***Improving the Management of Brain Infections in the UK and Internationally***

**Staff**

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**Summary**

The devastating impact of brain infections can be markedly reduced through prompt recognition, diagnosis and treatment. Research at the University of Liverpool has improved surveillance, diagnosis and management leading to new UK guidelines, with global impact. With close patient and public involvement, the Liverpool team increased awareness of brain infections, reaching millions through publications, courses and outreach events. Patients are thus recognised, diagnosed and treated quicker; e.g. the median time to antiviral treatment for encephalitis in the UK fell from 48 hours to 10 hours leading to better outcomes, and saving up to an estimated £1,183,997,971 since 2013.

**The Challenge**

Many brain infections are treatable. Yet brain infections such as meningitis (inflammation of the brain membranes) and encephalitis (inflammation of the brain itself) are a major emerging cause of disability and death. Liverpool research aimed to understand the causes of this problem and improve practice through its NIHR-funded “Brain Infections UK” Programme, delivered in collaboration with national hospitals, charities and the NHS, and the linked NIHR “Brain Infections Global” Programme, delivered through international partnerships.

**Our Research**

The team examined treatment for encephalitis and meningitis nationally, through two major NIHR-funded programmes, Enceph-UK and UK-Meningitis, part of the Brain Infections UK Portfolio. The former recruited 1,930 patients, the latter 1,870 (**3.2**). Misdiagnosis of encephalitis was common; 85% of cases showed subtle behavioural or personality changes which were often misinterpreted as psychiatric illness, rather than treatable brain infection (**3.4**).

In Lower- and Middle-Income Countries, even fewer brain infections are diagnosed because the full range of causes is not yet known. The Brain Infections Global Programme showed the importance of viral brain infections in Africa (**3.3**), and the role of emerging viruses on the brain including Zika, Ebola, Japanese encephalitis and in the UK, COVID-19 (**5.1**)**.**

**Working in partnership**

The team collaborated with Public Health England to examine trends in prevalence of both viral and bacterial brain infections in the UK. They showed that herpes simplex virus is the most common infectious cause of encephalitis, but that autoimmune encephalitis (caused by the body’s host defences) is growing in importance (**3.1**). The team showed viral meningitis is also increasing numerically in the UK and leads to a significant health economic burden (**3.2**). Similar international studies strengthened surveillance in Asia, Latin America and Africa (**3.3**).

The UK and international research was supported by an extensive patient and public involvement programme run through the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (Professor Solomon is Director), working closely with the Encephalitis Society (Professor Solomon, Chair of the Society’s Scientific Advisory Panel 2010-2019, President since 2019; Dr Michael, Vice Chair 2019), and the Meningitis Research Foundation (Dr Kneen, Dr McGill and Dr Michael members of the Medical Advisory Group since 2015); this included joint grant applications with the patient and public involvement partners, co-delivery of the research, joint publications and shared dissemination events.

**Impact of Research**

Liverpool research has greatly improved the likelihood that those suffering a brain infection, in the UK or further afield, will survive and avoid devastating disability (**5.1**). The impacts have been achieved through two main areas: firstly, improved awareness of brain infections among health care professionals and the public (vital to promoting early presentation and appropriate initial medical assessment); secondly, better hospital management (because correct and timely treatment has a dramatic effect on outcome) (**5.2**)

***Raising awareness to promote early presentation***

In 2014 just 1 in 1,000 people had heard of encephalitis; by 2020, the figure was 1 in 5. Liverpool researchers drove this change through devising and supporting a plethora of innovative patient and public engagement initiatives, in conjunction with the Encephalitis Society. In 2014 they instigated the first annual World Encephalitis Day with a Guinness World Record-winning science-art installation, the “World’s Largest Brain” made of people, which featured in national and international media. In 2015 there was a World-Wide-Webinar with patients and families from Lower- and Middle-Income Countries describing their own case studies. By World Encephalitis Day 2020, 186,000,000 people world-wide (22,600,000 in the UK) had been reached. (**5.3**)

To reach a different audience, the Liverpool group’s work was described in Professor Solomon’s 2016 popular science book, *Roald Dahl’s Marvellous Medicine*. This is Liverpool University Press’ best ever seller, and had widespread coverage, including Sky News, and BBC Radio 4’s “Saturday Live” and “All in the Mind”. The group’s work also featured in Professor Solomon’s sell-out show at Edinburgh Fringe Festival 2017, which visited 7 other UK venues including London’s West End. (**5.3**)

***Guidelines and their uptake (5.2, 5.4, 5.5)***

The group’s research resulted in the production of new national meningitis and encephalitis guidelines (**5.2**), which are now the primary reference point for all medical practitioners in the UK. In a survey of neurologists and other specialists, 75% of respondents recalled one or more occasions when following the guidelines had made an impact on patient outcome (**5.4**). Because of their clarity and simplicity, the guidelines are also popular beyond the UK; e.g. their importance is acknowledged in the International Encephalitis Consortium’s Consensus Statement, and they are cited in the Australia and New Zealand consensus guidelines (**5.5**).

***Impact through education (5.4, 5.6)***

The guidelines feature heavily alongside other work from the team in the annual Liverpool Neurological Infectious Diseases Course (established in 2007), engaging 1,017 UK delegates (from 193 NHS Trusts) and 327 foreign delegates from 40 countries since 2013 (**5.6**). 88% of respondents from the 2019 course agreed or strongly agreed that the course had informed their practice, with 71% recalling of one or more specific patients who had been helped (**5.4**). Supplementing the course, 22 free online Neuro-ID e-learning modules that are Royal College of Physicians recognised and credit bearing, have had 19,000 visitors since 2013; the linked free online educational videos have been viewed more than 3,500,000 times (**5.6**).

***Neurological COVID-19 Disease*** *(****5.7****,* ***5.8****)*

The wider impact of the team’s research into recognising, diagnosing and managing neurological manifestations of infectious diseases is exemplified by their response to COVID-19 (**5.7**). The team rapidly modified and distributed their standardised case definitions for neurological COVID-19 disease. Through leadership of national and international collaborations (the UK Coronerve Study, Covid CNS - the Clinical Neuroscience Study, - and the Global COVID-Neuro Network), they determined the range of neurological manifestations of COVID-19, which proved critical in caring for such patients. The findings were disseminated through the WHO Brain Unit’s Neuro-Covid Forum, monthly COVID-Neuro webinars, through the Brain Infections Global Network and the Covid-Neuro Global Research Coalition (**5.8**).

***Improved health outcomes (5.9, 3.6)***

The impact of the group’s work on improving management is best demonstrated by the case study of time to treatment for herpes simplex virus encephalitis with the antiviral drug aciclovir. Before the start of the Liverpool programme, the median time to treatment in the UK (as elsewhere) was 48 hours; and yet several studies show that delays beyond 48 hours are associated with a worse outcome in terms of death and neurological disability. Following the introduction of the national guidelines, which emphasise the need for a rapid lumbar puncture, and their implementation through the Enceph UK Programme, the median time to treatment dropped from 48 to 23 hours by 2013, and 10 hours by 2016 (**5.9**).

***Health economic implications*** *(****5.10****)*

To calculate the benefits of this more rapid treatment, the team conducted a health economic evaluation. Initiation of treatment for herpes simplex virus encephalitis within 48 hours was associated with improvement in outcome (58% had good recovery on Glasgow Outcome Scale Score, compared with 16%), shorter hospital stays, and reduced total NHS costs by £25,895 (from £56,916 to £31,022) per patient in the first year after diagnosis (**5.10**).

**References**

**3.1**: Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN, Lunn MP, Irani SR, Vincent A, Brown DW, Crowcroft NS; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010 Dec;10(12):835-44. [https://doi.org/10.1016/S1473-3099(10)70222-X](https://doi.org/10.1016/S1473-3099%2810%2970222-X).

**3.2**: McGill F, Griffiths MJ, Bonnett LJ, Geretti AM, Michael BD, Beeching NJ, McKee D, Scarlett P, Hart IJ, Mutton KJ, Jung A, Adan G, Gummery A, Sulaiman WAW, Ennis K, Martin AP, Haycox A, Miller A, Solomon T; UK Meningitis Study Investigators. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis*. 2018 Sep;18(9):992-1003.

**3.3**: Mallewa M, Vallely P, Faragher B, Banda D, Klapper P, Mukaka M, Khofi H, Pensulo P, Taylor T, Molyneux M, Solomon T. Viral CNS infections in children from a malaria-endemic area of Malawi: a prospective cohort study. *Lancet Glob Health* 2013; 1: e153-60. <http://dx.doi.org/10.1016/S2214-109X>(13)70060-3.

**3.4**: Cooper J, Kierans C, Defres S, Easton A, Kneen R, Solomon T. Diagnostic Pathways as Social and Participatory Practices: The Case of Herpes Simplex Encephalitis. *PLoS One* 2016; 11: e0151145. <https://doi.org/10.1371/journal.pone.0151145>.

**3.6**: Backman R, Foy R, Diggle PJ, Kneen R, Easton A, Defres S, McGill F, Michael BD, Solomon T, on behalf of the ENCEPH UK Programme Steering Committee. A pragmatic cluster randomised controlled trial of a tailored intervention to improve the initial management of suspected encephalitis. *PLoS One* 2018; 13: e0202257. <https://doi.org/10.1371/journal.pone.0202257>.

**5.1:** **International application of the surveillance and diagnostic approaches the team developed in the UK strengthened the global impact of the work**, for example demonstrating neurological manifestations of emerging viruses such as Zika, Chikungunya and Ebola:

1. Ferreira MLB, … Solomon T. Neurological disease in adults with Zika and chikungunya virus infection in Northeast Brazil: a case series. *The Lancet Neurology* 2020; 19: 826-39. [https://doi.org/10.1016/S1474-4422(20)30232-5](https://doi.org/10.1016/S1474-4422%2820%2930232-5)
2. Howlett PJ, … Scott JT. Case Series of Severe Neurologic Sequelae of Ebola Virus Disease during Epidemic, Sierra Leone. *Emerg Infect Dis* 2018; 24: 1412-21. <https://dx.doi.org/10.3201/eid2408.171367>

**5.2:** **New UK guidelines for Meningitis**

c. McGill F, … Solomon T. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. Journal of Infection. 2016 Apr;72(4):405-38. https://doi.org/10.1016/j.jinf.2016.01.007

d. Solomon T, … Beeching NJ. Management of suspected viral encephalitis in adults - Association of British Neurologists and British Infection Association National Guidelines. Journal of Infection 2012; 64: 347-73. <https://doi.org/10.1016/j.jinf.2011.11.014>;

**5.3: Raising awareness through public engagement activities**

e. **Evidence of raised awareness**, YouGov Plc survey 2017, for Encephalitis Society.

f. **Information on World Encephalitis Day**, since 2014 <https://www.encephalitis.info/wed-history> and BMJ 2014;348:g1747 <https://doi.org/10.1136/bmj.g1747>

g. **Roald Dahl’s Marvellous Medicine book**, figures from: Liverpool University Press; Broadcasters Audience Research Board (BARB); Radio Joint Audience Research (RAJAR); <https://www.tomsolomon.co.uk/upcoming-events>

**5.4: Practioner views on the guidelines and education initiatives**

 h. Brain Infections Group, Impact Survey: <https://www.liverpool.ac.uk/infection-and-global-health/research/brain-infections-group/education/>

**5.5: International impact of UK guidelines**

i. Table of guidelines citations in international policy and policy-related documents.

j. A. Venkatesan, A. R, … James Cherry. Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium, *Clinical Infectious Diseases*, Volume 57, Issue 8, 15 October 2013, Pages 1114–1128, <https://doi.org/10.1093/cid/cit458>

k. Britton PN, … Public Health Association of Australia (PHAA). Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. *Intern Med J*. 2015 May;45(5):563-76. <https://doi.org/10.1111/imj.12749>

**5.6:** **Clinician/professional education initiatives**

l. NeuroID course, <https://www.liverpool.ac.uk/neuroidcourse/> NeuroID e-learning modules, <https://braininfectionsglobal.tghn.org/brain-infections-global-training/neuroid-elearning/>

m. Table of participation numbers and country representation, 2013 to 31 Dec 2020.

**5.7:** **COVID neurology response, Liverpool leadership**

n. Ellul MA, … Solomon T. Neurological associations of COVID-19. *Lancet Neurol*. 2020 Sep;19(9):767-783. [https://doi.org/10.1016/S1474-4422(20)30221-0](https://doi.org/10.1016/S1474-4422%2820%2930221-0) Epub 2020 Jul 2.

o. Winkler AS, … Solomon T. A call for a global COVID-19 Neuro Research Coalition. Correspondence. *Lancet Neurol*. 2020 June; 19(6):482-484. [https://doi.org/10.1016/S1474-4422(20)30150-2](https://doi.org/10.1016/S1474-4422%2820%2930150-2) Epub 2020 May 26.

p. House of Lords, Science and Technology Committee. 15 Sept 2020, Oral evidence session: The science of COVID-19. ‘What are the long-term health impacts and healthcare requirements of COVID-19?’ <https://committees.parliament.uk/event/1910/formal-meeting-oral-evidence-session/>

 q. Media engagement: Table supplied with national and international examples, Jun-Oct 20.

r. COVID-Neuro webinar series: <https://braininfectionsglobal.tghn.org/webinars/>. Details of and participation figures supplied.

**5.8: Informing UK and international public health policy**

s. Zika: ZikaPLAN/ Neuro-Zika work, Latin America <https://zikaplan.tghn.org/zikaplan-at-work/neurological-manifestations/>

t. Ebola: House of Commons, Science and Technology Select Committee (2015/16), UK readiness in case of Ebola outbreak. <https://publications.parliament.uk/pa/cm201516/cmselect/cmsctech/469/469.pdf>

**5.9: Improved health outcomes in the UK. Group’s audit results**

u. Ennis, K et al, 2018, ‘Economic impact of delays in treatment for Herpes Simplex Virus Encephalitis patients in the U.K’, presented at NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, [Annual Conference](http://hpruezi.nihr.ac.uk/media/s5mefz4v/final-programme-nihr-hpru-in-emerging-and-zoonotic-infections-annual-conference.pdf), Public Health England Collindale. 21st November 2018. With pre-publication expanded results draft paper.

**5.10:** **Reduced costs of care for encephalitis**

v. **Costings evaluation comes from**: Ennis, K et al, 2018, ‘Economic impact of delays in treatment for Herpes Simplex Virus Encephalitis patients in the U.K’, presented at NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, [Annual Conference](http://hpruezi.nihr.ac.uk/media/s5mefz4v/final-programme-nihr-hpru-in-emerging-and-zoonotic-infections-annual-conference.pdf), Public Health England Collindale. 21st November 2018.

w. **Incidence estimates come from**: Granerod, J, … Thomas, S. L. (2013). New estimates of incidence of encephalitis in England. *Emerging infectious diseases*, 19(9), 1455–1462. <https://doi.org/10.3201/eid1909.130064>