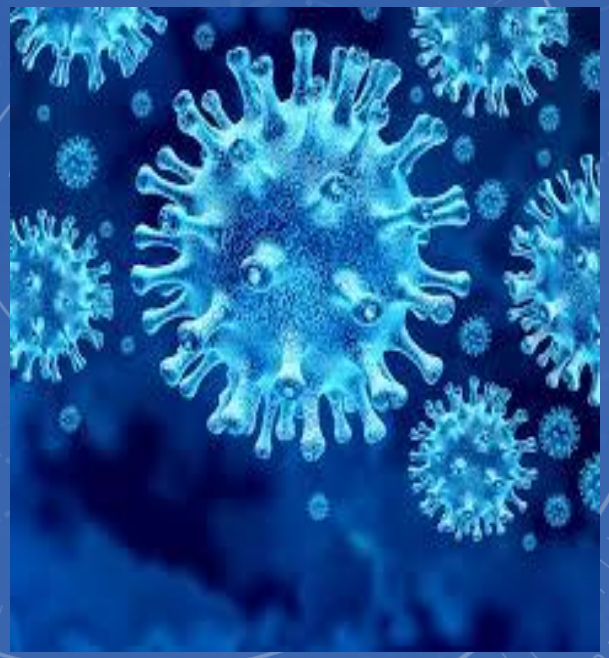


NEUROPSYCHIATRIC SEQUELAE IN POST COVID-19 ILLNESS

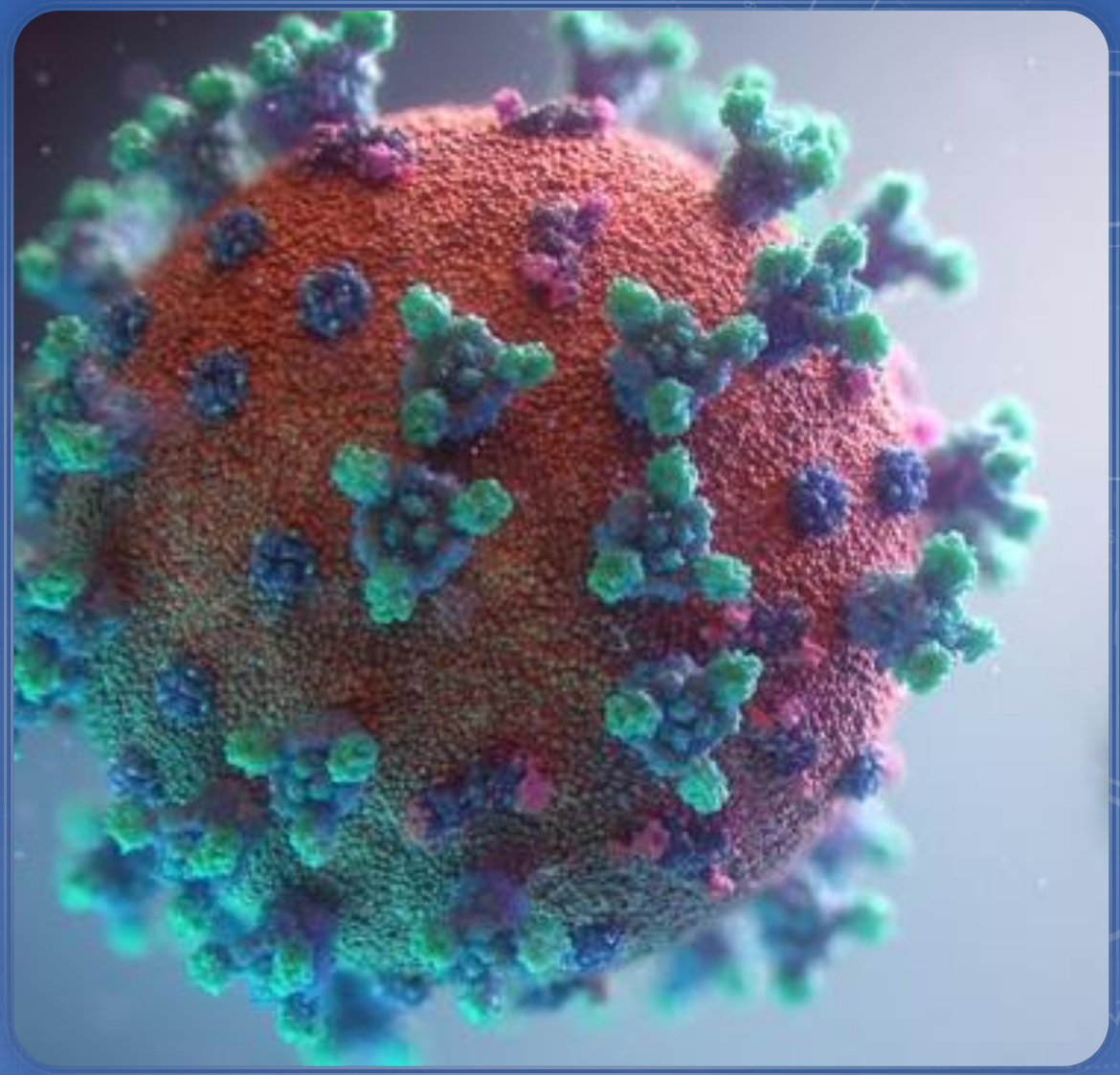
DR SANDRA FERNANDES

NEUROPSYCHIATRIST

TARA HOSPITAL AND UNIVERSITY OF THE WITWATERSRAND

SARS-COV-2

- As of 29th September 2020:
  - NUMBER INFECTED 33 353 614
  - TOTAL DEATHS 1 001 644
- SOUTH AFRICA INFECTED 671 669
- SOUTH AFRICA DEATHS 16 586



John Hopkins Resource Centre September 2020

TABLE. Summary of memorable epidemics/pandemics

Pandemics	Period in history	Estimated number of deaths
Black plague	1346-1350	25 million people[a]
HIV/AIDS	1981-present	529,113, with more than 940,000 cases reported
Tuberculosis		WHO estimates that 1.3 million people die every year from this disease
Smallpox	1633; 1790s; 1949[b]	Approximately 1.5 million
Cholera	Of the 3 million cases every year 100,000 to 120,000 result in death	
SARS	2003	774
Malaria[c]		>200 million people infected; approximately 660,000 deaths every year
Influenza	This virus has been responsible for 3 pandemics, including the H1 Spanish flu, the H1N1 swine flu, and the H5N1 avian (bird) flu	
Avian (bird) flu	2003	>700 cases reported
H1N1	2009	274,304 hospitalizations and 12,469 deaths
Ebola	1976; 2014-2015	20,000

[a]One-third of Europe's population.
[b]Most recent case in the US.
[c]Affects many tropical regions of the world including Africa, Asia, parts of the Americas.
SARS, severe acute respiratory syndrome.

MENTAL HEALTH IN PANDEMICS

- Spanish Flu 1918-1919: 500 million infected, 50 million deaths
- Presented in waves (USA had 4 waves)
- HINI virus of avian origin from USA to EUROPE
- NEUROPSYCHIATRIC SEQUELAE:
  - Sleep disturbances, depression, dizziness, difficulty in coping at work, etc
  - Encephalitis lethargica coincided with Spanish Flu

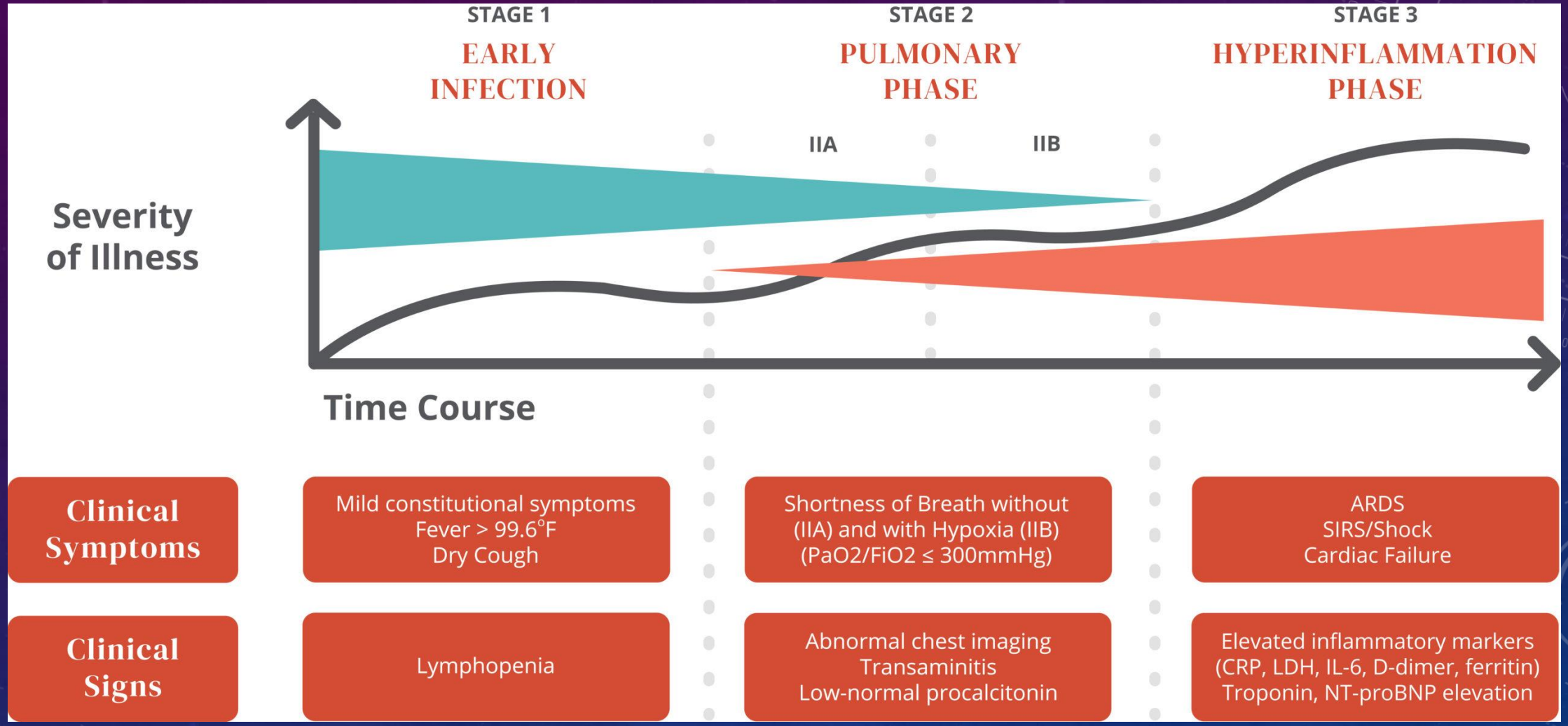
(Taubenberger JK. The origin and virulence of the 1918 “Spanish” Influenza Virus, Proceedings of the American Philosophical Society 2006;150:86-112
Mamelund SE. The impact of Influenza on Mental Health in Norway, 1872-1929. Workshop. May 2010.Carlsberg Academy, Copenhagen, Denmark)

OTHER OUTBREAKS

- Varied neuropsychiatric presentations in:
  - SARS
  - MERS
  - HINI in Europe
  - ZIKA
  - NIPAH
  - EBOLA

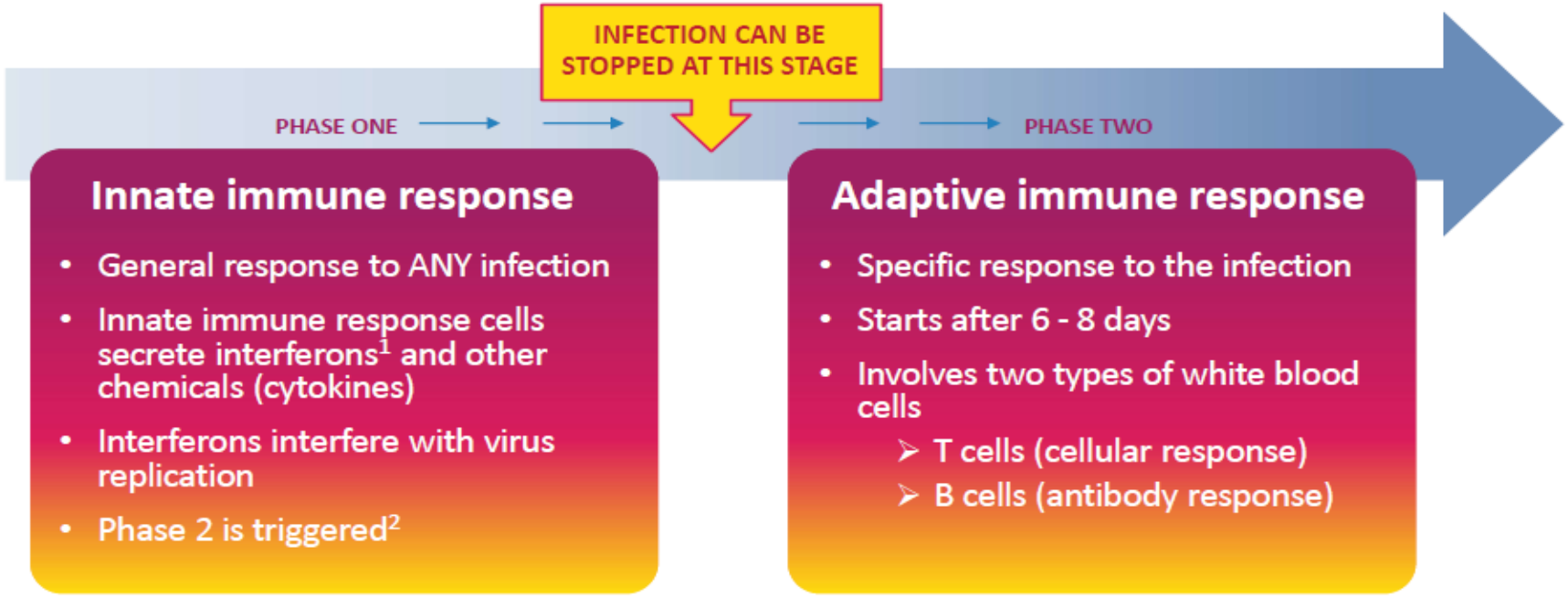
- PRESENTATIONS INCLUDED:
  - Acute meningoencephalitis, anosmia, demyelination, agitation, delirium, Guillain-Barre syndrome (GBS) and peripheral neuropathies

Honingsbaum, M, 2013. A History of the Great Influenza Pandemics: Death, Panic and Hysteria, 1830-1920, vol. 30. IB Tauris



Infection with SARS-COV-2 (COVID-19) can be classified into three inflammatory stages of increasing severity : early infection, pulmonary stage, and hyperinflammation phase. Adapted from Siddiqi, HK; and Mehra, MR. 2020

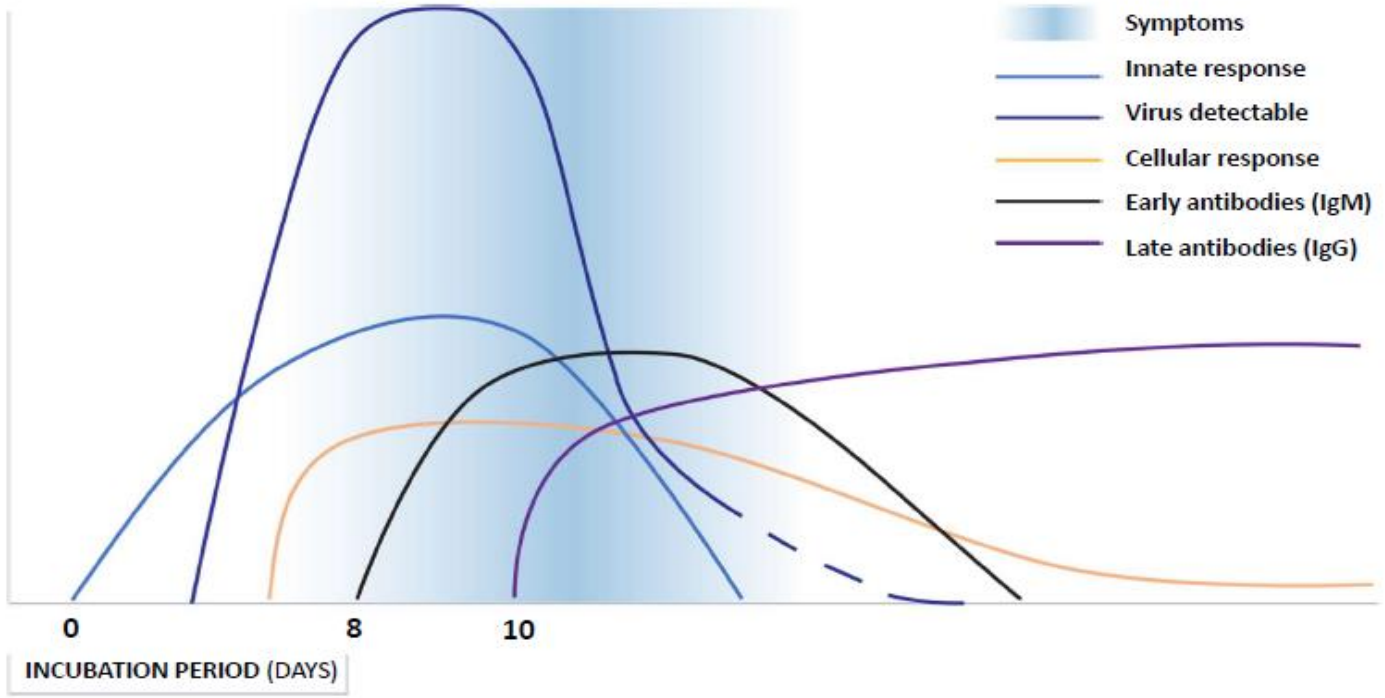
The immune response to viral infections



[1] Interferons and cytokines cause fever, muscle aches, etc - the early symptoms of infection

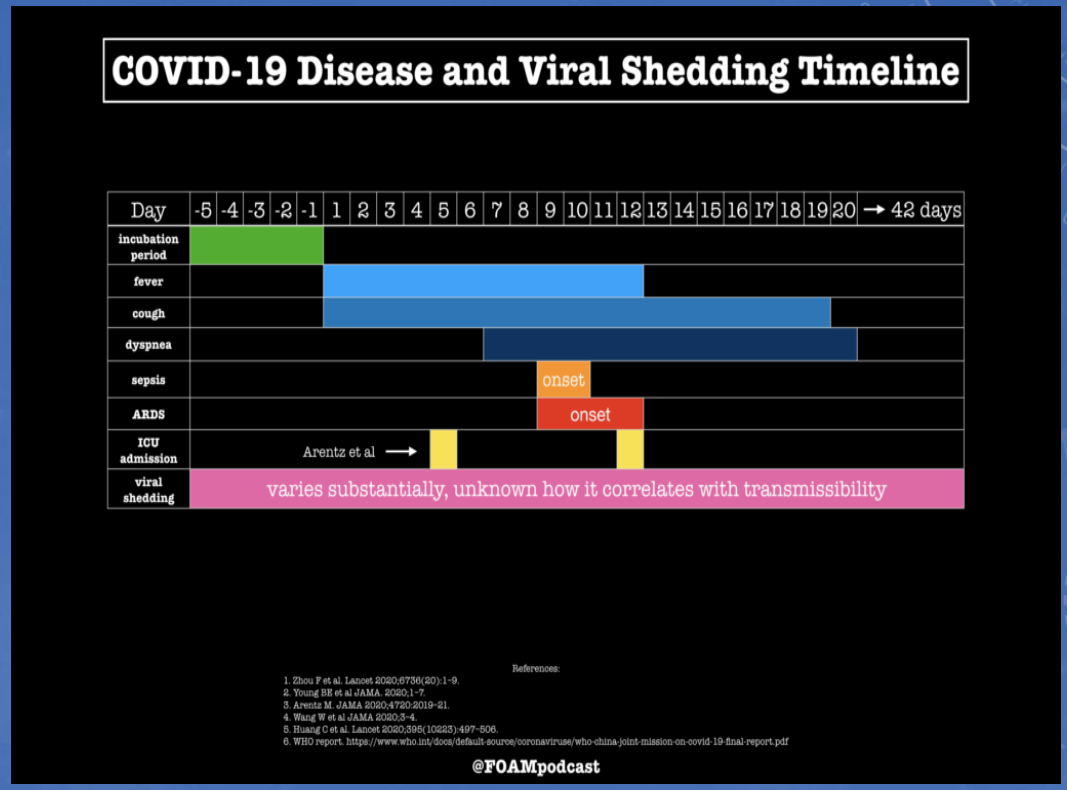
[2] A 'weaker' innate response (e.g. in elderly people or those with underlying health problems) may result in delayed stimulation of the adaptive response.

The immune response to viral infections in general



VIRAL SHEDDING OF SARS-COV-2

- Level and duration of infectious virus replication is important
- Viral RNA tests are used as a marker of infectious coronaviruses
- SARS-COV third of patients had viral RNA up till 4 weeks
- SARS-COV-2:
  - poorly described
  - median duration of viral shedding up till 20 days in survivors, longest 37 days



Zhou, F et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-1062

CORONAVIRUSES

- HCOV-229E
- HCOV-NL63
- HCOV-HKU1
- HCOV-OC43

- MERS-COV
- SARS-COV-1
- SARS-COV-2

HCOV PRIMARILY CAUSES RESPIRATORY DISEASE
3 HAVE SHOWN TO INFECT NEURONS

Zubair, A et al. Neuropathogenesis and Neurological Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019. A Review. JAMA neurology,
August 2020

NEUROPSYCHIATRIC SEQUELAE OF COVID-19: MECHANISM

DIRECT EFFECTS:

- Neurotropism under debate
- Possible haematogenous spread
- Olfactory neural pathways
- Direct invasion through ACE-2 receptor on neurons, glia, gut epithelial cells
- Direct neuroinvasion

INDIRECT:

- Host anti-SARS-COV-2 responses make BBB permeable with inflammation and stress-autoimmunity
- Secondary immune dysregulated response in chronic sequelae HPA axis activation due to stress involving release of steroids
- Gut microbial translocation (gut-brain axis): 40% patients GIT symptoms and viral shedding in stools for >5 weeks post-infection
- Lymphatic drainage from microglia via perivascular spaces along olfactory system to nasal mucosa
- Infection of endothelial cells lining brain vasculature

(https://www.immunopaedia.org.za/breaking-news/will-the-covid-19-pandemic-result-in-significant-neuropsychiatric-sequelae/?print=pdf)
Steardo, L et al. Psychiatric face of COVID-19. Translational Psychiatry July 2020

MECHANISMS MAY DIFFER IN DIFFERENT GROUPS PUBLIC AT LARGE AND HCW

- **PSYCHOLOGICAL SEQUELAE:**
  - SOCIAL ISOLATION
  - STIGMA
  - FAMILY CONFLICT AND ABUSE
  - UNCERTAINTY OF THE FUTURE
  - WORK LOSS
  - ECONOMIC IMPACT

- **HCW AND FRONTLINE WORKERS:**
  - EXPOSURE TO ONGOING STRESS-physical & psychological
  - HIGH INTENSITY WORK
  - BURNOUT 1-2 years post end of outbreak
  - FEARS ON LACK OF PPE AND VIRAL EXPOSURE
  - UNCERTAINTY AROUND FUTURE FOR FAMILIES
  - LOSS OF MAIN BREAD WINNER IN FAMILY
  - PTSD 11-73%
  - DEPRESSION ESPECIALLY IN FEMALES

NEUROPSYCHIATRIC PRESENTATIONS: STILL EVOLVING, UNANSWERED QUESTIONS

HOW COMMON ARE THESE ?

PROPORTION OF NEUROLOGICAL AND PSYCHIATRIC COMPLICATIONS ?

PROPORTION OF CNS VS PERIPHERAL NERVOUS SYSTEM ?

LACK OF COMPREHENSIVE AND INTEGRATED EPIDEMIOLOGICAL CHARACTERISATION

LACK OF MULTIDISCIPLINARY TEAM WORK APPROACH

ONLY 133 NEUROLOGY AND 371 PSYCHIATRIC PUBLICATIONS

ONLY SMALL CASE SERIES OR CASE REPORTS

NEUROLOGICAL PRESENTATIONS

- Spanish study COVID-19 patients, 57.4% had one neurological symptom
- Mild to moderate infection: Multicentre European Study
  - Headache 13%
  - Myalgias 12%
  - Altered sense of smell and taste 85-88% (Lechien et al 2020)
  - Encephalopathies
  - Encephalitis
  - Meningitis
  - Stroke 3%
  - Altered sensorium 8%
  - Sleep disorders 3.4%

Dinakaran, D et al. Neuropsychiatric aspects of COVID-19: a selective review. Asian J Psychiatr. 2020 Oct,53:102188

NEUROLOGICAL PRESENTATIONS

CNS

- Disorders of consciousness: 22%
- Seizures: 10% with critical illness
- Strokes: 5%
- Encephalopathy: 20%

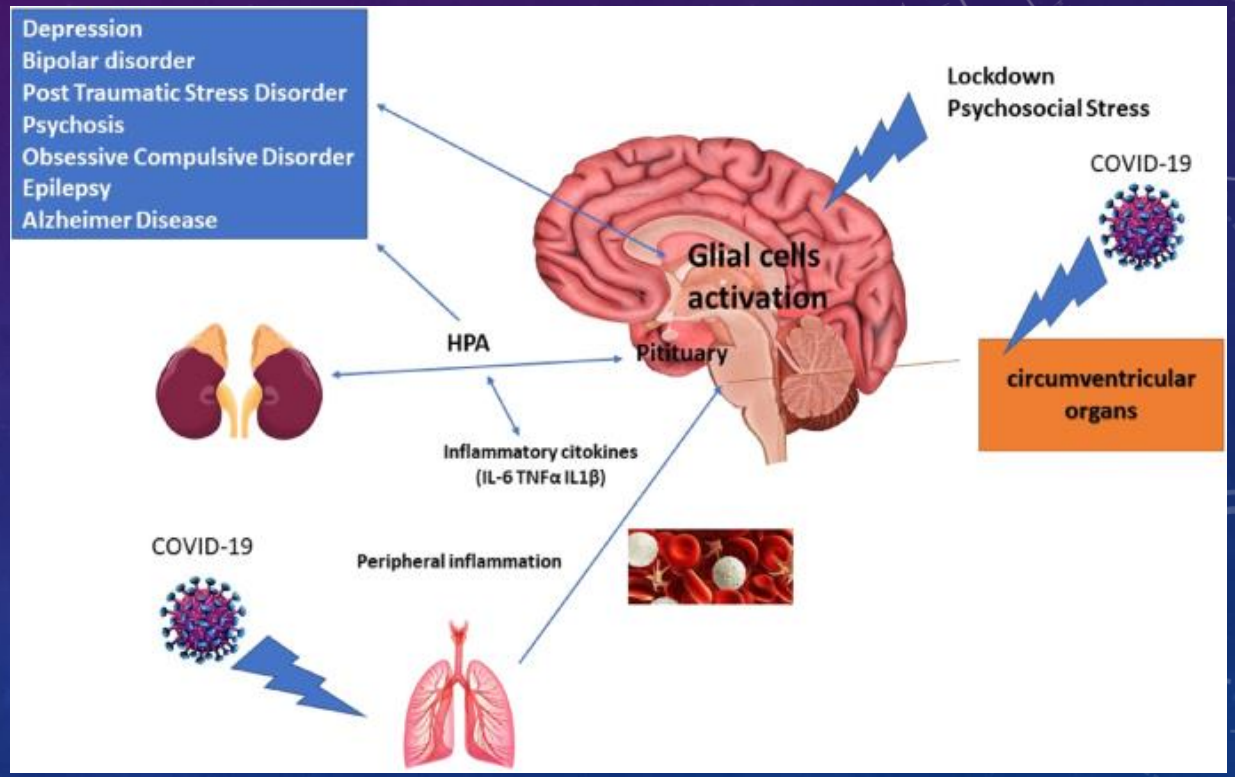
PNS

- Cranial neuropathies
- Anosmia/ageusia 80-85%
- Peripheral neuropathies: 5 cases in Wuhan
- Myopathy
- Demyelinating disorders

Probable illness: SARS-COV-2 CNS + by PCR in CSF
Possible illness: SARS-COV-2 CNS – by PCR in CSF

ACUTE NEUROPSYCHIATRIC PRESENTATIONS

- Small case series and limited data
- Cerebrovascular events in older patients via vasculopathy, endothelitis in organs
- Altered mental state-common with severe infection
- Neuropsychiatric features common in younger groups
  - Psychosis
  - Neurocognitive disorder
  - Other psychiatric disorders



Varatharaj,A; Thomas, N et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. The Lancet/psychiatry 2020;published online June 25

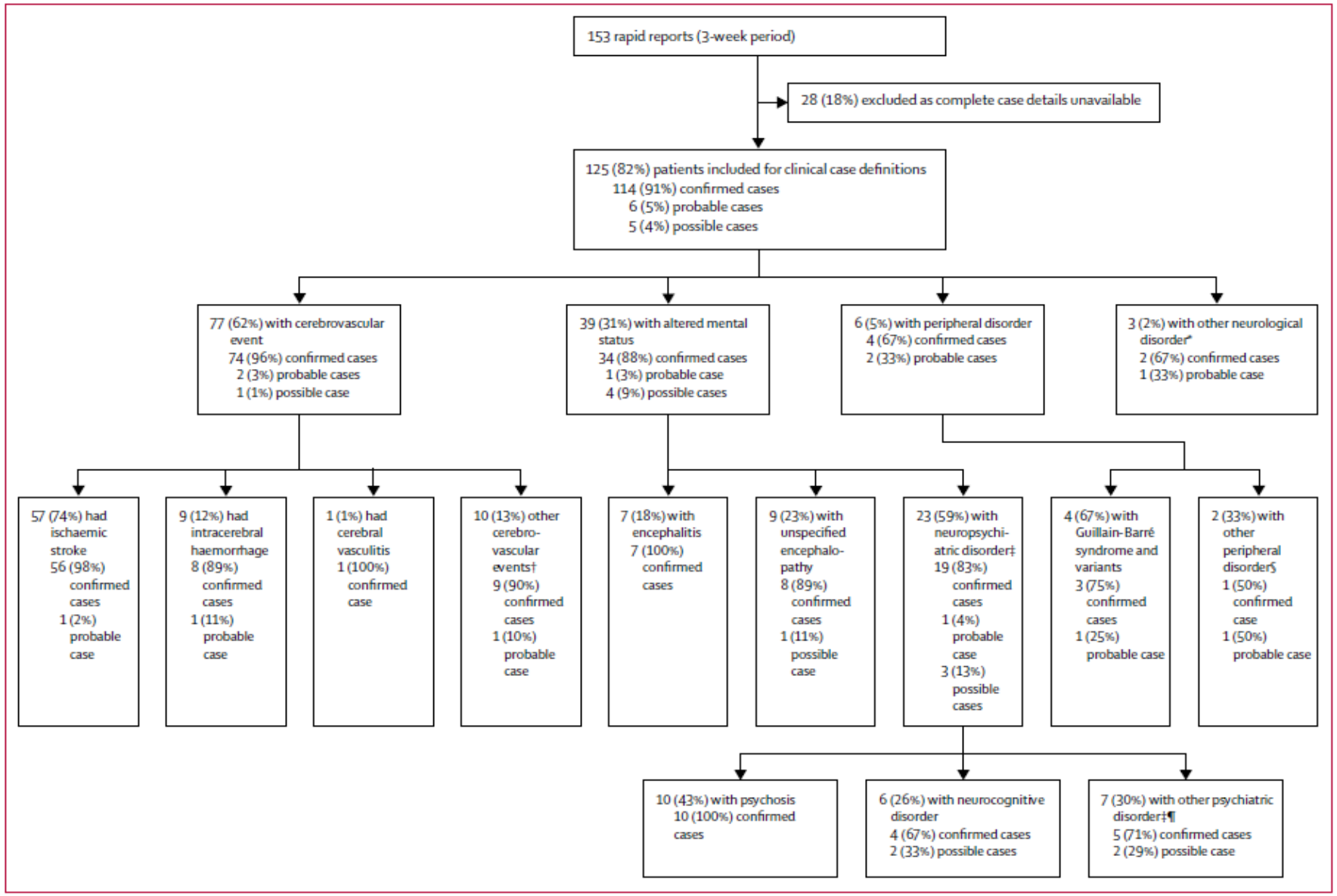


***Figure 3*: Number of broad and specific clinical case definitions notified in the dataset, including evidence for severe acute respiratory syndrome coronavirus 2 within each grouping, according to the clinical case definition**

* One patient with opsoclonus-myoclonus syndrome, one patient with sixth nerve palsy, and one patient with seizures. †Two patients with cerebral venous thrombosis, two patients with transient ischaemic attack, one patient with subarachnoid haemorrhage, and five unspecified. ‡1 case with missing SARS-CoV-2 data. §One patient with brachial neuritis and one patient with myasthenic crisis.

CHRONIC NEUROPSYCHIATRIC PRESENTATIONS

- Depression: 15-33%
- Anxiety: 15-36%
- Trauma related symptoms: 35-49% in HCW, 3-7% in public
- Psychosis: 26%
- Neurodegenerative/ neurocognitive disorders : 34%
- Side-effects of medications
- Post-viral syndrome as in EBV?

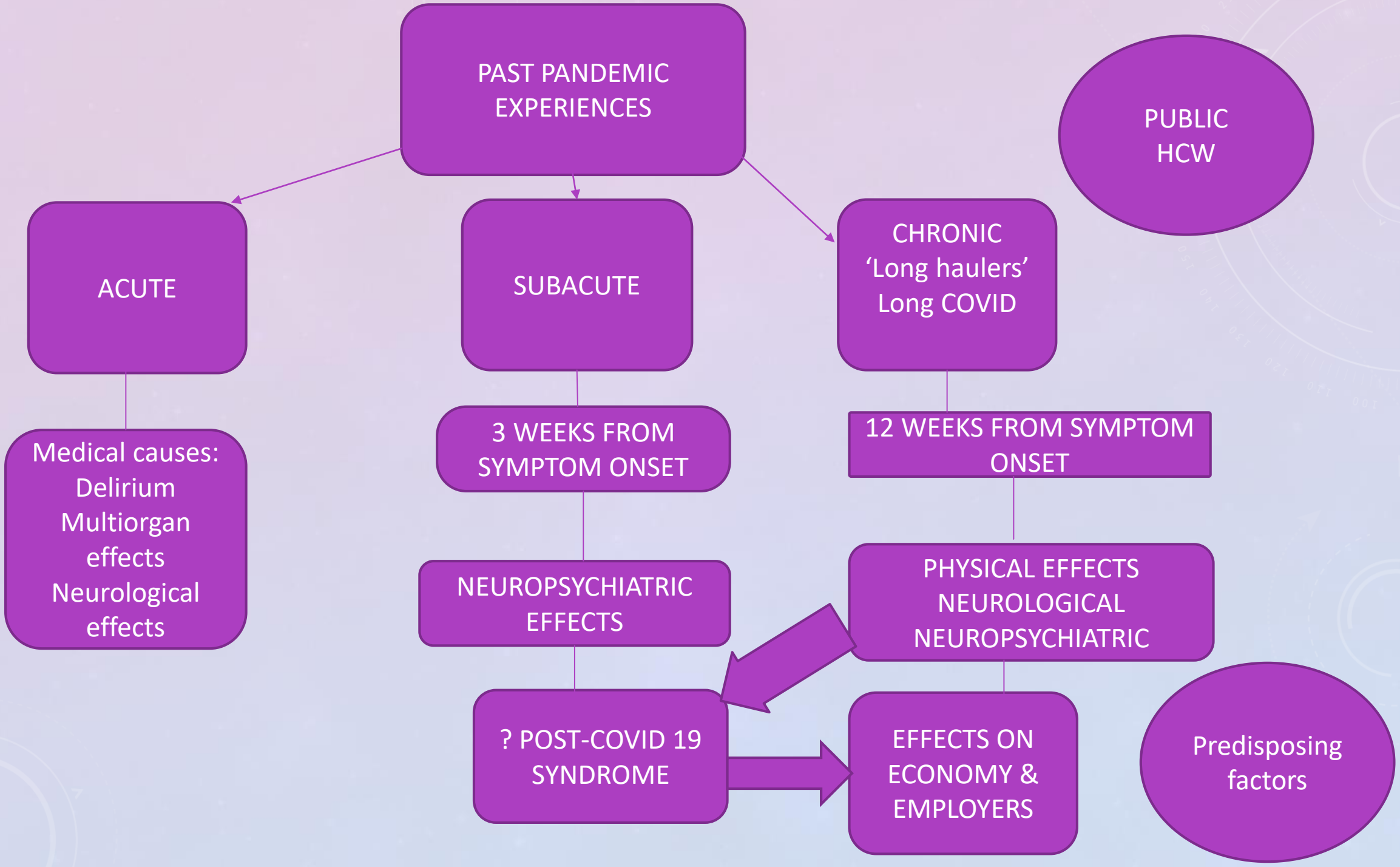
Banerjee, D et al. Neuropsychiatric manifestations of COVID-19 and possible pathogenic mechanisms: Insights from other coronaviruses.A Journal of Psychaitry. August 2020
Nalleballe,K et al. Spectrum of neuropsychiatric manifestations in COVID-19. Brain, Behaviour, Immunity.14 June 2020

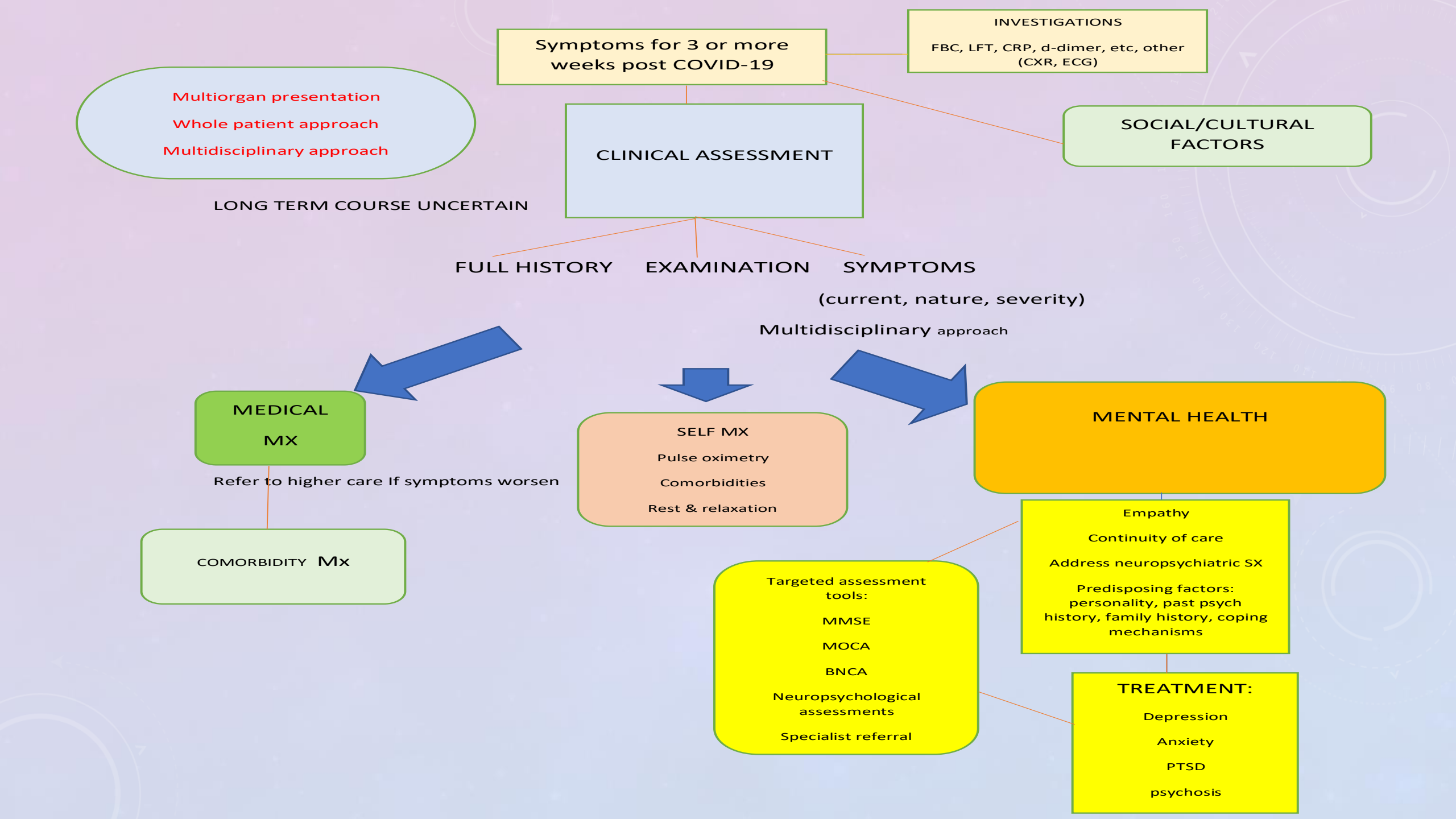
POST COVID-19 SYNDROME ('LONG HAULERS')

- **SYMPTOMS: fatigue, diffuse myalgia, depression, sleep disturbances, brain fog, anxiety**

- CDC reports that up to 35% COVID-19 positive people have ongoing symptoms
- Study in Italy has shown large proportion of patients have persistent symptoms or re-develop symptoms after a brief recovery
- Lack of clarity on agreed definitions of post-COVID-19, lack of requiring positive test for covid-19
- Chronic covid-19 has been defined by some as extending beyond 3-12 weeks
- Is there an element of post-infectious process? Similar to Chronic Fatigue Syndrome (CFS/ME)?
- Anectotal reports, small case series
- Pre-existing function of people not available
- Often associated with normal blood results and PCR tests often not positive

Davido, B , et al. Post-COVID-19 chronic symptoms: a post-infectious entity? Clinical Microbiology and Infection.
Perrin, R et al. Into the looking glass: Post-viral syndrome post COVID-19. Med Hyotheses. 2020 Nov; 144:110055


PAST PANDEMIC EXPERIENCES
PUBLIC
HCW
ACUTE
SUBACUTE
CHRONIC
'Long haulers'
Long COVID
Medical causes:
Delirium
Multiorgan effects
Neurological effects
3 WEEKS FROM SYMPTOM ONSET
12 WEEKS FROM SYMPTOM ONSET
NEUROPSYCHIATRIC EFFECTS
PHYSICAL EFFECTS
NEUROLOGICAL
NEUROPSYCHIATRIC
? POST-COVID 19 SYNDROME
EFFECTS ON ECONOMY & EMPLOYERS
Predisposing factors


Symptoms for 3 or more weeks post COVID-19
INVESTIGATIONS
FBC, LFT, CRP, d-dimer, etc, other (CXR, ECG)
Multiorgan presentation
Whole patient approach
Multidisciplinary approach
CLINICAL ASSESSMENT
SOCIAL/CULTURAL FACTORS
LONG TERM COURSE UNCERTAIN
FULL HISTORY
EXAMINATION
SYMPTOMS
(current, nature, severity)
Multidisciplinary approach
MEDICAL MX
SELF MX
Pulse oximetry
Comorbidities
Rest & relaxation
MENTAL HEALTH
Refer to higher care If symptoms worsen
COMORBIDITY Mx
Empathy
Continuity of care
Address neuropsychiatric SX
Predisposing factors: personality, past psych history, family history, coping mechanisms
Targeted assessment tools:
MMSE
MOCA
BNCA
Neuropsychological assessments
Specialist referral
TREATMENT:
Depression
Anxiety
PTSD
psychosis

CASE REPORT

- Young 29 year old female with no known psychiatric history or family history. She decides to visit her boyfriend in Cape Town in July after losing her job. He lives in Khayelitsha. She describes becoming unwell while there. Having a fever, physically unwell. She stayed in a 2 bedroomed house with other people there. One had a 'bad cough'. There was no social distancing and no mask wearing while at home. She remains there for 2 months. But still not feeling well after 2 months. She comes back to Gauteng via a bus. On arrival to Park Station she is confused, finds herself in Thembisa with no recollection on how she got there. A friendly Samaritan woman takes her in and manages to contact her brother who fetches her and takes her to CMJAH. She presents with psychotic symptoms of new onset. Ends up in the psychiatric ward. Is tested negative for COVID-19. But is in a cubicle with another patient who was positive. Is referred to Tara Hospital after a week at CMJAH for further care. On arrival due to history which is very acute onset and possibly COVID-19 related, is tested by us and is COVID-19 Positive.
- She completed her 10 day in our dedicated COVID-19 ward.
- Now is completely well. No psychiatric symptoms. No physical symptoms at all. Fully recovered.
    - ?? NEUROPSYCHIATRIC PRESENTATION – MILD INITIAL ILLNESS.? RE-INFECTION WITH DELIRIUM/ SEIZURES (CPS/FUGUE STATE), FALSE NEGATIVE COVID-19 RESULT,
    - TESTS POSITIVE FOR COVID-19 AT TARA HOSPITAL- HAS SHE BEEN POSITIVE ALL ALONG??

WAY FORWARD POST COVID-19

- Potentially faced with unprecedented amount of long term effects post COVID-19 infection
- Increased amount of disability claims and workplace assessments
- Social media driven disability
- Collaboration between all disciplines needed for research to move forward
- Occupational Therapy – level of functioning and work assessments, S/W, psychologists, nursing
- Detailed histories, resilience factors, personality
- Pre-existing depression, anxiety, traumatic experiences in past, gender differences
- Agreed structured criteria for diagnosis of post COVID-19
- Not overly pathologise symptoms, but to also acknowledge empathically

SOUTH AFRICA HAS SHOWN THAT WE CAN UNITE TO FIGHT COVID-19 AND THAT WE CAN ESTABLISH FURTHER COLLABORATIONS TO LEARN MORE

THANK YOU

sandra.fernandes@gauteng.gov.za
sandra@sfernandes.co.za