BIOLOGICAL FACTORS UNDERLYING THE NEUROLOGICAL EFFECTS OF THE COVID-19 PANDEMIC

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EPASSA CONFERENCE 2023

OUTLINE

INFECTIONS AND THE DEVELOPING BRAIN

NEUROLOGICAL MANIFESTATIONS OF COVID-19

PATHOPHYSIOLOGY

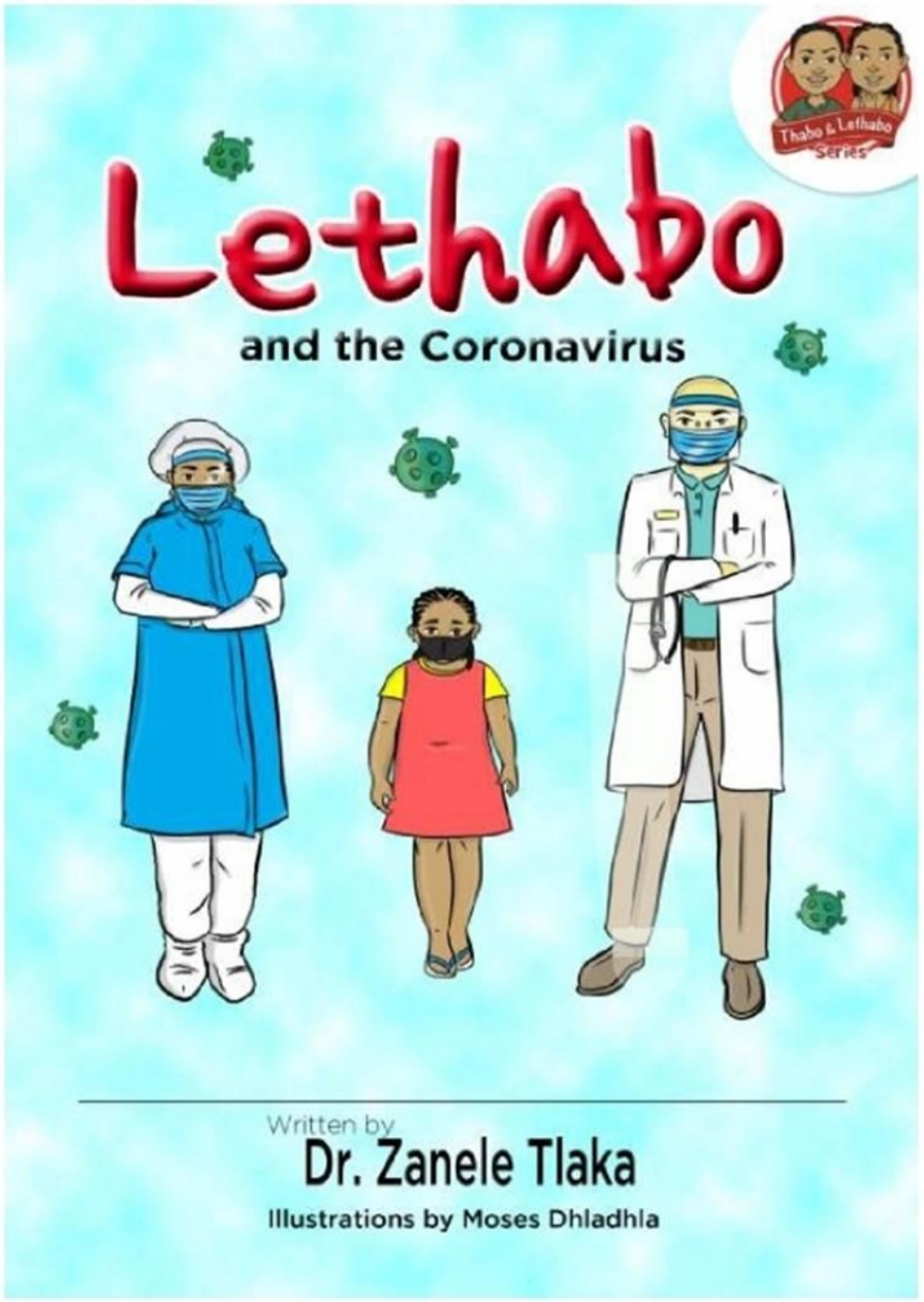
SEQUELAE OF COVID-19 EXPOSURE IN NEWBORNS

SEQUELAE OF COVID-19 INFECTION AND PIMS-TS IN THE OLDER CHILD

SUMMARY


KLEIN JEANS


BBC NEWS


Thabo & Lethabo Series
Lethabo
and the Coronavirus
Written by
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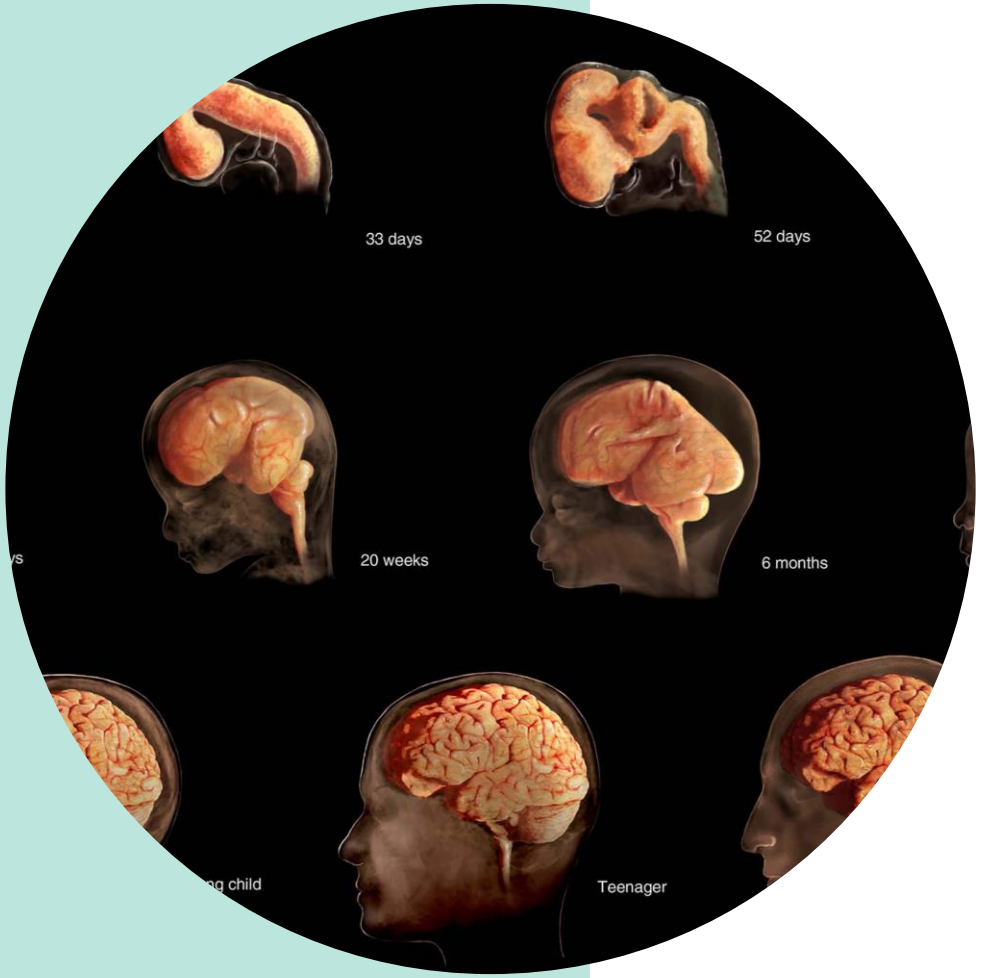
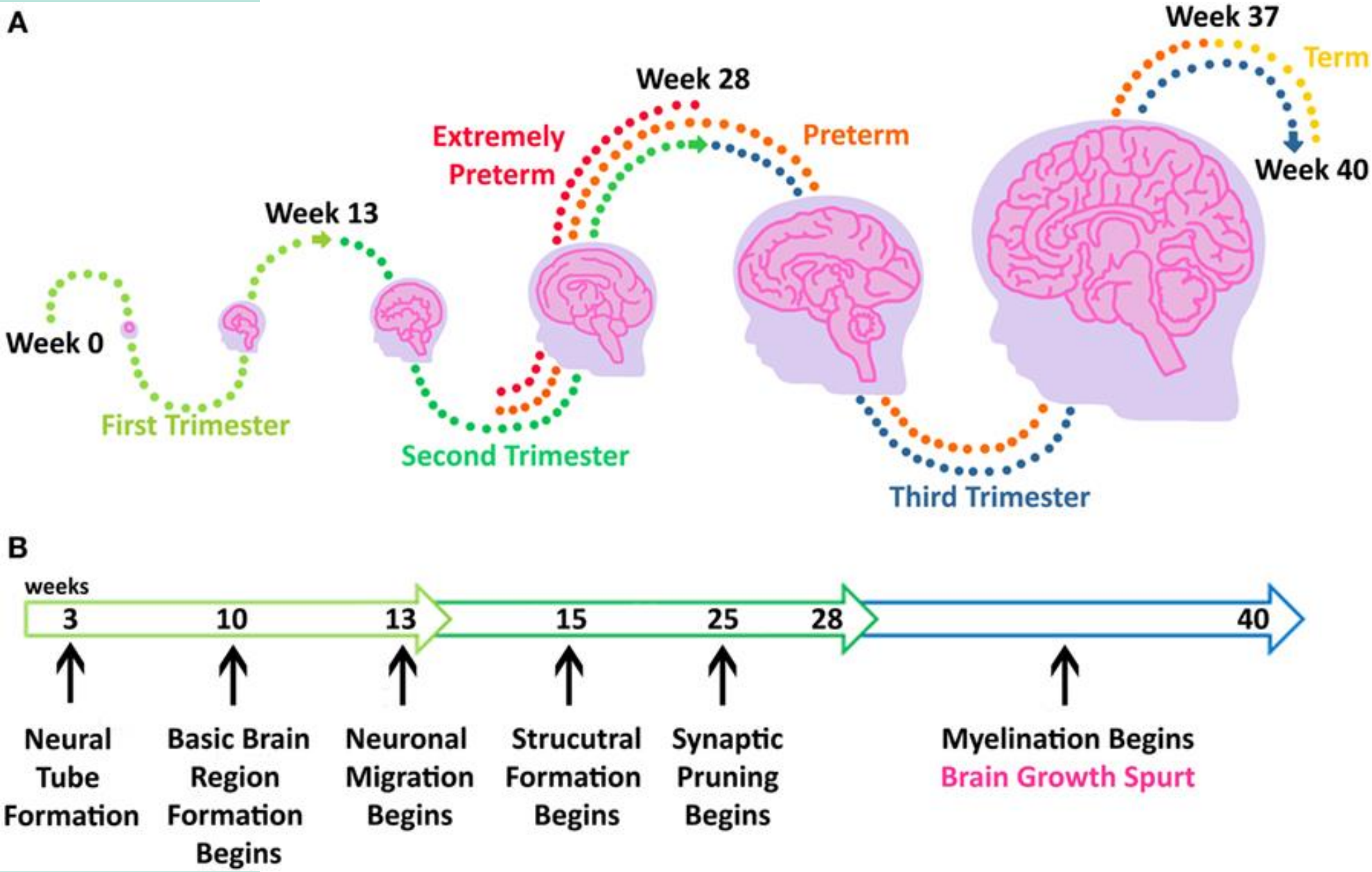
Illustrations by Moses Dhladhla

INFECTIONS AND THE DEVELOPING BRAIN



INFECTION AND THE DEVELOPING BRAIN

- Association between infection and altered brain development is well established
- The human brain undergoes ongoing development during the foetal period and continued development through childhood into adulthood. An insult at crucial points during this development may have adverse neurocognitive consequences.



Newville J et al. Front Young Minds. 2018

INFECTION AND THE DEVELOPING BRAIN

Association between maternal infection and the development of cognitive and psychiatric disease has been demonstrated.

Bacterial infections and Autism

- Study looking into records of Danish Medical Birth Register and Danish Psychiatric Central Register 1980 – 2005
- 21 266 mothers admitted with bacterial infections
- 156 neonates born to these mothers diagnosed with autism on follow up
- no overall association
- subgroup analysis found significant association between second trimester antenatal infection and subsequent development of ASD

INFECTION AND THE DEVELOPING BRAIN

Bacterial infections and schizophrenia

- transplacental passage of cytokines resulting from the bacterial infection speculated to be the cause of development of schizophrenia in adulthood

Viral illness and the brain

- maternal influenza infection has been associated with differences in cognitive test scores and development of schizophrenia and bipolar disorder; noted to be irrespective of trimester

Human Immunodeficiency Virus

- maternal infection conclusively associated with poor neurodevelopmental outcomes (cognitive and neurodevelopmental delays)

INFECTION AND THE DEVELOPING BRAIN

Anatomical structure of foetal brain can be altered by some infectious illnesses.

Pathogen	Pathology
Varicella-zoster virus	Hydrocephalus Porencephaly Calcifications Polymicrogyria lissencephaly
Cytomegalovirus	Pseudocysts Microcephaly Ventriculomegaly Cerebellar hypoplasia Hypoplastic corpus callosum
Syphillis	Hydrocephalus
Toxoplasmosis	Diffuse calcifications in basal ganglia Periventricular calcifications

NEUROLOGICAL MANIFESTATIONS OF COVID-19 IN CHILDREN

NEUROLOGICAL MANIFESTATIONS

NON-SPECIFIC

- 16% IN META-ANALYSIS OF 3707 CHILDREN

Headache
Myalgia
Fatigue
Somnolence

SPECIFIC

- 1% IN META-ANALYSIS OF 3707 CHILDREN

Encephalopathy
Seizures
Stroke
Meningeal signs

NEUROLOGICAL MANIFESTATIONS

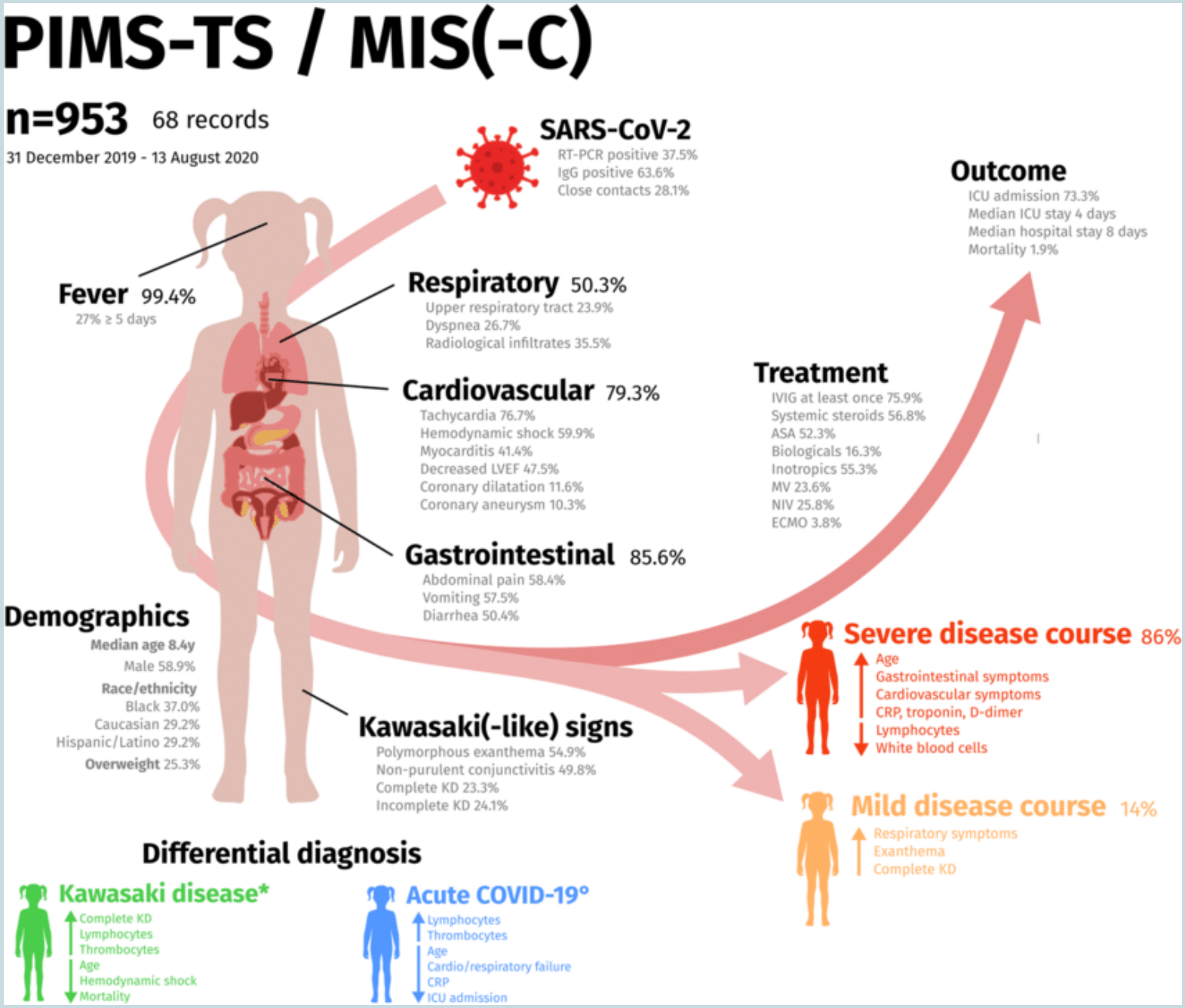
POST-INFECTIOUS

- MIS-C: MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

  PIMS-TS: PAEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME TEMPORALLY ASSOCIATED WITH SARS-COV-2

- POST-INFECTIOUS HYPERINFLAMMATORY CONDITION RELATED TO SARS-COV-2 INFECTION

- NEUROLOGICAL MANIFESTATIONS (IN 12-50% OF PATIENTS) INCLUDE
  - Status epilepticus
  - Focal deficits
  - Headache
  - Hallucinations
  - encephalopathy



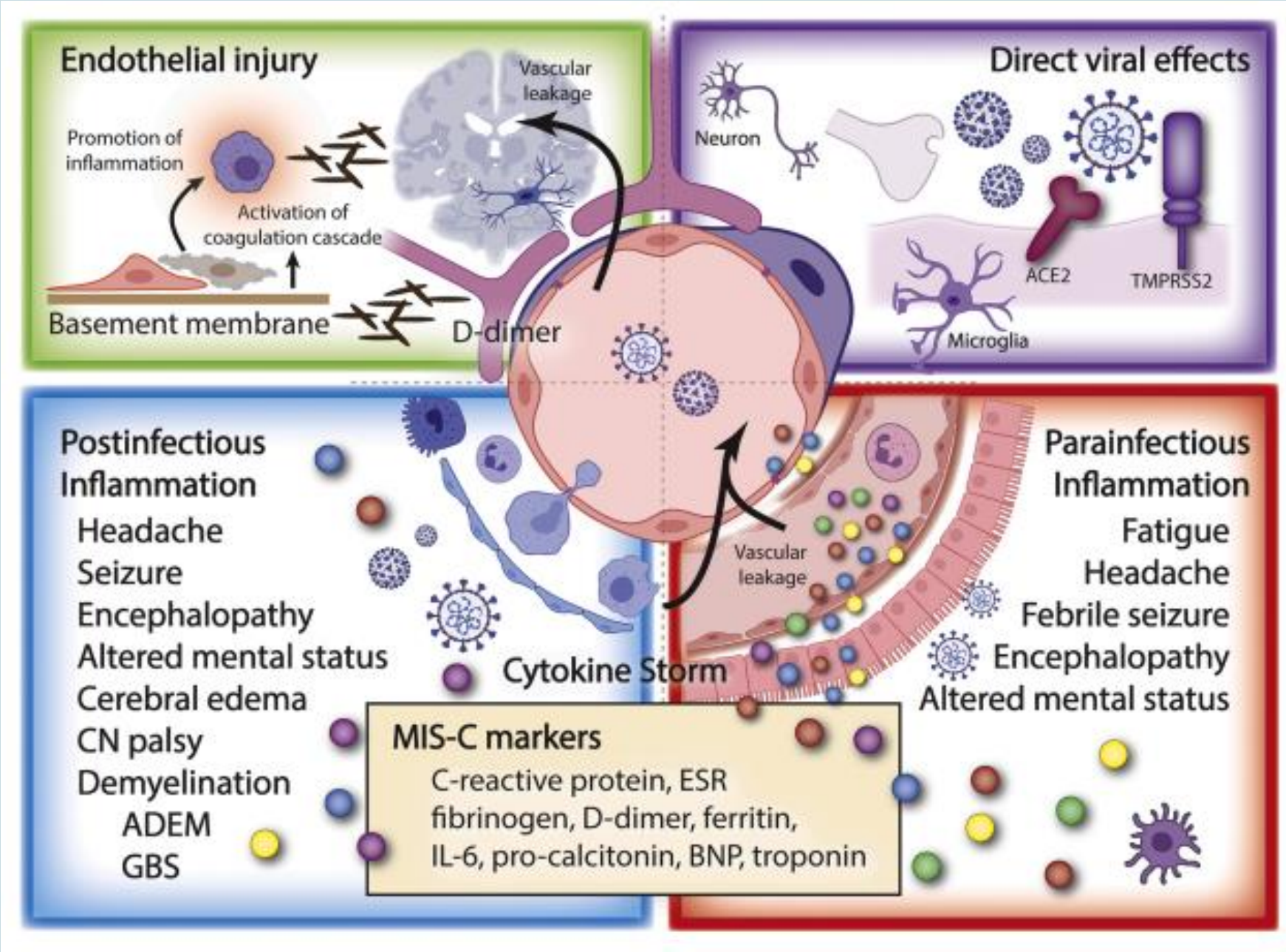
Hoste L et al. Eur. J. Pediatr. 2021

PATHOPHYSIOLOGY

SARS-CoV-2 invasion of nervous system by targeting:

- angiotensin converting enzyme 2 (ACE-2) receptor [neurons & glial cells]
- transmembrane serine protease 2 (TMPRSS2) [some glial cells]

1. Direct viral injury to neural cells
   - direct viral invasion of olfactory nerves after intranasal inoculation
   - neurological effects of SARS-Co-V2 may be different between children and adults due to age-related morphologic and molecular changes in blood brain barrier and its constituent neurovascular units
2. Vascular endothelial injury
   - ACE-2 receptors expressed on vascular endothelial cells
   - virus binding to receptor triggers inflammatory and pro-coaguable states
3. Inflammatory and autoimmune injury
   - activation of immune process may result in excessive inflammation seen in severe COVID-19 and MIS-C
   - genetically susceptible individuals
   - resultant neuroinflammation



Lin JE, et al. Neurosci. Lett. 2021

PATHOPHYSIOLOGY

- Pro-inflammatory cytokines including IL-1B, IL-6, TNF-a, IL-17 can
    - disrupt BBB
    - activate neuronal hyperexcitation and seizures
    - functional disturbance
    - fatique
    - encephalopathy
    - loss of synapses
    - neuronal death
- Molecular mimicry between SARS-CoV-2 and gangliosides on the peripheral nerves may lead to autoimmunity

SEQUELAE OF COVID-19 EXPOSURE IN NEWBORNS

SEQUELAE IN THE NEWBORN

- Antenatally acquired viral infections have the potential to have adverse effects on the developing foetal brain
- Neuroinvasiveness: ability of a virus to enter the peripheral or central nervous system
- Neurotropism: ability of a virus to infect and and replicate in cells of the nervous system
- Neurovirulence: ability of viral infection to cause CNS pathology independently from its ability to invade or infect CNS cells (do not cross the blood brain barrier).
- Neuroinvasive and neurotropic viruses, (eg. Zika, CMV), can cause direct damage to the foetal brain
- Neurovirulent viruses (eg. Influenza) cause maternal, placental and foetal brain immune activation, often resulting in adverse neurodevelopmental outcomes.
    - Autism spectrum disorder
    - Attention deficit hyperactivity disorder
    - Cognitive dysfunction
    - Anxiety
    - Depression
    - Schizophrenia

*1957 Influenza pandemic: individuals who were foetuses during the pandemic had increased risk of hospitalization for schizophrenia as adults

*1964 Rubella pandemic: offspring had 10-15 fold increase in ASD and schizophrenia

SEQUELAE IN THE NEWBORN

- Early signals of adverse neurodevelopmental outcomes in children exposed to the virus in utero, when assessed at 6 months, 12 months and 18months of age

LONGITUDINAL COHORT STUDY

[Wang Y et al. 2020]

57 infants with in utero exposure in China

Deficits in the social-emotional domain at 3 months of age

PRELIMINARY REPORT

[Ayed M et al. 2021]

298 exposed infants

Developmental delay in 10% at 12 months

PRELIMINARY REPORT

[Edlow et al. 2022]

7000 infants born during the pandemic

222 exposed to COVID-19

14..4% preterm births in infected mothers vs 8.7% in unifected mothers

Higher neurodevelopmental diagnosis rate in exposed infants at 12 months

SEQUELAE IN THE NEWBORN

- Estimated that number of children exposed to maternal COVID-19 infection in utero could reach up to 20 million per year worldwide

- Potential pathophysiological pathways:

1. Maternal Immune Activation (MIA)during important neurodevelopmental windows during the pregnancy
2. Transplacental transmission of virus with foetal neuroinvasion
3. Placental insufficiency resulting in adverse pregnancy outcomes associated with increased risk of neurological injury. (prematurity, abruption, growth restriction)

SEQUELAE IN THE NEWBORN

Maternal Immune Activation

- Causes rapid activation of immune and proinflammatory responses in the placenta and foetal brain

- **Dysregulated serotonin signaling** in the placenta (the primary source of serotonin for the developing foetal brain)

↓

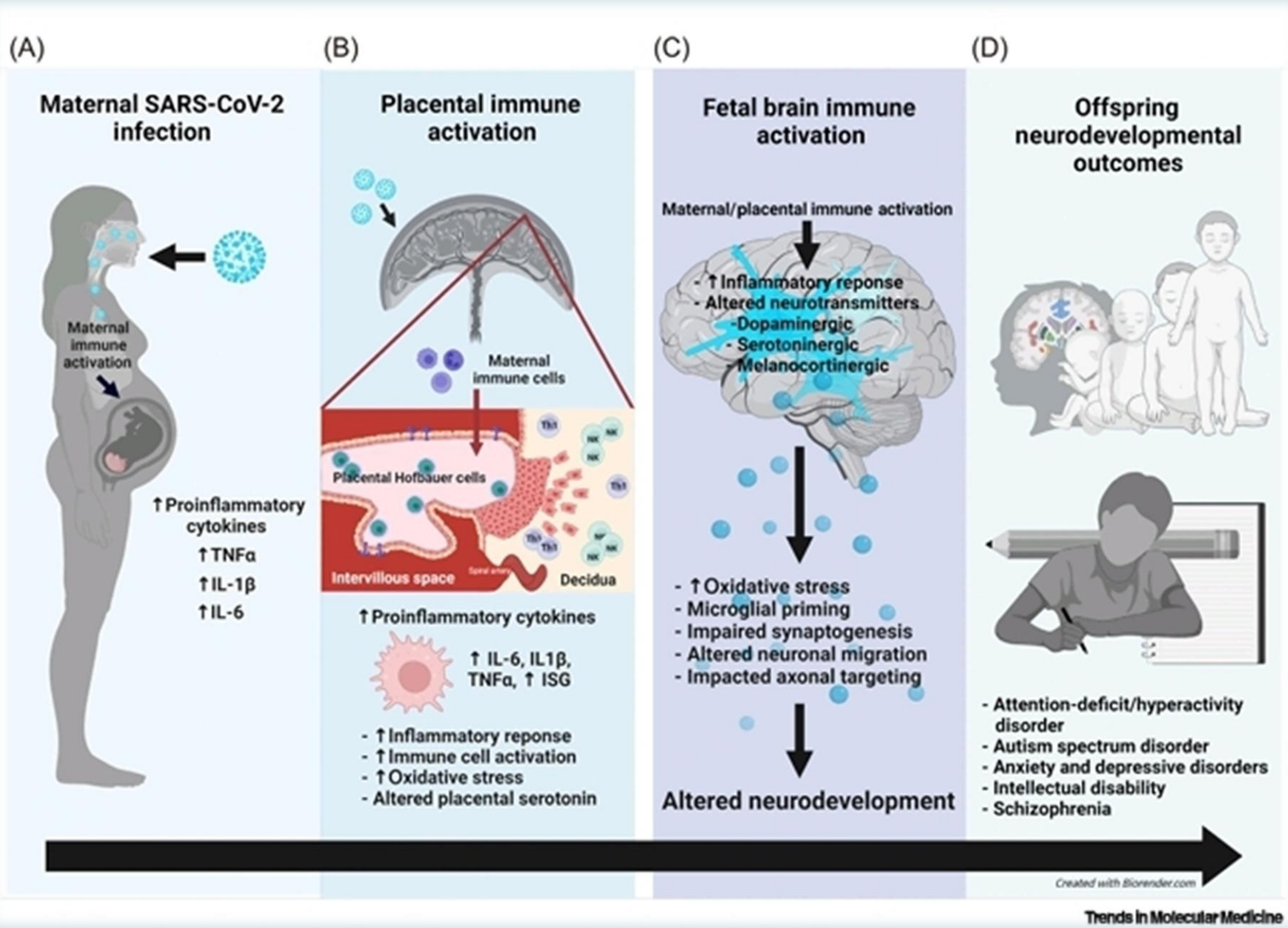
Impaired synaptogenesis, neuronal migration, and axonal targeting

- **Altered foetal brain neurotransmitter signalling**, including dopaminergic, cholinergic, GABA-ergic, glutamatergic, and melanocortinergic systems

↓

Adverse effect on foetal brain development, risk for conditions such as schizophrenia, addiction, and eating disorders.

- Placental and foetal brain **mitochondrial dysfunction**, oxidative stress, and disrupted protein homeostasis
- MIA research models suggest aberrant programming of foetal microglia and dysregulation of cytokine networks is key mechanism responsible for abnormal foetal brain development



Shook LL, et al. Trends Mol. Med0, 2022

SEQUELAE IN THE NEWBORN

Transplacental transmission

- Found to be rare occurrence
- 3.2% in a review of 38 studies
- Garrido-Pontnou et al. (2021): SARS-CoV-2 can infect trophoblasts in the placenta, cause foetal demise in 2.5% of cases

Placental insufficiency and prematurity

- SARS-CoV-2 infection during pregnancy associated with higher risk for pre-eclampsia and premature birth
- Both pregnancy complications associated with neurodevelopmental risk for the offspring

SEQUELAE OF COVID-19 INFECTION AND PIMS-TS IN THE OLDER CHILD

SEQUELAE IN THE OLDER CHILD

POST-COVID-19 CONDITION

- Children also experience it
- Italian study 129 children:

fatigue (10.8%)

respiratory symptoms eg chest tightness or pain (14.7%)

nasal congestion (12.4%)

insomnia (18.6%)

concentration difficulties (10.1%)

myalgia (10.1%)

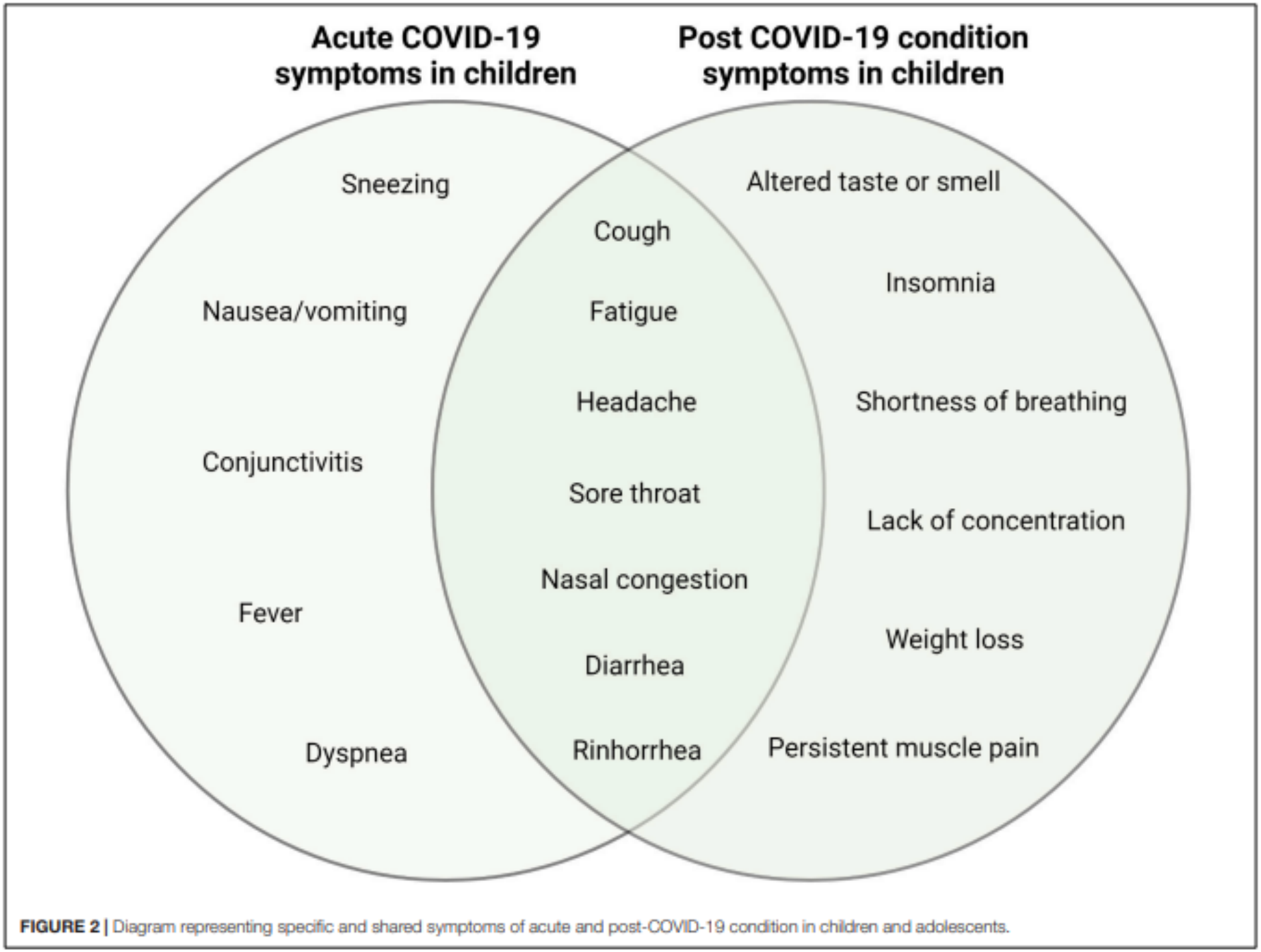


FIGURE 2 | Diagram representing specific and shared symptoms of acute and post-COVID-19 condition in children and adolescents.

SEQUELAE IN THE OLDER CHILD

Pathophysiology of post COVID-19 condition:

- poorly understood
- Predictors: Older age
  Muscle pain at admission
  Admission to ICU during acute infection
- Exaggerated immune response
- Children with long-term symptoms had high levels of IL-6 and IL-1B

SEQUELAE IN THE OLDER CHILD

NEUROPSYCHIATRIC SEQUELAE

- Depression, anxiety, post-traumatic stress disorder
- Pathophysiology:

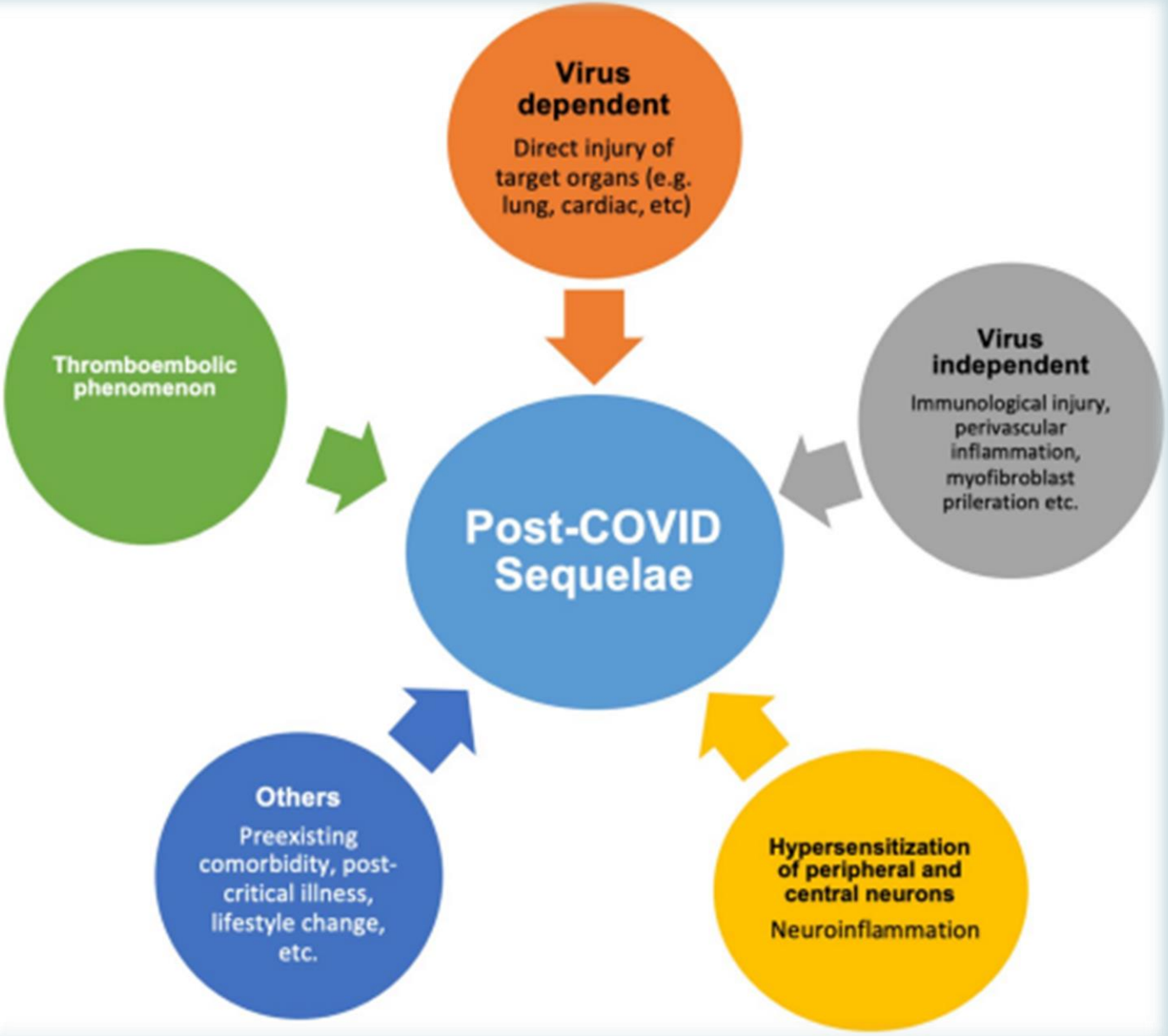
Neuroinflammation upregulates tryptophan degradation → Sequential decrease in 5-hydroxytrytamine and serotonin level + Dysregulation of N-methyl-D-aspartate receptor activity → Precipitates Depression and PTSD

AUTOIMMUNE DISEASES

- Rheumatic fever, Guillain Barre Syndrome
- Pathophysiology:

auto-antibodies are generated during a COVID-19 illness according to severity of disease

Fig. 1 Postulated pathophysiology mechanisms of post-COVID sequelae



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TAKE HOME POINTS

- As with many other infectious pathogens, the SARS-CoV2 virus appears to have adverse consequences for the developing brain
- Literature thus far describes sequelae in various facets of the nervous system:

Poor concentration	Autism Spectrum Disorder
Learning difficulties	Anxiety
Speech delays	Depression
Headaches	Post-traumatic stress disorder
Fatigue	ADHD
Guillaine Barre Syndrome	

- In addition to the environmental stress imposed on children during the COVID-19 pandemic, it is important to appreciate the significant pathophysiological alterations to a developing child's nervous system, that have resulted from the disease itself. The neurocognitive consequences require our vigilance and appropriate treatment in order to optimise children's physical and mental health.

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THANK YOU

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