**Table 1**. Participant-level variables of interest

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Variable of interest** | **Var name in dataset** | **Definition** | **Include in imputation model?** | **Imp4** |
| Exposure | Maternal ZIKV infection | zikv\_preg | Was pregnant woman diagnosed with ZIKV during this pregnancy using any criteria (clinical or laboratory diagnosis or self report) as defined by the study?  0=No; 1=Yes; 666=Not applicable; 888=Not reported by study; 999=Missing | Yes | 1 |
|  | Fetal or placental ZIKV infection | fet\_zikv (can also be defined based on other variables) | Fetal ZIKV infection? As defined by the study.  0=No; 1=Yes; 888=Not reported by study | Yes |  |
| Primary outcomes | Miscarriage (<20 weeks gestation) | miscarriage | Documented miscarriage: spontaneous loss of the product of the gestation <20 wks  0=No; 1=Yes; 555=Unknown; 888=Not measured by the study; 999=Missing | As bdeath | 1 |
|  |  | miscarriage\_ga | Gestational age of miscarriage (Weeks; miscarriage defined as spontaneous loss prior to 20 weeks is a miscarriage)  1-20 weeks; 666=Unknown; 888=Not measured by the study; 999=Missing | As bdeath\_ga | 1 |
|  |  | loss\_etiology | Cause of infant/fetus death  0=any live births (even if resulted in early/neo/perinatal death)  1=abortion/miscarriage (any loss, spontaneous or voluntary <20 weeks);  2=fetal demise (any loss after 20 weeks);  3=Stillbirth or Intrapartum death (death during labor)  666= Not Applicable (Not Pregnant)  888=Not reported by study  999=Missing | No, only use before imputation to solve some missings in bdeath |  |
|  | Fetal loss (≥20 weeks gestation) | loss | Pregnancy loss (anything that is not a live birth is a pregnancy loss) | As bdeath | 1 |
|  |  | loss\_ga | Gestational age at pregnancy loss (Weeks)  1-45 weeks; 666=Unknown; 888=Not measured by the study; 999=Missing | As bdeath\_ga | 1 |
|  | Microcephaly (diagnosis: severe microcephaly, microcephaly, normocephaly, macrocephaly; Z-score) | microcephaly (defined based on inf\_head\_circ\_birth -> microcephaly2) | Level of microcephaly - as defined by the study.  0=Normocephaly; 1=Microcephaly; 2=Severe microcephaly; 888=Not reported by study; 999=Missing | No | 1 |
|  |  | microcephaly\_bin (can also be defined based on inf\_head\_circ\_birth -> microcephaly\_bin2) | Ever diagnosed with microcephaly? As defined by the study.  1=Yes; 0=No; 888=Not reported by study; 999=Missing | Yes, include microcephaly\_bin |  |
|  | CZS (diagnosis: confirmed, probable, unlikely) | czs (can also be defined based on other variables)  czs2 | Diagnosis of congenital Zika syndrome (as measured by the study)  0=No; 1=Yes; 555=Unknown; 888=Not measured by the study; 999=Missing  WHO definition: Presence of confirmed maternal or fetal ZIKV infection AND presence of severe microcephaly AND presence of other malformations (eye, nose, ears etc.) | Yes | 1 |
| Secondary fetal outcomes | Induced abortion with microcephaly (diagnosis: confirmed, probable, unlikely) | inducedabort | Did the pregnancy result in an induced abortion?  0=No; 1=Yes; 888=Not reported by study; 999=Missing | Yes | 1 |
|  |  | fet\_micro | Prenatal Diagnosis of Microcephaly (Fetal microcephaly)  0=No; 1=Yes; 555=Unknown; 888=Not measured by the study; 999=Missing | No |  |
|  | Early fetal death (20-27 weeks gestation) | loss | Pregnancy loss (anything that is not a live birth is a pregnancy loss) | No (see above) | 1 |
|  |  | loss\_ga | Gestational age at pregnancy loss (Weeks)  1-45 weeks; 555=Unknown; 888=Not measure by the study; 999=Missing | No (see above) | 1 |
|  | Late fetal death (≥28 weeks gestation) | loss; loss\_etiology; loss\_ga |  | No (see above) | 1 |
|  | Late fetal death (≥28 weeks gestation) with microcephaly | loss; loss\_etiology; loss\_ga; fet\_micro |  | No (see above) | 1 |
|  |  | loss\_etiology | Cause of infant/fetus death  0=any live births (even if resulted in early/neo/perinatal death)  1=abortion/miscarriage (any loss, spontaneous or voluntary <20 weeks);  2=fetal demise (any loss after 20 weeks);  3=Stillbirth or Intrapartum death (death during labor)  666= Not Applicable (Not Pregnant)  888=Not reported by study  999=Missing | No (see above) |  |
|  | Placental insufficiency (diagnosis: confirmed, probable, unlikely)‡ | No match (in pilot data) |  | No match |  |
|  | Intrauterine growth restriction | igr\_curr\_preg | Evidence of Intrauterine Growth Restriction (IGR)  0=No; 1=Yes; 555=Unknown; 888=Not measured by the study; 999=Missing | Yes (59% missing but let’s give it a try, recode 888 to missing) | 1 |
| Secondary infant outcomes | Postnatal microcephaly (diagnosis: severe microcephaly, microcephaly, normocephaly, macrocephaly; Z-score) | microcephaly\_bin | Ever diagnosed with microcephaly? As defined by the study.  1=Yes; 0=No; 888=Not reported by study; 999=Missing | Already listed above |  |
|  |  | fet\_micro | Prenatal Diagnosis of Microcephaly (Fetal microcephaly)  0=No; 1=Yes; 555=Unknown; 888=Not measured by the study; 999=Missing | No |  |
|  | Gestational age at birth | birth\_ga | Gestational age in weeks at birth (live births) (note, value must be >=21 weeks)  555=Unknown; 888=Not measure by the study; 999=Missing | As bdeath\_ga | 1 |
|  | Birth weight (diagnosis: normal birth weight; low birth weight; very low birth weight; extremely low birth weight; Z-score) | inf\_weight | Birth weight in grams (<12 hours after delivery)  555555=Unknown; 888=Not measure by the study; 999=Missing; 666= missing?? | Yes (continuous variable with 26% missing. Do not forget to recode 888, 999, 666 to missing) | 1 |
|  | Craniofacial disproportion | inf\_craniofac\_abn\_bin | Presence of any other cranio-facial abnormalities (head abnormalities) - other than microcephaly  1=Yes; 0=No; 888=Not reported by study; 999=Missing | Yes (56% missings, do not forget to recode 888 and 999 to missing) |  |
|  | Neuroimaging abnormalities (intracranial calcification, lissencephaly, hydranencephaly, porencephaly, ventriculomegaly, posterior fossa abnormalities, cerebellar hypoplasia, corpus callosal and vermian dysgenesis; focal cortical dysplasia) | neuroabnormality   * Variable created based on the following:   fet\_us\_abn\_spec\_tri1, if it is equal to 0, then fet\_us\_cns\_tri2 and fet\_us\_cns\_tri3.  also, the following:  hydrocephaly  corticalatrophy  calcifications  ventriculomegaly | Abnormal finding for central nervous system (anencephaly, microcephaly, spina bifida, encephalocele, hydrocephalus, holoproscencephaly, corticalatrophy, brain calcifications, ventriculomegaly)  0=No; 1=Yes | Yes |  |
|  | Postnatal intraventricular hemorrhage | No match (in pilot data) |  | No match |  |
|  | Any congenital abnormality on MRI or ultrasound | anyabnormality  Variable created based on the following:  inf\_craniofac\_abn\_bin,  neuroabnormality, ocularabnormality, contractures, nonneurologic, fet\_us\_bin\_tri1, fet\_us\_bin\_tri2, fet\_us\_bin\_tri3, othabnorm, microcephaly\_bin if equal to 1 | Abnormal finding for cranio-facial abnormalities,musculoskeletal system (club foot, Limb deficiency, Reduction deformity upper limbs, Reduction deformity upper limbs, hip dysplasia), cardiovascular system (ventricular septal defect without an associated genetic syndrome, transposition or totally anomalous pulmonary venous connection, Tetralogy of Fallot, functionally univentricular heart, hypoplastic left heart syndrome), gastrointestinal system (Gastroschisis, omphalocele, Diaphragmatic hernia, Atresia: choanal, esophageal, intestinal, biliary, rectal), oro-facial finding (cleft palate, cleft lip), eye-ear finding (Anophthalmia, microphthalmia, cataracts, anotia, microtia), genitourinary system (Hypospadias, Hermaphroditism, Phimosis, renal agenesis) | Yes |  |
|  | Motor abnormalities (hypotonia, hypertonia, hyperreflexia, spasticity, clonus, extrapyramidal symptoms)§ | No match (in pilot data) |  | No match |  |
|  | Seizures, epilepsy§ | No match (in pilot data) |  | No match |  |
|  | Ocular abnormalities (blindness, other)§ | ocularabnormality   * Variable created based on the following:   Fet\_us\_eyeear\_tri2, fet\_us\_eyeear\_tri3; fet\_us\_abn\_spec\_tri1 if equals to 5 | Abnormal eye-ear finding (Anophthalmia/microphthalmia, Cataracts, anotia, microtia) detected on 1st, 2nd or 3rd trimester ultrasound  0=No; 1=Yes | No, 71% missing values. |  |
|  | Congenital deafness or hearing loss§ |  |  | No, this variable is merged with ocular abnormalities. |  |
|  | Congenital contractures (arthrogryposis, uni or bilateral clubfoot) | contractures  Created based on the following:  Fet\_us\_msk\_tri2, Fet\_us\_msk\_tri3,  fet\_us\_abn\_spec\_tri1 if equals to 1 | Abnormal finding for musculoskeletal system (club foot, Limb deficiency, Reduction deformity upper limbs, Reduction deformity upper limbs, hip dysplasia) detected on 1st, 2nd or 3rd trimester ultrasound  0=No; 1=Yes | No, 68% missing values. |  |
|  | Other non-neurologic congenital abnormalities | nonneurologic  Created based on the following:  fet\_us\_msk\_tri2,  fet\_us\_cardio\_tri2,  fet\_us\_gastro\_tri2,  fet\_us\_orofac\_tri2,  fet\_us\_eyeear\_tri2,  fet\_us\_genur\_tri2,  fet\_us\_msk\_tri3,  fet\_us\_cardio\_tri3,  fet\_us\_gastro\_tri3,  fet\_us\_orofac\_tri3,  fet\_us\_eyeear\_tri3,  fet\_us\_genur\_tri3, if equal to 1  fet\_us\_abn\_spec\_tri2, fet\_us\_abn\_spec\_tri3 if equal to 1, 2, 3, 4, 5, or 6  fet\_us\_bin\_tri3 -> no abnormalities if 0 | Abnormal finding for musculoskeletal system (club foot, Limb deficiency, Reduction deformity upper limbs, Reduction deformity upper limbs, hip dysplasia), cardiovascular system (ventricular septal defect without an associated genetic syndrome, transposition or totally anomalous pulmonary venous connection, Tetralogy of Fallot, functionally univentricular heart, hypoplastic left heart syndrome), gastrointestinal system (Gastroschisis, omphalocele, Diaphragmatic hernia, Atresia: choanal, esophageal, intestinal, biliary, rectal), oro-facial finding (cleft palate, cleft lip), eye-ear finding (Anophthalmia, microphthalmia, cataracts, anotia, microtia), genitourinary system (Hypospadias, Hermaphroditism, Phimosis, renal agenesis) detected in 2nd or 3rd trimester ultrasound | No, 67% missing values. |  |
| Secondary outcomes after infant period | Cortical auditory processing | No match (in pilot data) |  | No match |  |
|  | Neurodevelopment (expressive and receptive language, fine and gross motor skills, attention and executive function, memory and learning, socioemotional development, overall neurodevelopmental score) | No match (in pilot data) |  | No match |  |
|  | Vision (Cardiff test) | No match (in pilot data) |  | No match |  |
| Confounders | Demographic factors - age | age | Age of the mother in years. Continuous.  888=Not measured by the study; 999=Missing | Yes | 1 |
|  | Demographic factors - education | educ | Mother's highest level of education received  0= No education; 1=Primary school ; 2=Secondary school ; 3=Some college; 4=Bachelor's degree ; 5=Graduate or Professional degree ; 777=Other ; 888=Not reported by study ;999=Missing | Yes |  |
|  | Demographic factors – marital status | maritalstat | Mother's marital status  1=Single; 2=Married/Living as married/Cohabitating; 3=Divorced/Separated; 4=Widowed; 777=Other; 888=Not reported by study; 999=Missing | Yes |  |
|  | Demographic factors – racial / ethnic group | ethnicity | Maternal ethnicity as defined by the study  0=Caucasian descent; 1=African descent; 2=East Asian descent; 3=South Asian descent; 4=Indigenous descent; 5=Mixed; 777=Other; 888=Not reported by study; 999=Missing | Yes |  |
|  | Demographic factors - BMI | pre\_pregweight | Pre-pregnancy weight, in kg  888=Not measured by the study;  999=Missing | No, 100% missing |  |
|  |  | height | Height, in cm  888=Not measured by the study;  999=Missing | No, 90% missing |  |
|  | Socioeconomic factors | ses | Maternal socioeconomic status identified as low, medium or high SES, or income  0=Low; 1=Medium; 2=High ; 777=Other ; 888=Not reported by study ; 999=Missing | No, 90% missing |  |
|  | Maternal smoking, illicit drug and alcohol use | tobacco  drugs  alcohol | Mother smokes tobacco during the current pregnancy  0=No; 1=Yes (Smoking currently, during current pregnancy); 2=Previous smoker (Before current pregnancy); 888=Not reported by study; 999=Missing (including unknown)  Current maternal (illicit) drug use or opioid substitution therapy (during pregnancy)  0=No; 1=Yes; 888=Not reported by study; 999=Missing  Maternal alcohol consumption during the current pregnancy  0=No; 1=Yes (any amount); 888=Not reported by study; 999=Missing (inlcuding unknonw) | Yes, >50% missing but let’s give it a try  Not now, >50% missing  Not now, >50% missing |  |
|  | Maternal prescription drug use | drugs\_prescr   * Created based on the following:   med\_bin med\_anticonvuls\_bin, med\_preg\_bin, med\_fertil\_bin if 1 | Indicate if the (pregnant) woman use any type of medications during the current pregnancy  A, A Pain killer / antipyretic | B, B Anticonvulsants | C, C Anti-nausea drugs | D, D Diuretics | E, E Anti-hypertensive | S, S Sleep medication | G, G Antivirals or antiretrovirals | H, H Antibiotics | K, K Anti-depressive | I, I Immune suppressive medication | P, P Antitussive | T, T Mucolytic | W, W Inotropes | Y, Y Eye drops | 999, O Other (incl. vitamins/herbal remedies) | No, 85% missing, only 1 positive |  |
|  | Maternal vaccination | vaccination   * Created based on the following:   vac\_rub\_enroll,  vac\_vari\_enroll,  vac\_yf\_enroll if 1 | History of rubella, varicella or yellow fever vaccination at enrolment | No, 76% missing |  |
|  | Maternal experience of violence during pregnancy; infant or child exposure to intimate partner violence68 | No match (in pilot data) |  | No match |  |
|  | Workplace or environmental exposures to teratogenic substances (e.g. maternal exposure to lead, mercury) | No match (in pilot data) |  | No match |  |
| Effect measure modifiers | Genetic anomalies, metabolic disorders, perinatal brain injury | Inf\_chromoabn, chromoabn\_rx  facongendisord\_mat\_bin🡪 familial antecedents of congenital malformations  med\_bin🡪 medications chronic  med\_anticonvuls\_bin🡪 anticonvulsants y/n  med\_anticonvuls🡪 anticonvulsants(which)  med\_preg\_bin🡪 medications pregnancy y/n  med\_preg 🡪 medications pregnancy (which)  med\_fertil\_bin🡪 require assisted fertility treatments y/n  med\_fertil 🡪require assisted fertility (which)  Genetic testing:  chromoabn\_screen  chromoabn\_test  chromoabn\_risk  chromoabn\_rx  chromoabn\_test\_oth  inf\_chromoabn  inf\_chromoabn\_test  inf\_chromoabn\_test\_oth |  | No, needs recoding first |  |
|  | Gestational age, term at birth | birth\_ga (duplicate variable – also outcome) | Gestational age in weeks at birth (live births) (note, value must be >=21 weeks)  555=Unknown; 888=Not measure by the study; 999=Missing | NA |  |
|  | Timing of infection during pregnancy | zikv\_ga | Gestational age at which women diagnosed with ZIKV, by EITHER ultrasound or LMP, in weeks. If both (ultrasound and LMP) information is avaiblable, priorotize ultrasound's GA information.  1-45 weeks;  666=Not Applicable (tested before current pregancy); 888=Not measured by the study; 999=Missing | Not now, >50% missing |  |
|  | Clinical/subclinical illness |  | Could also use: zikv\_confirmtest, if equals to =0, then was diagnosed but not confirmed  Also, could see the answers from arb\_symp or either arb\_clindiag or arb\_clindiag\_plus | No, needs recoding first |  |
|  | Viral genotype and load | Genotype No match (in pilot data)  zikv\_pcr\_vl\_1 | Viral load (copies/µL) for a PCR for 1st ZIKV PCR  Continuous  666=Not applicable (no PCR done); 888=Not reported by study; 999=Missing | No match  No, 100% missing |  |
|  | Concurrent or prior flavi- or alphavirus infection | flavi\_alpha\_virus   * Created based on the following:   arb\_clindiag\_plus,  arb\_clindiag,  denv\_ever, chikv\_ever if 1 | Concurrent or prior arbovirus? | Yes |  |
|  | Maternal history of Yellow Fever (YF) or Japanese encephalitis (JE) vaccination | JE No match (in pilot data)  vac\_yf\_enroll | History of yellow fever vaccination at enrollment?  0=No; 1=Yes; 888=Not measured by the study; 999=Missing  Vaccination is already covered in variable vaccination | No match  Not now, 76% missing data |  |
|  | Maternal immunosuppressive conditions, disorders, comorbidities (e.g. chronic hypertension, diabetes), or pregnancy-related conditions (e.g. pre-eclampsia, gestational diabetes) | prev\_comorbid\_bin  Also could use hiv, which is specific. Details are in the master codebook for the next phase. | Presence of comorbidities (i.e: chronic/ pre-existent/ conditions) before the current pregnancy?  0=No; 1=Yes; 888=Not measured by the study; 999=Missing | Not now, >50% missing data |  |
|  |  | eclampsia | Eclampsia  0=No; 1=Yes; 888=Not measured by the study; 999=Missing | Yes (57% missing, but let’s give it a try – recode 888 to missing) |  |
|  |  | gestdiab | Gestational diabetes  0=No; 1=Yes; 888=Not measured by the study; 999=Missing | Yes (57% missing, but let’s give it a try – recode 888 to missing) |  |
|  | Intrauterine exposure to STORCH pathogens | storch\_patho   * Created based on the following:   storch\_bin, storch, toxo,  toxo\_treat, syphilis,  syphilis\_treat, varicella, parvo,  rubella, cmv, herpes, listeria, chlamydia, gonorrhea, genitalwarts if 1 | Evidence of any (overall) STORCH pathogen infection during the current pregnancy?  0=No; 1=Yes; 888=Not measured by the study; 999=Missing  All variables are binary complementary variables for specific STORCH patogens | Yes | 1 |
|  | Maternal malnutrition | Could use weight or pre\_pregweight and height for the available values |  | No, needs recoding first |  |
|  | Presence and severity of maternal and infant clinical symptoms | arb\_symp  fever  fever\_meas  fever\_n  fever\_dur\_1  rash  rash\_type  conjunctivitis  conjunctivitis\_n  muscle\_pain  muscle\_pain\_n  arthralgia  arthralgia\_n  arthritis  vomiting  headache  abd\_pain  bleed  runnynose  fatigue  sorethroat  symp\_oth |  | No, needs recoding first |  |

CZS=congenital Zika syndrome, JE=Japanese encephalitis; STORCH=syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes; YF=yellow fever virus; ZIKV=Zika virus

\*Fetal ZIKV infection will be considered as both an exposure and an outcome; definition of fetal infection will be based on clinical and radiological criteria defined by an expert panel

†Both with and without microcephaly

‡As estimated by antenatal consequences of placental insufficiency, including fetal growth restriction, oligohydramnios, non-reassuring fetal heart rate tracing or small for gestational age at birth as markers of placental insufficiency.

§May also be detected after the infant period

\*\* As measured by the Bayley Scale;69 Ages and Stages;70 INTERGROWTH-21st Neurodevelopmental Assessment49

Other variables that might be relevant for multiple imputation:

Metadata:

Source population: community / hospital / travelers

Other data: