S2 Table

S1 Table. Zika causality framework, version 9

1. Temporality

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**1.1a.** Does Zika virus (ZIKV) infection precede the development of congenital abnormalities in individuals? **1.2.** Is the timing of Zika infection during gestation and the observed pattern of congenital abnormalities compatible with the expected stage of embryological development?	**1.1a.** Does ZIKV infection precede the development of Guillain-Barré syndrome in individuals? **1.2.** Is the interval between exposure to ZIKV and occurrence of symptoms typical for para- or post-infectious Guillain-Barré syndrome?
Study types	Cohort study, case-control study, case series, case report	
Population level data	**1.1b.** Is there a consistent time-dependent relationship between the occurrence of ZIKV cases and cases with the outcome of interest at population-level?	
Study types	Ecological time-trend study	

2. Biological plausibility

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data [a.]	**2.1.** Which cell receptor(s) bind the ligand of ZIKV in humans? **2.2.** Which tissues express such receptor(s) and at which gestational age are they expressed? **2.3.** Can ZIKV particles be found in the placenta, umbilical cord blood and/or amniotic fluid of previously or currently infected mothers and if yes, with what probability? **2.4.** Are the ZIKV particles in the placenta/amniotic fluid/umbilical cord infectious/capable of replication? **2.5.** Can ZIKV particles be found in brain or other tissues of cases with congenital abnormalities? **2.6.** Are the ZIKV particles found in the brain infectious/capable of replication? **2.7.** Are there experimental studies that describe plausible biological mechanisms by which ZIKV infection could lead to congenital abnormalities?	**2.1.** Do ZIKV epitopes mimic host antigens (molecular mimicry)? **2.2.** Does ZIKV infection lead to an increase in detectable autoreactive immune cells or autoreactive antibodies? **2.3.** Are there other biologically plausible mechanisms by which ZIKV infection could lead to GBS?
Study types	Basic research (protein expression, cell culture), case report, case-control study, cohort study, systematic revie	

3. Strength of the association

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**3.1a.** How strong is the association between ZIKV infection and the outcome of interest at the individual level?	
Study types	Cohort study, case-control study, cross-sectional	
Population level data	**3.1b.** How strong is the association between ZIKV infection and the outcome of interest at the population level?	
Study types	Ecological study	

4. Exclusion of alternative explanations

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	Have other explanations/confounders been excluded, such as **4.1.** TORCHS or other congenital infections **4.2.** Maternal exposure to toxic chemicals (heavy metals, pesticides, drugs, alcohol, others) **4.3.** Maternal or foetal malnutrition **4.4.** Hypoxic-ischaemic lesions **4.5.** Genetic conditions **4.6.** Radiation	Have other explanations/confounders been excluded, such as **4.1.** Other infections **4.2.** Vaccines **4.3.** Underlying systemic disease **4.4.** concomitant medication, drugs or other chemicals
Study types	Case-control study, cohort study, case series, case report, environmental sampling	

TORCHS, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis

5. Cessation/reversibility/preventability

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**5.1a.** Does the intentional prevention/removal/elimination of ZIKV infection in individuals, e.g. by insect repellents, lead to a reduction in cases with the outcome of interest?	
Study types	Randomised controlled trials of insect repellents or other interventions	
Population level data	**5.1b.** Does the intentional removal/elimination/prevention of ZIKV at population-level, e.g. by vector control, lead to a reduction in cases with the outcome? **5.2b.** Does a natural removal/elimination/prevention of ZIKV at population-level, e.g. increase in immune individuals or decrease in vector abundance lead to a reduction in cases with the outcome?	
Study types	Experimental vector control interventions, ecological time-trend study, seroprevalence study	

6. Dose-response relationship (biological gradient)

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**6.1.** Are the risk and the clinical severity of congenital abnormalities associated with the viral load in maternal serum, urine, the placenta and/or amniotic fluid? **6.2.** Are the risk and the clinical severity of congenital abnormalities associated with the clinical severity (including being asymptomatic) of ZIKV infection in the mother?	**6.1.** Are the risk and the clinical severity of Guillain-Barré syndrome associated with viral titres or viral load in the urine?
Study types	Cohort study, case series, case reports	

7. Animal experiments

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**7.1.** Does inoculation of pregnant female animals with ZIKV cause congenital abnormalities in the offspring? **7.2.** Does intracerebral inoculation of animals with ZIKV lead to viral replication in the central nervous system? **7.3.** Does any other route of inoculation of animals with ZIKV lead to viral replication in the central nervous system? **7.4**. Do other experiments with animals or animal-derived cells support the association of ZIKV infection and congenital abnormalities?	**7.1.** Does inoculation of animals with ZIKV lead to an autoimmune reaction resulting in peripheral neuropathy? **7.2.** Do other animal experiments support the association of ZIKV infection and Guillain-Barré syndrome?

Study types	Basic research: animal experiments

8. Analogy

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**8.1.** Do other flaviviruses or arboviruses cause the outcome of interest and by which mechanism(s)? **8.2.** Do other pathogens cause the outcome of interest and by which mechanism(s)? **8.3.** Which pathogen or host factors facilitate the development of the outcome of interest?	
Study types	Systematic review	

9. Specificity

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	**9.1.** Are there pathological findings in cases with the outcome that are specific for ZIKV infection?	
Study types	cohort study, case-control study, case series, case report, review	

10. Consistency / replicability

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	Is the association between ZIKV infection and cases with the outcome consistently found across different **10.1.** Geographical regions **10.2.** Populations/subpopulations **10.3.** ZIKV lineages/strains **10.4.** Study designs	
Study types	Systematic reviews, other appropriate epidemiological study types	

Co-factors

	Congenital abnormalities	Guillain-Barré syndrome
Individual level data	Are there co-factors contributing to the development the outcome after ZIKV infection such as **1.** Concurrent or previous dengue infection (antibody dependent enhancement) **2.** Other concurrent or previous infections **3.** Underlying systemic diseases **4.** Polymorphism/deletion of specific host immune system genes or general genetic predisposition **5.** Specific pathogen factors **6.** Concomitant medication, recreational drugs or other chemicals **7.** Other	
Study types	Cohort study, case-control study, case series, case report	