

Institution: University of Liverpool		
Unit of Assessment: UoA1		
Title of case study: Improving the management of Brain Infections in the UK and internationally		
Period when the underpinning research was undertaken: 2000-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Tom Solomon	Professor of Neurology;	1998 - present
Dr Fiona McGill	Honorary Senior Clinical Lecturer in Infectious Diseases and Microbiology;	2011 - present
Dr Benedict Michael	Senior Clinical Lecturer in Neurology;	2008 - present
Dr Sylviane Defres	Honorary Senior Clinical Lecturer in Infectious Diseases and Microbiology;	2012 - present
Dr Lance Turtle	Senior Clinical Lecturer in Infectious Diseases and Microbiology;	2010 - present
Dr Michael Griffiths	Senior Clinical Lecturer in Paediatric Neurology;	2009 - present
Dr Rachel Kneen	Honorary Senior Clinical Lecturer in Paediatric Neurology	2005 - present
Period when the claimed impact occurred: 2013-2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact <p>The devastating impact of brain infections (meningitis and encephalitis) 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 group have 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 13 hours leading to better outcomes, and saving up to GBP1,183,997,971 since 2013.</p>		
2. Underpinning research <p>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. The Liverpool group's 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.</p> <p>Understanding the changing disease risk through enhancing surveillance: The group 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 group showed that 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).</p> <p>Strengthening Diagnosis: The group examined management of encephalitis and meningitis nationally, through two major NIHR-funded programmes, Enceph-UK and UK-Meningitis, both 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).</p>		

Even when organic brain disease was suspected, most encephalitis and meningitis patients had unnecessary brain imaging, causing delays before the critical diagnostic test, the lumbar puncture (3.2); this allows analysis of the cerebrospinal fluid to guide treatment, but is less informative if delayed. When lumbar puncture was performed the correct investigations were rarely requested. The group went on to show that the introduction of a simple lumbar puncture pack, which includes guidance on who needs brain imaging before lumbar puncture and which specific samples to send where, significantly increased the rate of diagnosis, supporting prompt specific treatments (3.5).

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 (see 5.5, 5.7).

Improving Management: Based on the UK findings, the group developed and piloted encephalitis guidelines in the NHS North West region, before leading the development of new national guidelines for encephalitis (2012) and meningitis (2016) (both chaired by Solomon, see 5.1). To improve implementation of the encephalitis guidelines nationally, an intervention was developed through the Enceph-UK Programme, based around the lumbar puncture pack, and assessed through a cluster randomised controlled trial (3.6). A similar programme improved the management of patients with brain infections globally.

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 (Solomon, Director 2014 to present), working closely with the Encephalitis Society (Solomon, Chair of the Society's Scientific Advisory Panel 2010-2019, President 2019 to present; Michael, Vice Chair 2019), and the Meningitis Research Foundation (Kneen, McGill and Michael, members of the Medical Advisory Group 2015 to present); this included joint grant applications with the patient and public involvement partners, co-delivery of the research, joint publications and shared dissemination events.

3. References to the research

- 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(10)70222-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. [https://doi.org/10.1016/S1473-3099\(18\)30245-7](https://doi.org/10.1016/S1473-3099(18)30245-7).
- 3.3. **Mallewa M**, Vally 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](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>.
- 3.5. **Michael B**, Menezes BF, Cunliffe J, **Miller A**, **Kneen R**, Francis G, **Beeching NJ**, **Solomon T**. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J*. 2010 Jun;27(6):433-8. <http://dx.doi.org/10.1136/emj.2009.075598>.
- 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>.

4. Details of the impact

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. 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) (5.1).

Raising awareness to promote early presentation

To ensure people with brain infections seek appropriate hospital care earlier it was essential to raise awareness among the public and professionals. In 2014 just 1 in 1,000 people had heard of encephalitis; by 2020, the figure was 1 in 5 (5.2). Liverpool researchers drove this change through devising and supporting a plethora of innovative patient and public engagement initiatives, in conjunction with the Encephalitis Society (5.2). For example, in 2014 the group instigated the first annual *World Encephalitis Day* with a Guinness World Record-winning science-art installation, the “World’s Biggest Brain”, which featured in national and international media (5.2). 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 (5.2).

To reach a different audience, the Liverpool group’s work was described in Solomon’s 2016 popular science book, *Roald Dahl’s Marvellous Medicine*, (5* Amazon rating). 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 Solomon’s sell-out show at Edinburgh Fringe Festival 2017, which visited 7 other UK venues including the West End (5.2).

Guidelines and their uptake

The group’s research resulted in the production of new national meningitis and encephalitis guidelines (5.1), 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 (5.3). Because of their clarity and simplicity, the guidelines are also popular beyond the UK; they are cited in numerous national and international guidelines documents, including the American-led International Encephalitis Consortium’s Consensus Statement, and European, Indian, Australia and New Zealand consensus guidelines (5.4). The approach developed in the guidelines also informed the group’s research on other emerging infections including Zika, Chikungunya and Ebola (5.5).

Impact through education

The guidelines feature heavily alongside other work from the group 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 (5.3); “it is actually done really very, very well” commented the Director of the US National Institute of Neurological Disorders and Stroke (5.6). 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

The wider impact of the group’s research into recognising, diagnosing and managing neurological manifestations of infectious diseases is exemplified by their response to

COVID-19 (5.7). The group rapidly modified and distributed their standardised case definitions for neurological COVID-19 disease. Through leadership of national and international collaborations (the UK Coroner 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 (5.7). The findings were disseminated through the WHO Brain Unit's Neuro-Covid Forum, monthly COVID-Neuro webinars (1,405 participants; 83 countries; all continents) and the Covid-Neuro Global Research Coalition (Solomon Co-Chairs all three). Solomon advises the UK Government and WHO on COVID-19 (5.7), building on his previous similar roles on Zika and Ebola (5.8).

Improved health outcomes

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 (5.9, 3.6). 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 (5.9). Following the introduction of 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 13 hours by 2014/15 (5.9).

Health economic impacts

To calculate the benefits of this more rapid treatment, the group conducted a health economic evaluation (5.9). Initiation of treatment for herpes simplex virus encephalitis within 48 hours was associated with improvement in outcome (58% had good recovery on Glasgow Outcome Score, compared with 16%), and shorter hospital stays (mean [95%CI] 40 [31.30 - 49.16] versus 87 [52.74 - 122.11] days). There was a reduced total NHS cost of GBP25,895 (from GBP56,916 [£36,224 - £77,607] to GBP31,022 [95%CI £16,923 - £45,121]) per patient in the first year after diagnosis. The saving for all UK encephalitis patients, based on the estimated incidence of 3.45-8.66 per 100,000, was GBP58,960,638 to GBP147,999,746 per year, or GBP471,685,104 to GBP1,183,997,971 since 2013 (5.9).

5. Sources to corroborate the impact

[5.1] New UK guidelines for Meningitis

a) 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>,
b) 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>.
Both guidelines are endorsed by The British Infection Association
<https://www.britishinfection.org/guidelines-resources/published-guidelines>

[5.2] Raising awareness through public engagement activities

c) Evidence of raised awareness, YouGov Plc survey 2017, for Encephalitis Society.
d) Information on World Encephalitis Day, since 2014 <https://www.encephalitis.info/world-history> and BMJ 2014;348:g1747 <https://doi.org/10.1136/bmj.g1747>
e) 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>

[5.3] Practitioner views on the guidelines and education initiatives

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

[5.4] International impact of UK guidelines

g) Table showing the citations of the UK guidelines in international policy or policy-related documents since 1 August 2013, underscoring the global impact of the guidelines, including the following two key papers:

h) 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>

i) 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>

[5.5] International application of the surveillance and diagnostic approaches the group 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:

j) 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(20)30232-5)

k) 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>

[5.6] Clinician/professional education initiatives

l) NeuroID course, <https://www.liverpool.ac.uk/neuroidcourse/>; Neuro-ID International, <https://www.liverpool.ac.uk/neuroidcourse/international/>; 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.i) 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(20)30221-0). Epub 2020 Jul 2; and

n.ii) Varatharaj A, ... **Michael BD**, Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. **Lancet Psychiatry** 2020; 7: 875-82. [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X)

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(20)30150-2). 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

u) **The time to treatment and costings evaluations come 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](#), Public Health England Collindale. 21st November 2018.

v) **Estimates of the incidence of encephalitis comes from:** Granerod, J., Cousens, S., Davies, N. W., Crowcroft, N. S., & 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>