COVID-Neuro Network

# The COVID-Neuro Network Individual Patient Data Meta-Analysis

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COVID-Neuro Network

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- Tom Solomon
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    - The Team
      - Suzannah Lant
      - Bhagteshwar Singh
      - Catrin Tudur-Smith
      - Eva-Maria Hodel
    - Brain Infections Global
    - COVID-Neuro Network
- Suzannah Lant
  - The Individual Patient Data Meta-Analysis
- Discussion

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# Walton Centre NHS Foundation Trust


Brain Infections Global

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COVID-Neuro Network

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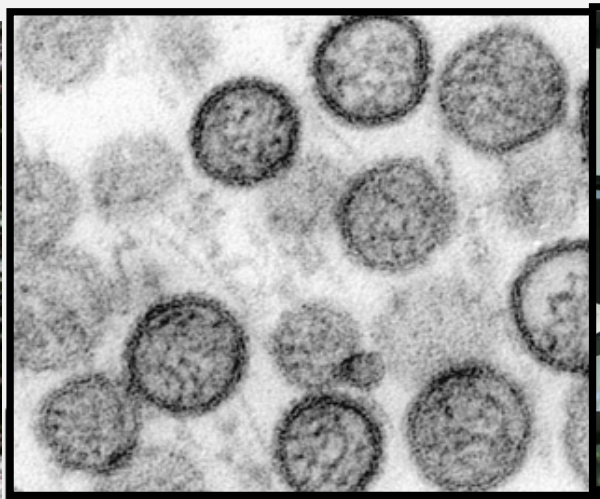
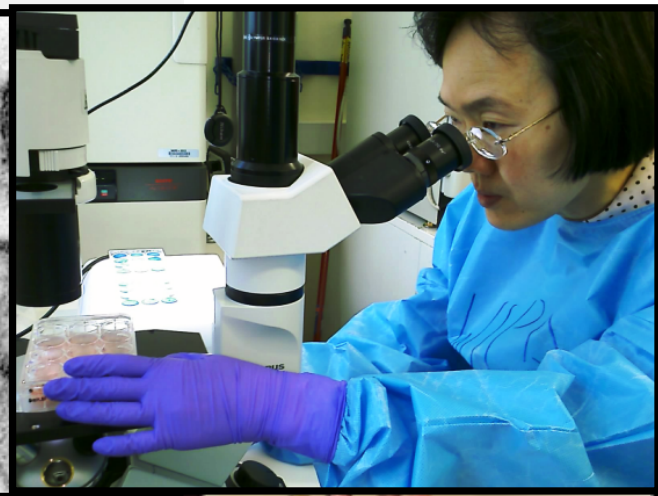
Established 2010
Director 2010-17



Brain Infections Global

**Improving the health of humans and animals by tackling key infectious disease in both a UK and global context**

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Public Health England

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LSTM LIVERPOOL SCHOOL OF TROPICAL MEDICINE

# NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections (EZI)

## Since 2014

Ebola

Zika

**Covid-19**

NIHR | National Institute for Health Research

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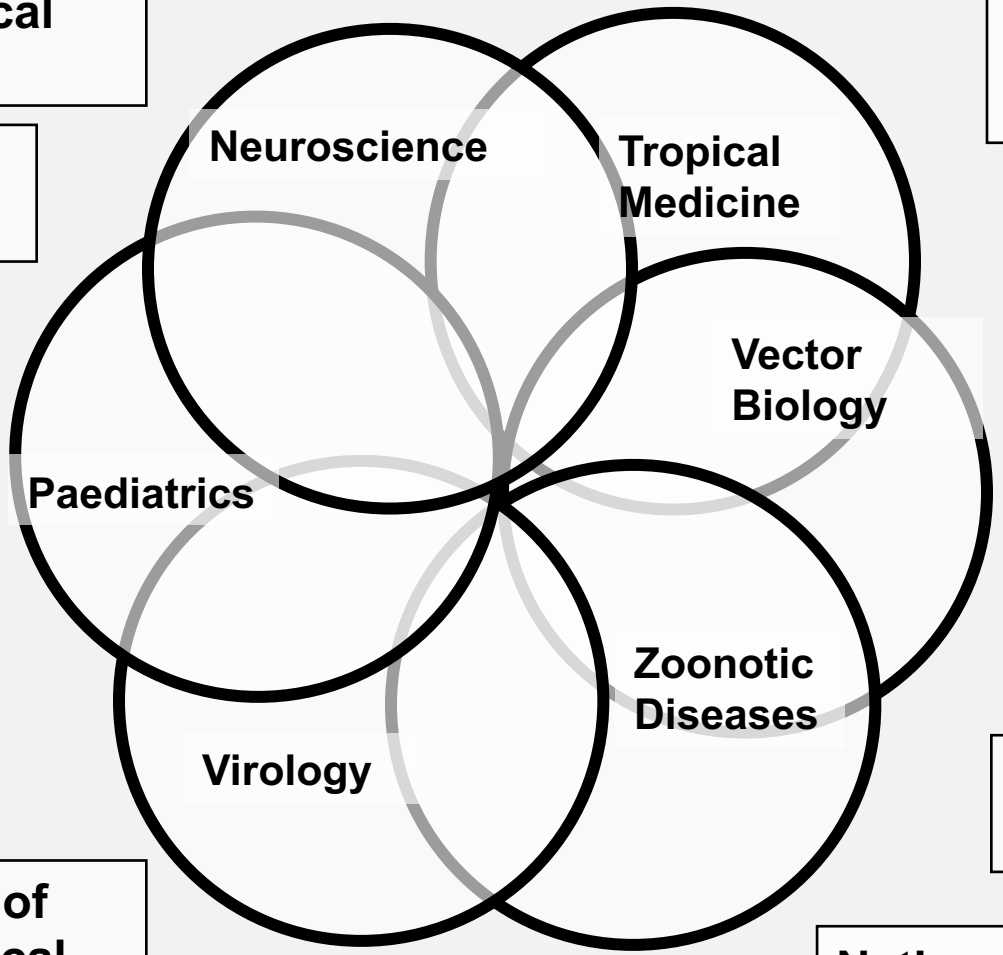
Neurological Science

Division of Child Health

Division of Medical Microbiology

School of Biological Science

School of Biomedical Science




NIHR Biomedical Research Centre in Microbial Diseases

Infectious Diseases

School of Tropical Medicine

Wellcome Trust Tropical Medicine

Veterinary Medicine

National Centre for Zoonotic Diseases

# £43M (US$56)

in research funding

Liverpool
**Brain Infections Group**

**30** members

- Epidemiology
- Clinical studies
- Diagnostics
- Host Response
- Theraputics

Laura Benjamin
Clinical Lecturer

Sylviane Defres
Hon Sen Clinical Lecturer

Mike Griffiths
Senior Clinical Lecturer

Fiona McGill
Clinical Lecturer

Benedict Michael
Senior Clinical Lecturer

Lance Turtle
Senior Clinical Lecturer

# Neurological Infectious Diseases in Liverpool

- Liverpool Brain Infections Research Group
  - Since 2003
- Neurological Infectious Diseases Course
  - since 2007
- Neurological Infectious Diseases Clinic
  - Since 2005
- Joint Inpatient Rounds
- Joint Outpatient Consults

Liverpool Brain Infections Group

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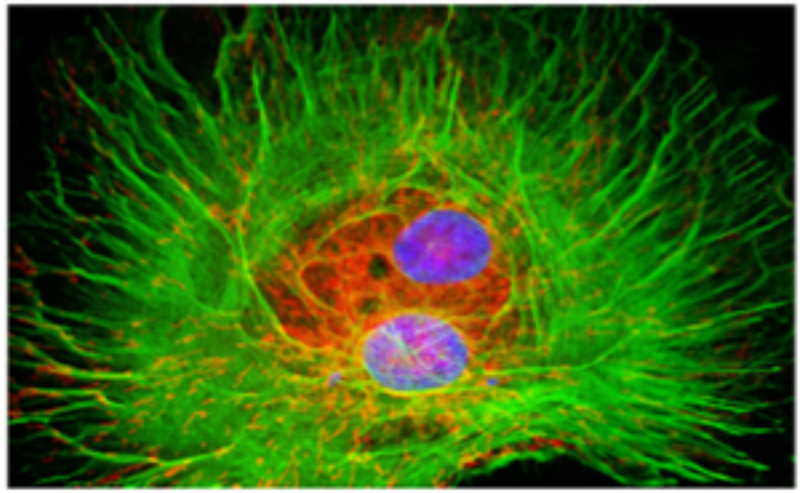
# Brain Infections UK



## Brain Infections UK

Welcome to Brain Infections UK, a group of new clinical research studies aiming to improve our understanding of potentially debilitating infections that can affect the brain such as encephalitis, meningitis and HIV. These conditions have a tremendous impact on the quality of life of large numbers of people in UK, but until now there has been little research done to try and tackle this.

Our studies cover brain infections in both adults and children and bring together leading experts with a range of specialisms including neurology, infectious diseases, acute and emergency medicine, medical microbiology and virology.

## Latest Updates from Brain Infections UK

more news

## Current Studies

> Enceph UK (341 patients recruited)

> UK-ChiMES (3009 patients recruited)

> UK Meningitis (1870 patients recruited)

> Partition (225 patients recruited)

> UK TB Meningitis (360 patients recruited)

> BASICS (1606 patients recruited)

> DexEnceph (12 patients recruited)

(Recruitment figures updated 03-10-2017)

## Publications and Outcomes

> The Interleukin-1 Balance During Encephalitis Is Associated With Clinical Severity, Blood-Brain Barrier Permeability, Neuroimaging Changes, and Disease Outcome.

> Characteristic Cytokine and Chemokine Profiles in Encephalitis of Infectious, Immune-Mediated, and Unknown Aetiology.

> The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults.

more publications

Liverpool Brain Infections Group

University of Liverpool

Liverpool Brain Infections Group

# International Collaborations

- University of Oxford-Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City (since 1994)
- Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand (since 1994)
- Institute of Health and Community Medicine, Universiti Malaysia Sarawak, Malaysia (Since 1997)
- University of Texas Medical Branch, Galveston, Texas (since 2001)
- Queen Elizabeth Hospital, Blantyre, Malawi (since 2003)
- National Institute for Mental Health and Neurological Science (NIMHANS), Bangalore, India (since 2004)
- Centres for Disease Control Atlanta, and Colorado, Texas (since 2007)
- Kanti Children's Hospital, Kathmandu, Nepal (since 2009)
- Indian Institute for Science, Bangalore (2009)
- John Hopkins Baltimore, USA (2009)
- Washington University St Louis, USA (2009)
- Lerner Research Institute, Cleveland, Ohio (2010)

# Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

*Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Walsh, Dilys Morgan, Richard Cunningham, Mark Zuckerman, Ken J Mutton, Tom Solomon, Katherine N Ward, Michael P T Lunn, Sarosh R Irani, Angela Vincent, David W G Brown, Natasha S Crowcroft, on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group*

## Summary

**Background** Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical differences between causes in patients with encephalitis in England.

**Methods** Patients of all ages and with symptoms suggestive of encephalitis were actively recruited for 2 years (staged start between October, 2005, and November, 2006) from 24 hospitals by clinical staff. Systematic laboratory testing included PCR and antibody assays for all commonly recognised causes of infectious encephalitis, investigation for less commonly recognised causes in immunocompromised patients, and testing for travel-related causes if indicated. We also tested for non-infectious causes for acute encephalitis including autoimmunity. A multidisciplinary expert team reviewed clinical presentation and hospital tests and directed further investigations. Patients were followed up for 6 months after discharge from hospital.

*Lancet Infect Dis* 2010; 10: 835–44

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on January 24, 2011

Published Online October 18, 2010

DOI:10.1016/S1473-3099(10)70222-X

# Viral Central Nervous System Infections in Children from a Malaria-Endemic Area of Malawi: a Prospective Cohort Study

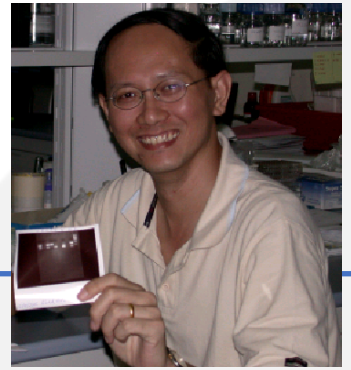
513 children with suspected CNS infection
- Excluded bacterial
- 94 (18%) died.

163 (32%) had *P. falciparum* parasitaemia, of whom 34 died;

133 (26%) had at least one virus detected in the central nervous system (CNS) by polymerase chain reaction (PCR), with 43 deaths.

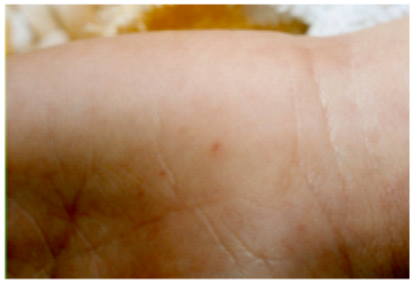
Twelve different viruses were detected,
- adenovirus most common (42 patients).

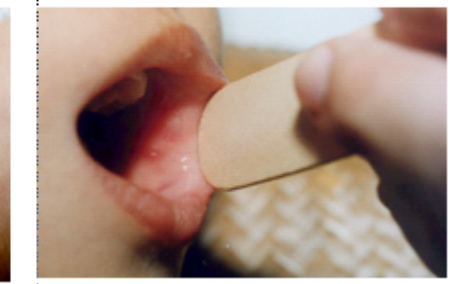
**45 (9%) children had both parasitaemia and viral infection;**
- **27 (35%) of 78 diagnosed clinically with cerebral malaria.**

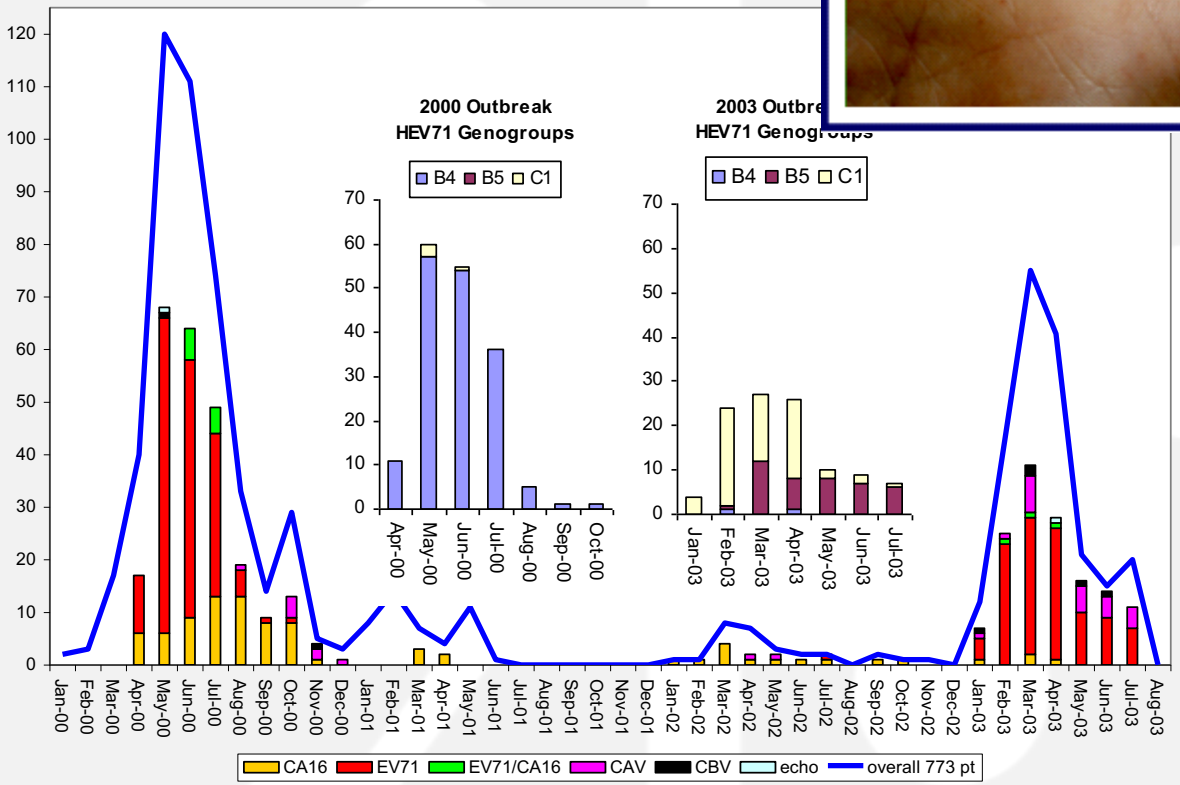


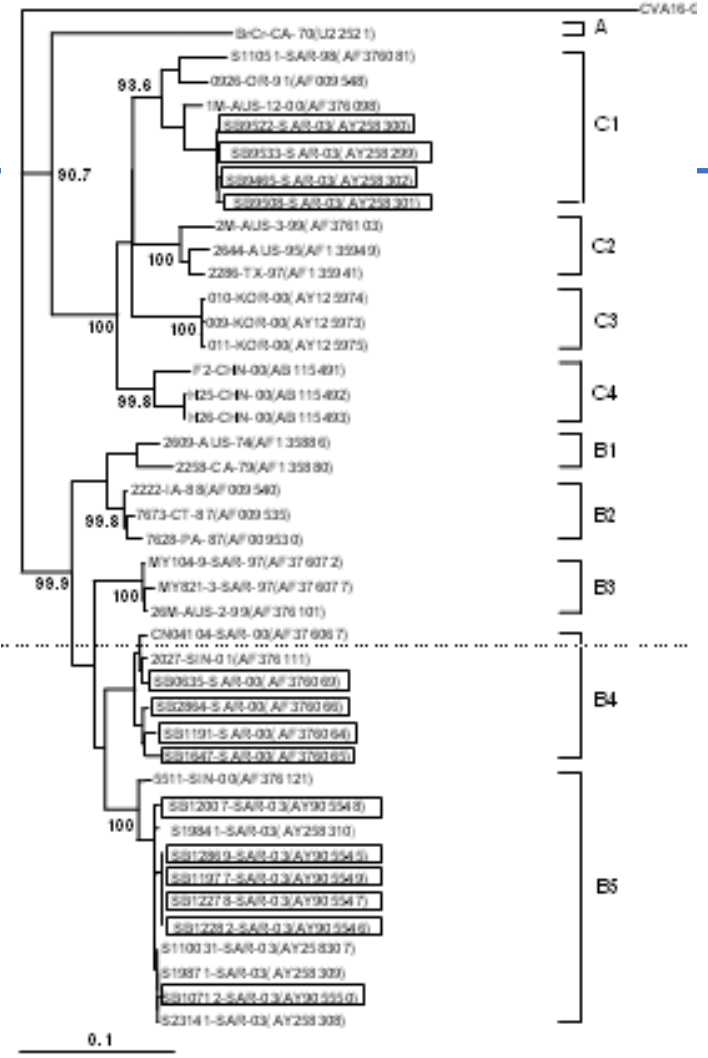
# Enterovirus 71 is an important cause of CNS disease in Asia

Hand and mouth leasions in a Malaysian Child with EV71 Hand foot and mouth disease )








Liverpool Brain Infections Group

Solomon et al, Lancet ID, 2010
Ooi et al, Lancet Neurology 2010

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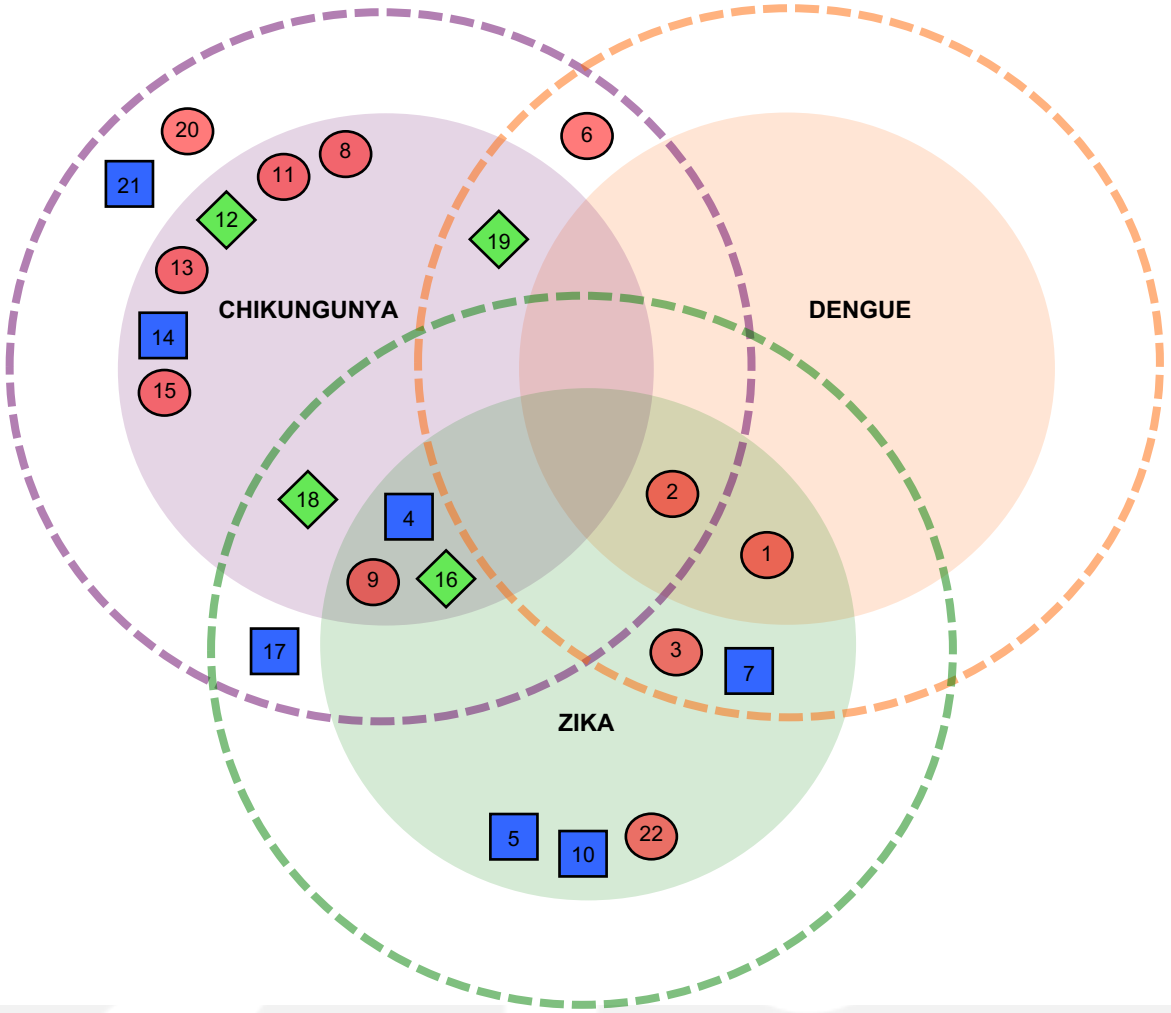
# Neurological disease associated with Zika and chikungunya viruses in adults Brazil




Of 35 patients studied, 22 had evidence of recent arboviral infection.

Twelve had **positive PCR or IgM for Zika**

- 5 of these coinfected with Chikungunya virus

Virological evidence of CNS infection

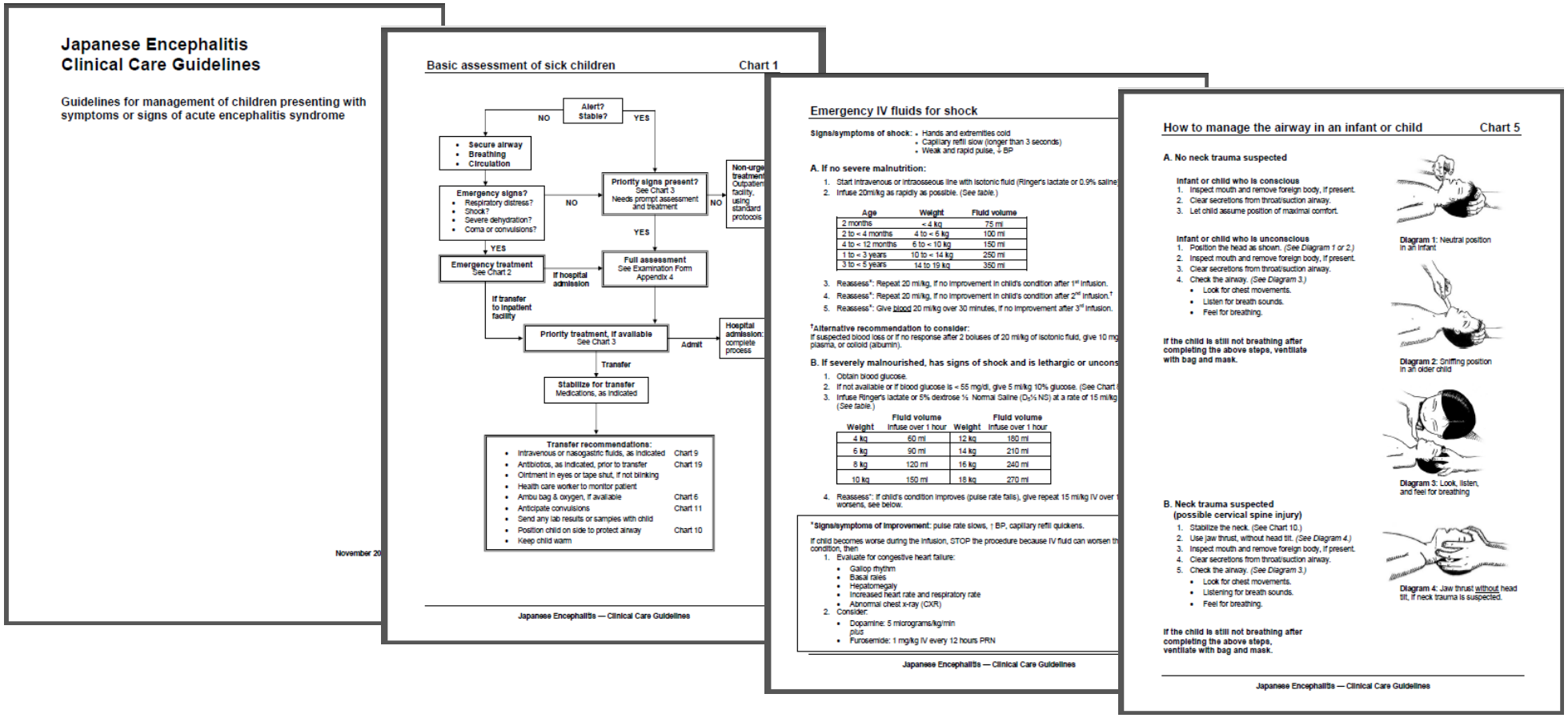
Virological evidence of systemic infection

Patient (number) with clinical evidence of CNS disease only

Patient (number) with clinical evidence of peripheral nervous system disease only

Patient (number) with clinical evidence of CNS and peripheral nervous system disease

# WHO JE Clinical Care Guidelines 2005



**Japanese Encephalitis**
**Clinical Care Guidelines**

Guidelines for management of children presenting with symptoms or signs of acute encephalitis syndrome

November 20

**Basic assessment of sick children** Chart 1

Alert? Stable?
NO
YES
Secure airway
Breathing
Circulation
Emergency signs?
Respiratory distress?
Shock?
Severe dehydration?
Coma or convulsions?
NO
Priority signs present? See Chart 3 Needs prompt assessment and treatment
NO
Non-urge treatment Outpatient facility, using standard protocols
YES
YES
Emergency treatment See Chart 2
If hospital admission
Full assessment See Examination Form Appendix 4
If transfer to inpatient facility
Priority treatment, if available See Chart 3
Admit
Hospital admission: complete process
Transfer
Stabilize for transfer Medications, as indicated
Transfer recommendations:
- Intravenous or nasogastric fluids, as indicated — Chart 9
- Antibiotics, as indicated, prior to transfer — Chart 19
- Ointment in eyes or tape shut, if not blinking
- Health care worker to monitor patient
- Ambu bag & oxygen, if available — Chart 6
- Anticipate convulsions — Chart 11
- Send any lab results or samples with child
- Position child on side to protect airway — Chart 10
- Keep child warm

Japanese Encephalitis — Clinical Care Guidelines

**Emergency IV fluids for shock**

**Signs/symptoms of shock:**
- Hands and extremities cold
- Capillary refill slow (longer than 3 seconds)
- Weak and rapid pulse, ↓ BP

**A. If no severe malnutrition:**

1. Start intravenous or intraosseous line with isotonic fluid (Ringer's lactate or 0.9% saline)
2. Infuse 20ml/kg as rapidly as possible. (See table.)

| Age | Weight | Fluid volume |
|---|---|---|
| 2 months | < 4 kg | 75 ml |
| 2 to < 4 months | 4 to < 6 kg | 100 ml |
| 4 to < 12 months | 6 to < 10 kg | 150 ml |
| 1 to < 3 years | 10 to < 14 kg | 250 ml |
| 3 to < 5 years | 14 to 19 kg | 350 ml |

3. Reassess*: Repeat 20 ml/kg, if no improvement in child's condition after 1st infusion.
4. Reassess*: Repeat 20 ml/kg, if no improvement in child's condition after 2nd infusion.†
5. Reassess*: Give blood 20 ml/kg over 30 minutes, if no improvement after 3rd infusion.

†Alternative recommendation to consider:
If suspected blood loss or if no response after 2 boluses of 20 ml/kg of isotonic fluid, give 10 mg plasma, or colloid (albumin).

**B. If severely malnourished, has signs of shock and is lethargic or uncons**

1. Obtain blood glucose.
2. If not available or if blood glucose is < 55 mg/dl, give 5 ml/kg 10% glucose. (See Chart
3. Infuse Ringer's lactate or 5% dextrose ½ Normal Saline ($D_5$½ NS) at a rate of 15 ml/kg (See table.)

| Weight | Fluid volume Infuse over 1 hour | Weight | Fluid volume Infuse over 1 hour |
|---|---|---|---|
| 4 kg | 60 ml | 12 kg | 180 ml |
| 6 kg | 90 ml | 14 kg | 210 ml |
| 8 kg | 120 ml | 16 kg | 240 ml |
| 10 kg | 150 ml | 18 kg | 270 ml |

4. Reassess*: If child's condition improves (pulse rate falls), give repeat 15 ml/kg IV over worsens, see below.

*Signs/symptoms of improvement: pulse rate slows, ↑ BP, capillary refill quickens.

If child becomes worse during the infusion, STOP the procedure because IV fluid can worsen th condition, then
1. Evaluate for congestive heart failure:
   - Gallop rhythm
   - Basal rales
   - Hepatomegaly
   - Increased heart rate and respiratory rate
   - Abnormal chest x-ray (CXR)
2. Consider:
   - Dopamine: 5 micrograms/kg/min *plus*
   - Furosemide: 1 mg/kg IV every 12 hours PRN

Japanese Encephalitis — Clinical Care Guidelines

**How to manage the airway in an infant or child** Chart 5

**A. No neck trauma suspected**

**Infant or child who is conscious**
1. Inspect mouth and remove foreign body, if present.
2. Clear secretions from throat/suction airway.
3. Let child assume position of maximal comfort.

**Infant or child who is unconscious**
1. Position the head as shown. *(See Diagram 1 or 2.)*
2. Inspect mouth and remove foreign body, if present.
3. Clear secretions from throat/suction airway.
4. Check the airway. *(See Diagram 3.)*
   - Look for chest movements.
   - Listen for breath sounds.
   - Feel for breathing.

**If the child is still not breathing after completing the above steps, ventilate with bag and mask.**

**Diagram 1:** Neutral position in an infant

**Diagram 2:** Sniffing position in an older child

**Diagram 3:** Look, listen, and feel for breathing

**B. Neck trauma suspected (possible cervical spine injury)**

1. Stabilize the neck. (See Chart 10.)
2. Use jaw thrust, without head tilt. *(See Diagram 4.)*
3. Inspect mouth and remove foreign body, if present.
4. Clear secretions from throat/suction airway.
5. Check the airway. *(See Diagram 3.)*
   - Look for chest movements.
   - Listening for breath sounds.
   - Feel for breathing.

**If the child is still not breathing after completing the above steps, ventilate with bag and mask.**

**Diagram 4:** Jaw thrust without head tilt, if neck trauma is suspected.

Japanese Encephalitis — Clinical Care Guidelines

Liverpool Brain Infections Group

Solomon et al, Lancet 1998 Bulletin WHO 2008

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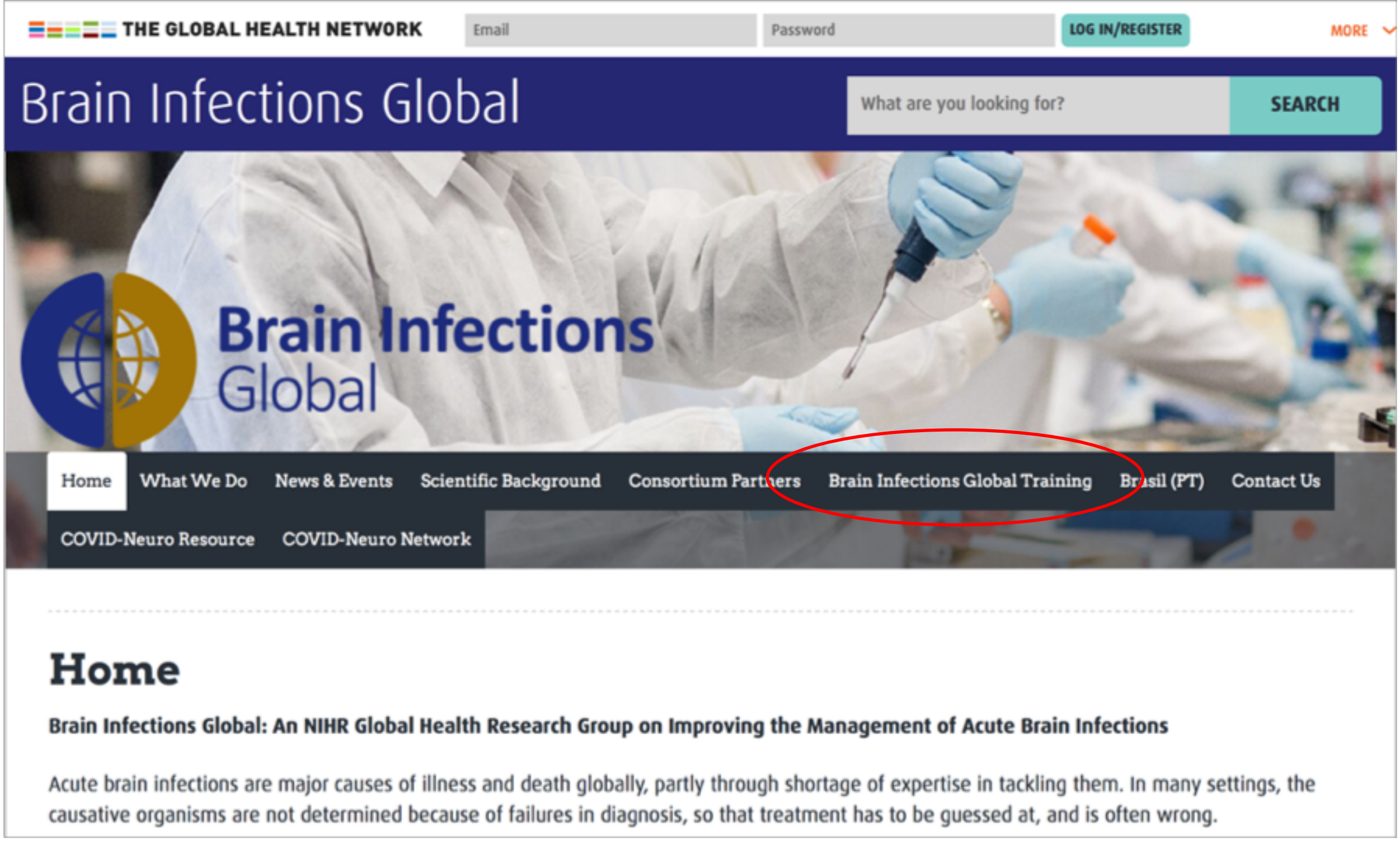



# Home

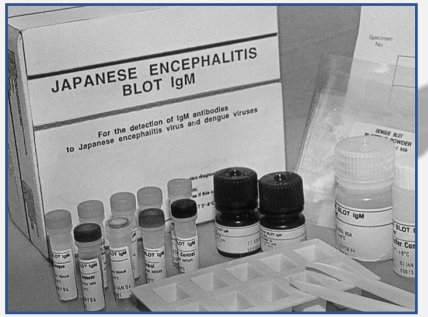
**Brain Infections Global: An NIHR Global Health Research Group on Improving the Management of Acute Brain Infections**

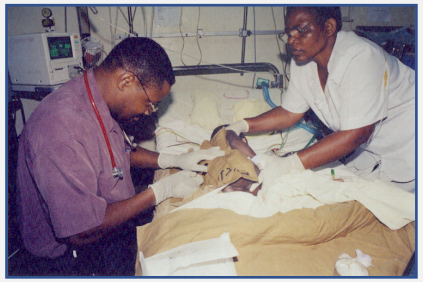
Acute brain infections are major causes of illness and death globally, partly through shortage of expertise in tackling them. In many settings, the causative organisms are not determined because of failures in diagnosis, so that treatment has to be guessed at, and is often wrong.

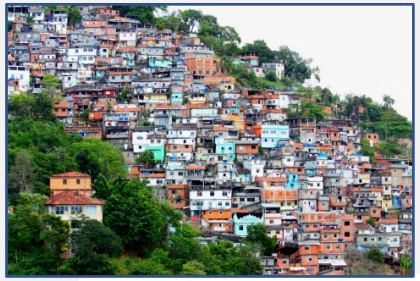
# NIHR Global Health Research Group on Brain Infections

COVID-Neuro Network

Brain Infections Global





- University of Liverpool – Institute of Infection and Global Health
- Liverpool School of Tropical Medicine
- Warwick Centre for Applied Health Research and Delivery

- Oswaldo Cruz Foundation, (FioCruz) Recife, Brazil.

- National Institute for Mental Health & Neuroscience (NIMHANS), Bangalore, India
- Christian Medical College (CMC), Vellore, India

- College of Medicine (CoM), Malawi,
- Malawi-Liverpool-Wellcome Trust Unit, (MLW) Malawi

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# Brain Infections Global

## A global network and community of practice for research in acute brain infections, embedded within The Global Health Network

19,000 visitors and 1800 members

Including over 500 new users in the past 2 weeks

From across the world

Top 5 countries:

1) UK
2) India
3) Brazil
4) Kenya
5) Nigeria

Learning, joining events and accessing resources

With COVID-Neuro Resources accessed by over 1000 people to date

And over 2900 e-learners taking Neuro-ID online courses

Visit braininfectionsglobal.tghn.org

THE GLOBAL HEALTH NETWORK

COVID-Neuro Network

Liverpool Brain Infections Group

NeuroID Course

Brain Infections Global

NeuroID e-learning

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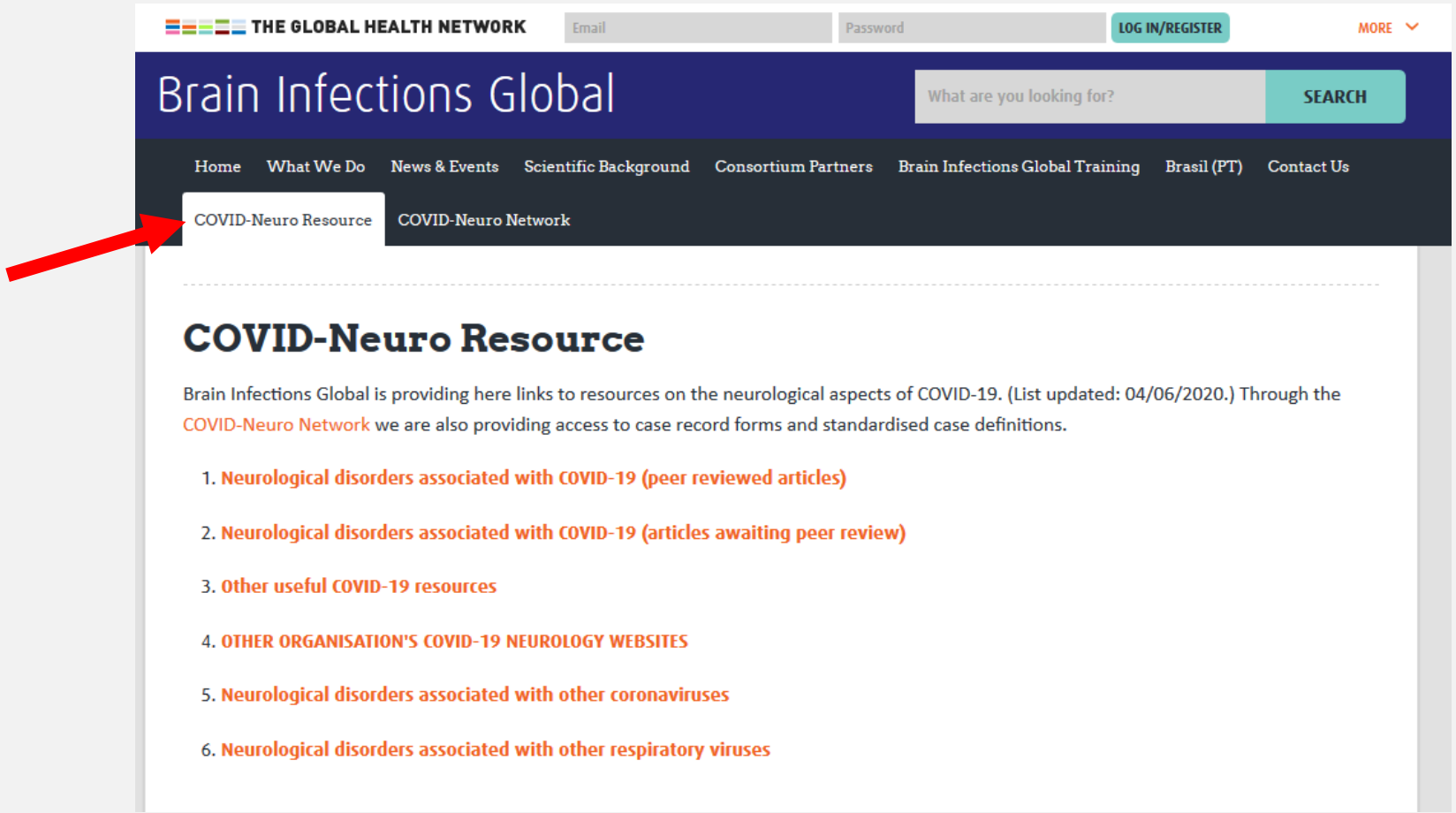
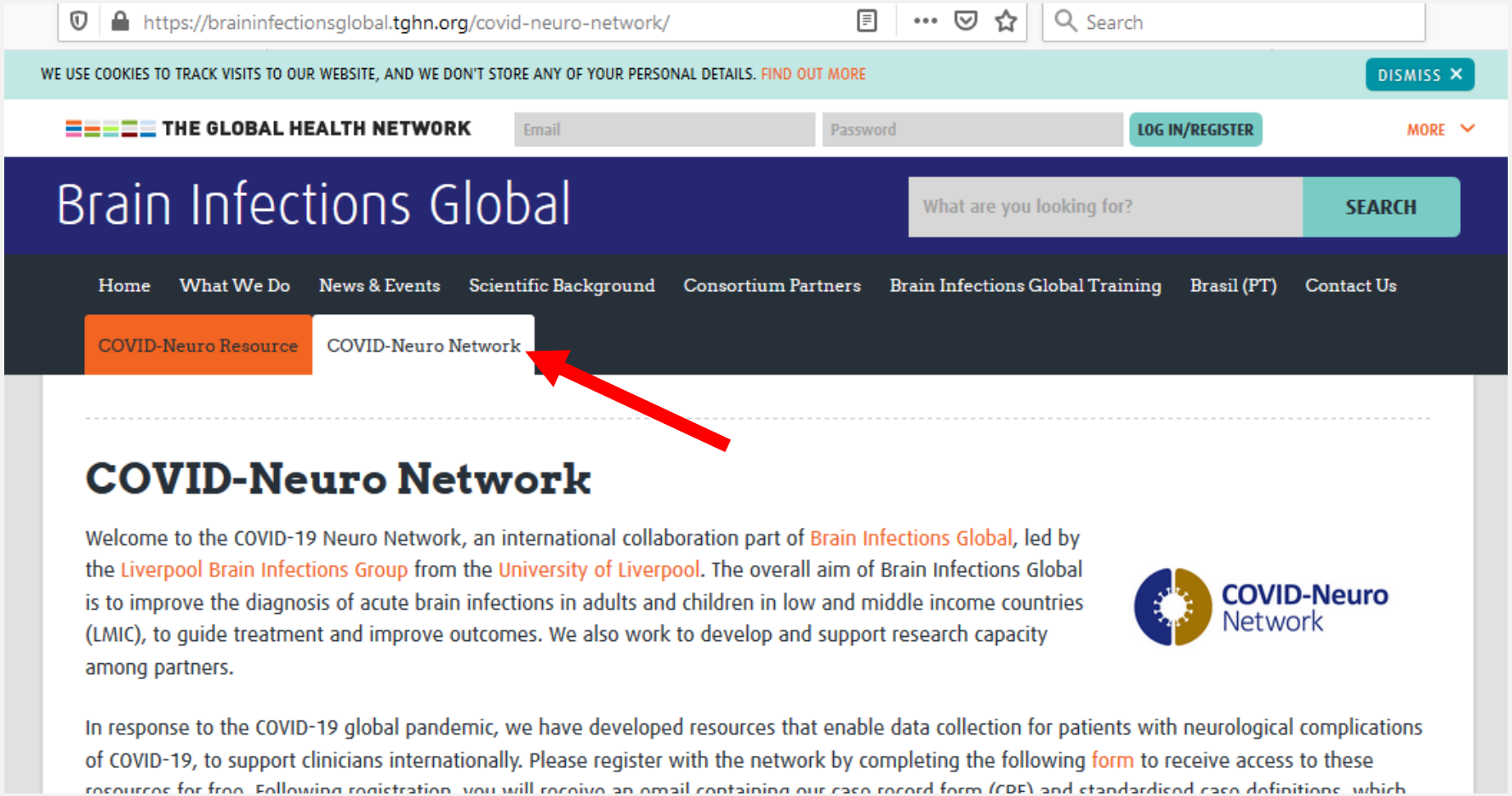
University of Liverpool

# Latest COVID-Neuro resources freely available



# Join our network

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# Data collection tools

COVID-Neuro Network

## COVID-NEURO NETWORK - CASE RECORD FORM (CRF)

Liverpool Brain Infections Group

Brain Infections Global

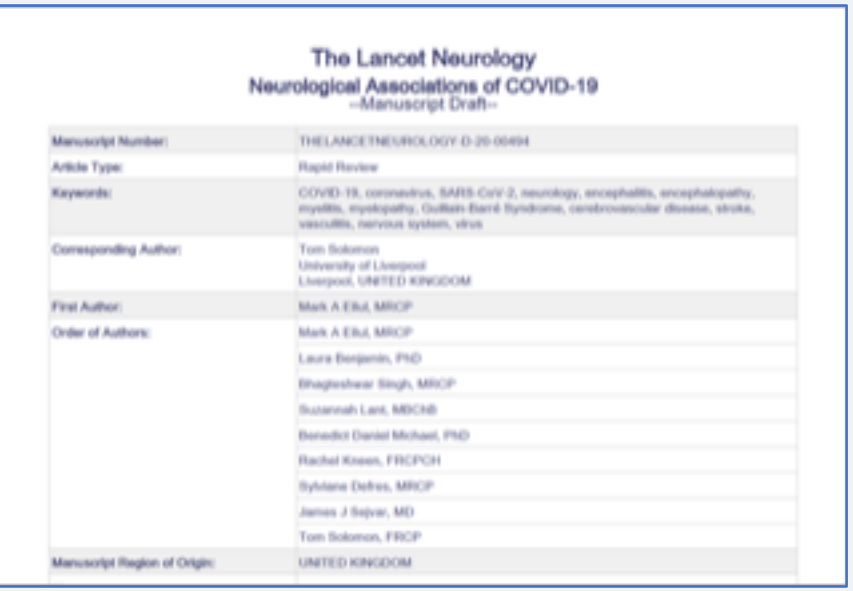
The COVID-Neuro Network is an international collaboration that is part of Brain Infections Global (**https://braininfectionsglobal.tghn.org/**), led by the Liverpool Brain Infections Group from the University of Liverpool. The overall aim of Brain Infections Global is to improve the diagnosis of acute brain infections in adults and children in low and middle income countries (LMIC), to guide treatment and improve outcomes. We also work to develop and support research capacity among partners.

In response to the COVID-19 global pandemic, we have developed this CRF to enable data collection for patients with neurological syndromes that may be related to COVID-19, to support clinicians internationally. Thank you for registering with the COVID-Neuro Network and accessing this form. If you have not registered, please do so at **https://www.liverpool.ac.uk/covid-neuro-network/** . Through our network, we aim to standardise data collection and facilitate subsequent comparison and sharing of information, and will be in touch with you about how we can do this, so that ultimately we strengthen the global COVID-19 research response.

Note: This is CRF v2.2 29/04/2020. All members registered with the COVID-Neuro Network will be sent any updated versions of the data collection tool.

COVID-Neuro Network

# Neurological Associations of COVID-19
## (The Lancet Neurology, IN PRESS)



The Lancet Neurology

Neurological Associations of COVID-19

--Manuscript Draft--

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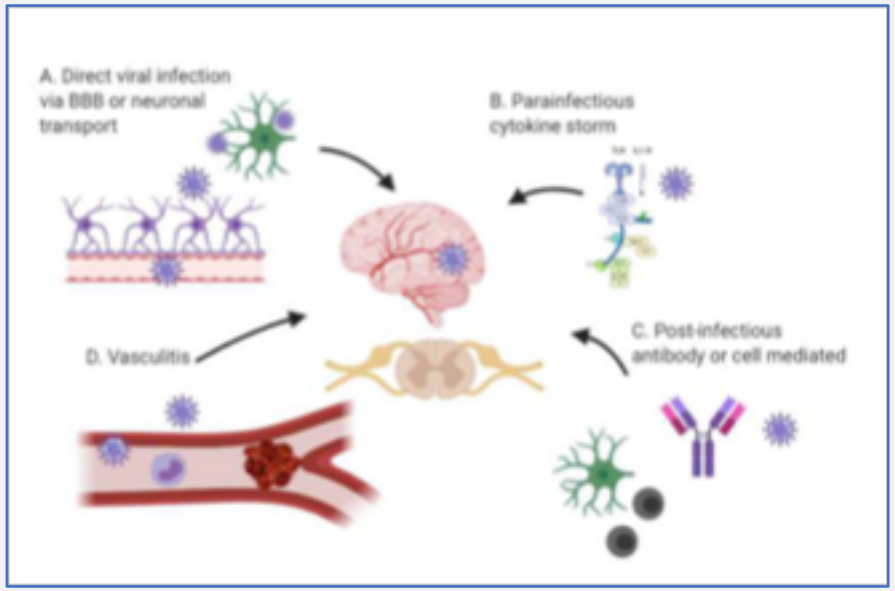


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Health

# Coronavirus: Scientists use genetic code to track UK spread

Fergus Walsh
Medical correspondent
@BBCFergusWalsh

9 March 2020 Share

Prof Hiscox's team are using MinION, a hand-held sequencer developed by Oxford Nanopore Technologies

**Scientists are analysing the unique genetic code of individual samples from infected patients to track how the coronavirus is spreading across the UK.**

Each sample of its genetic material, RNA, reveals another step in the chain of infections - who infected whom.

University of Liverpool scientists can also identify other viruses and bacteria in patients' throat swabs.

And this may help explain why some patients with no known underlying health conditions become seriously ill.

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Prof **Tom Solomon** Presents

The **Scouse Science** Podcast

With guests

**Professor Sally Sheard** and **Frank Cottrell Boyce**

COVID-Neuro Network

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# INDIVIDUAL PATIENT DATA META-ANALYSIS

ACTION

- Sign Up to the IPD on Survey Monkey:
- **https://www.surveymonkey.co.uk/r/GPY5RH3**
- Complete the Data Sharing Agreement
- Complete the Data Collection Case Record Form
  - Patients already published
  - Patients not yet published
- Recruit your Friends to the IPD Meta-analysis
- Join Brain Infections Global
- https://braininfectionsglobal.tghn.org