6. Criterion A-2: Uncertain LMP	☐ 1. Approximate date of LMP for Pregnant woman (PW) first seen in 1st trimester (≤13 6/7 weeks) corroborated by pelvic bimanual examination confirming enlarged uterus ☐ 2. Approximate date of LMP for PW first seen in 1st trimester corroborated by 1st trimester US ☐ 3. Approximate date of LMP for PW first seen in 1st trimester **not** corroborated by 1st trimester US (if discrepancy of >7 days between the LMP and 1st trimester US, then US established dates used for GA assessment) ☐ 4. Approximate date of LMP for PW first seen in 2nd trimester (14 0/7 weeks to 27 6/7 weeks) corroborated by fundal height ☐ 5. Approximate date of LMP for PW first seen in 2nd trimester corroborated by 2nd trimester US

	☐ 6. Approximate date of LMP for PW first seen in 2nd trimester **not** corroborated by 2nd trimester US (if discrepancy of >10 days between the LMP and 2nd trimester US, then US established dates used for GA assessment) ☐ 7. Approximate date of LMP for PW first seen in 3rd trimester (>28 weeks) corroborated by 3rd trimester US ☐ 8. No LMP date (use US established dates OR 2nd trimester fundal height AND/OR newborn physical examination) ☐ 9. Unknown
7. Criterion B: Intrauterine insemination date, or embryo transfer date	☐ 1. Intrauterine insemination date known ☐ 2. Embryo transfer date known ☐ 3. None of the above ☐ 4. Unknown

8. Criterion C: Ultrasound scan	☐ 1. 1st trimester scan (≤ 13 6/7 weeks) which confirms certain LMP, intrauterine insemination date or embryo transfer date ☐ 2. 1st trimester scan (with certain LMP and 1st trimester scan not correlating) ☐ 3. 2nd trimester scan (14 0/7–27 6/7 weeks) which confirms certain LMP ☐ 4. 2nd trimester scan (when certain LMP is available, and 2nd trimester scan and certain LMP do not correlate, so US GA assessment is used) ☐ 5. 2nd trimester scan ☐ 6. 3rd trimester scan (≥ 28 0/7 weeks) ☐ 7. None of the above ☐ 8. Unknown
9. Criterion D: Physical examination of mother (pelvic bimanual examination which confirms enlarged uterus)	☐ 1. Physical examination of mother done in the 1st trimester ☐ 2. Physical examination of mother not done in the 1st trimester ☐ 3. Unknown
10. Criterion E: Fundal height measurement (In cms, by Gestation Related Average Weight (GRAW) tool, please	☐ 1. Done in 1st trimester and value known

select relevant box if any measurement done in a trimester)	☐ 2. Done in 2nd trimester, value known ☐ 3. Done in 2nd trimester, value known, and confirms certain LMP ☐ 4. Done in 3rd trimester, value known ☐ 5. None of the above ☐ 6. Unknown
11. Criterion F: Birth weight (gms)	☐ 1. Birth weight known ☐ 2. Birth weight unknown
12. Criterion G: Newborn assessment of physical and neuromuscular maturity (by New Ballard Score)	☐ 1. Total score available ☐ 2. Total score unavailable

TABLE 5. 3. INTERPRETATION FORM FOR GESTATIONAL AGE ASSESSMENT CRITERION VALUES:

Based on clinical data entered into Table 2, assign a value to each criterion using the rules in the Criterion Options columns.

CRITERIA	CRITERION OPTIONS: Criterion =			Criterion Value
	YES (Y) IF:	NO (N) IF:	UNKNOWN (U) IF:	
A-1. Certain LMP	__≥1 of A-1 = 1, 2 or 3	__ A-1 = 4	__ A-1 = 5	A-1 = Y N U
A-2. Uncertain LMP	__≥1 of A-2 = 1, 2, 3, 4, 5, 6 or 7	__ A -2= 8	__ A-2 =9	A-2 = Y N U
B. Intrauterine insemination date or embryo transfer date	__≥1 of B = 1 or 2	__ B = 3	__ B = 4	B = Y N U
C. Ultrasound scan	__≥1 of C = 1, 2, 3, 4, 5 or 6	__ C = 7	__ C = 8	C = Y N U
D. Physical examination of mother in the 1st trimester	__ D = 1	__ D = 2	__ D = 3	D = Y N U
E. Fundal Height measurement	__≥1 of E = 1, 2, 3 or 4	__ E = 5	__ E = 6	E = Y N U
F. Birth weight	__ F = 1	__ F = 2	__F = 2	F = Y N U
G. Newborn physical assessment	__G = 1	__ G = 2	__G = 2	G = Y N U

TABLE 5.4. SUMMARY OF GESTATIONAL AGE CRITERION VALUES Record final values for each Criterion from Table 5.3.

Criterion	A-1	A-2	B	C	D	E	F	G
Final Value								

TABLE 5. 5 TABULAR ALGORITHMS TO DETERMINE GESTATIONAL AGE LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES

Use the final values of all criteria recorded in Table 5.4 to determine LOC based on the formulae below. The highest row in the table where **all criteria are met** will be the LOC.

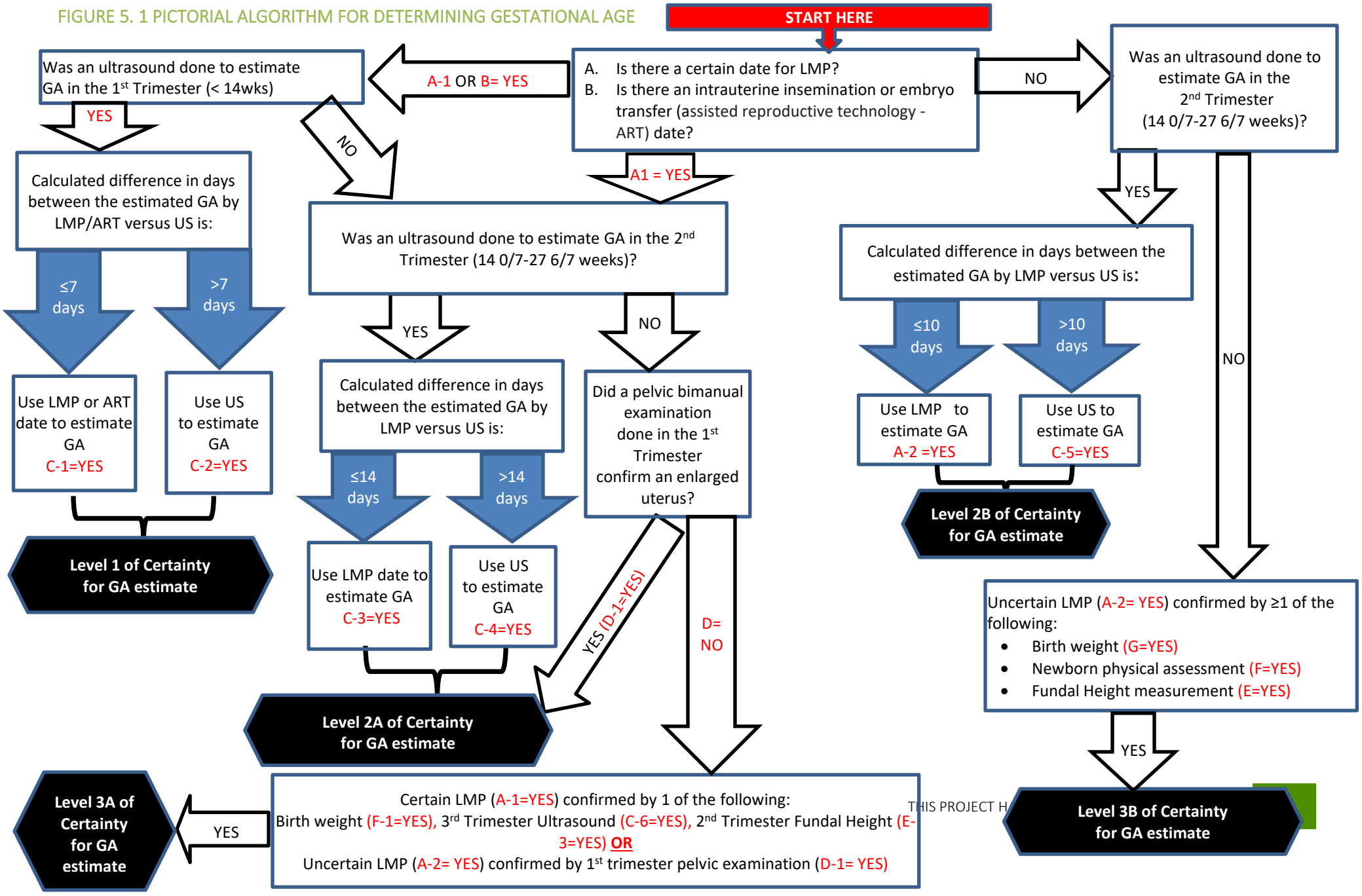
Level of Certainty	Assessment of Gestational Age
Level 1 :	-(A-1 OR B = YES) AND (C-1 OR C-2 = YES)
Level 2A	(A-1 AND C-3 = YES) OR (C-4=YES) OR (A-1 AND D-1= YES)
Level 2B :	(A-2 AND C-5= YES)
Level 3A :	(A-1 AND C-6 = YES) OR (A-1 AND E-3 = YES) OR (A-1 AND F-1= YES) OR (A-2 AND D-1= YES)
Level 3B :	(A-2 AND E= YES) OR (A-2 AND F= YES) OR (A-2 AND G= YES)
Level 4	Assessment of Gestational age fails to meet any level of certainty

TABLE 5. 6 TABLE TO DETERMINE PRETERM BIRTH LEVEL OF CERTAINTY (LOC) BASED ON GESTATIONAL AGE LOC

Level of Certainity of Preterm Birth (birth before 37 weeks completed weeks of gestation)	
Level 1 :	
Level 2A	
Level 2B :	
Level 3A :	
Level 3B :	
Level 4	Reported Preterm Birth with insufficient evidence to meet the case definition

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

FIGURE 5. 1 PICTORIAL ALGORITHM FOR DETERMINING GESTATIONAL AGE



APPENDIX 6.

Methodology: Brief Summary

6.1. Preterm Birth ICD-9/10-CM and MedDRA Codes [2-6]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[2] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[3] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[4,5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (SK) familiar with the Preterm Birth Brighton case definitions for all Tier 1 AESI. The concepts identified for Preterm Birth were considered relevant for background incidence rate determination as well as to study hypotheses related to Preterm Birth as a vaccine-product related reaction.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

6.2. Preterm Birth Background Incidence

A systematic literature search to estimate the incidence of Preterm Birth in the population was conducted using the following search strategy:

"Preterm birth" OR "premature birth" OR "premature delivery"

AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND English[lang]

AND ("2000/01/01"[PDAT]: "3000/12/31"[PDAT])

AND ("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type])

NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp])

NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti])

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for Preterm Birth were extracted. Preterm Birth incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer. Screened in articles were reviewed and relevant data abstracted for inclusion in the background rate table (MRV) when novel articles were found from systematic reviews, these were included. The spreadsheet with all extracted background incidence data is available in the CEPI Developers' Toolbox and on the Brighton Collaboration website.

6.3. Preterm Birth Risk Factors

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn

or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:
1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for Preterm Birth was reviewed for evidence related to associated risk factors. In addition, a systematic search was conducted to identify evidence for risk factors using the same search strategy shown for background incidence in section 6.2 above. The same expert (SK) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of Preterm Birth. Additional relevant articles were found by a hand search of the included article reference list and articles identified after expert consultation. The included articles were used not only to inform the Risk factor table(s) in Appendix 3, but also guidance on real time investigation in Appendix 4.

A PubMed search for articles focused on preterm birth following vaccination was conducted on August 10, 2022.
A single reviewer (SK) screened the articles first on title and abstract to identify case reports, case series, reviews, descriptive and research studies focused on humans. Editorials, letters to the editor, other commentaries, erratum, guidelines and articles focused only on management or therapy were excluded. A full text review was conducted for all screened in articles. Articles were judged to be contributory or non-contributory for the purpose of the Companion guide which was to identify vaccine as a risk factor for preterm birth and to describe up to date information related to the preterm birth safety signal associated with maternal immunization. Hypothesis-testing studies as well as descriptive datalink or other epidemiologic studies that provided risk analyses (Incidence Rate, Incidence Reporting Ratio, Incidence Rate Difference) or disproportionality analyses (Reporting Odds Ratio, Information Component) or that systematically reviewed published case reports and case series or that provided endomyocardial histopathology were considered contributory.

6.4. Preterm Birth Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published Brighton case definition for Preterm Birth was reviewed and key aspects identified with particular relevance to real time assessment of Preterm Birth in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Preterm Birth case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

6.5. Tabular Checklist and Algorithms for Level of Certainty Determination [1]

The Brighton Collaboration case definition for Preterm Birth[1] and assessment of GA was thoroughly and repeatedly reviewed by one individual (SK) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The Preterm Birth and assessment of GA criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition.[1] Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.