Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Control of Japanese Encephalitis

1. Summary of the impact

Globally the most important cause of encephalitis (inflammation and swelling of the brain) is the mosquito-borne Japanese encephalitis virus (JEV), which causes an estimated 70,000 cases annually across Asia. Although vaccines were developed years ago, their uptake in Asian countries has been hampered through lack of disease burden data, a consequence of poor surveillance, complicated diagnostics, and insufficient knowledge about disease outcomes. Research at the University of Liverpool has addressed each of these areas in turn, to overcome the roadblocks in vaccine implementation. The University of Liverpool (UoL), through its leading role on all the relevant WHO committees groups and meetings, has ensured that its research findings are translated through to impact by supporting new vaccination programmes across Asia. By 2013 vaccination had begun in 11 new countries, and the vaccine had reached more than 200 million people. The public health benefits, estimated from a health economic modelling study, are 854,000 cases and 214,000 deaths avoided, with an associated saving across Asia of US$ 1.024 billion.

2. Underpinning research

Encephalitis is inflammation of the brain, most often caused by a virus. Numerically, the most important cause of epidemic encephalitis in the world is the mosquito-borne Japanese encephalitis virus (JEV), which UoL led research has shown to cause an estimated 70,000 cases annually across Asia. The virus's natural cycle is among wading birds and pigs; humans become infected when bitten by an infected mosquito. Approximately 4 billion people live in areas at risk of Japanese encephalitis (JE). Although vaccines were developed years ago, their uptake by governments has been hampered through lack of disease burden data. There were no reliable methods of diagnosing and tracking the disease, no standard diagnostic tests, no surveillance systems, and little knowledge about disease outcomes. Without these it was hard for countries in Asia to understand the extent of JE, prioritize it, and focus prevention efforts on the regions and people most needing protection.

At UoL, Professor Tom Solomon, of the Institute of Infection and Global Health, along with the multidisciplinary Brain Infections Group has been addressing these challenges. To strengthen surveillance the team demonstrated (1995-8), with Wellcome Trust funding, the wide range of clinical presentations the virus can cause, including a previously unknown poliomyelitis-like illness [1], and acute symptomatic seizure presentations. This was achieved through careful clinical descriptive and epidemiological studies led by Solomon in Vietnam

The UoL has had a leading role in the development by WHO of Surveillance Standards, Solomon chaired the WHO Group producing the Clinical Care Guidelines (2005), and then field-tested the Standards, by applying them to a cohort of patients with suspected central nervous system infections in Asia to see how many patients with JE were accurately identified [2].

To improve diagnostics, the UoL worked with colleagues at the University of Malaysia, Sarawak from 1995-8 to develop and field-test simple rapid kits for diagnosing JE in the rural field hospitals where it occurs [3]. Many of these have subsequently been further refined over subsequent years. These diagnostic kits allow JE to be distinguished from the related dengue virus, which can also cause neurological disease [4], and from other emerging causes of acute central nervous system infection such as enterovirus 71 [5]. In 2003, the team showed with a randomised controlled trial that interferon treatment, which was being used increasingly for JE and related flaviviruses such as West Nile virus, was ineffective [6], thus focusing attention on the importance of disease control through vaccination.

Approximately 20% of children with JE die, but those that survive with severe disability are actually a greater socio-economic burden. However there were no good data on the extent of the problem, making it difficult for governments to make rational choices on the cost effectiveness of vaccine implementation programmes. With funding from PATH/Gates Foundation and MRC, the UoL developed a simple outcome score (2008-10) with colleagues in India and Malaysia to assess disability after JE [7], and using it showed the extent of the problem in survivors.

3. References to the research

1. **Solomon T**, **Kneen R**, Dung NM, Khanh VC, Thuy TTN, Ha DQ, Day NPJ, Nisalak A, Vaughn DW, White NJ. Poliomyelitis-like illness due to Japanese encephalitis virus. Lancet. 1998;351:1094-7. Citations: 3 Impact Factor: 39.060

2. **Solomon T**, Thao TT, **Lewthwaite P**, **Ooi MH**, Kneen R, Dung NM, White N. A cohort study to assess the new WHO Japanese encephalitis surveillance standards. Bulletin of the World Health Organization. 2008;86:178-86. Citations: 30 Impact Factor: 5.250

3. **Solomon T**, Thao LT, Dung NM, **Kneen R**, Hung NT, Nisalak A, Vaughn DW, Farrar J, Hien TT, White NJ, Cardosa MJ. Rapid diagnosis of Japanese encephalitis by using an immunoglobulin M dot enzyme immunoassay. Journal of Clinical Microbiology. 1998;36:2030-4. Citations: 53 Impact Factor: 4.068

4. **Solomon T**, Dung NM, Vaughn DW, **Kneen R**, Thao LTT, Raengsakulrach B, Day NPJ, Farrar J, **Myint KSA**, Nisalak A, White NJ. Neurological manifestations of dengue infection. Lancet. 2000;355:1053-59. Citations: 218 Impact Factor: 39.060

5. **Ooi MH**, Wong SC, Podin Y, Akin W, Sel SD, Mohan A, Chieng CH, Perera D, Clear D, Wong D, Blake E, Cardosa J, **Solomon T**. Human enterovirus 71 disease in Sarawak, Malaysia: a prospective clinical, virological, and molecular epidemiological study. Clinical Infectious Diseases. 2007;44:646-56. Citations: 64 Impact Factor: 9.374

6. **Solomon T**, Dung NM, Wills B, **Kneen R**, Gainsborough M, Diet TV, Thuy TTN, Loan HT, Khanh VC, Vaughn DW, White NJ, Farrar JJ. Interferon alfa-2a in Japanese encephalitis: a randomised double-blind placebo-controlled trial. Lancet. 2003;361:821-6. Citations: 80 Impact Factor: 39.060

7. **Lewthwaite P**, Begum A, Ooi MH, **Faragher B**, Lai BF, Sandaradura I, Mohan A, Mandhan G, Meharwade P, Subhashini S, Abhishek G, Penkulinti S, Shankar MV, Ravikumar R, **Young C**, Cardosa MJ, Ravi V, Wong SC, **Kneen R**, **Solomon T**. Disability after encephalitis: development and validation of a new outcome score. Bulletin of the World Health Organization. 2010;88:584-92. Citations: 3 Impact Factor: 5.250

Key Research Grants

2005 – 2011. **Medical Research Council** Senior Clinical Fellowship (T Solomon). Inflammation in Japanese encephalitis. £946,704

2005 – 2008. **Wellcome Trust** Training Fellowship, (Dr Mong How Ooi), Enterovirus-71 associated hand foot and mouth disease in Sarawak, £110,845

2000 – 2005. **Wellcome Trust** Career Development Fellowship (T. Solomon; Grant no. 054682). The Host Immune Response and Strain Virulence Determinants in Japanese Encephalitis. £498,505, University of Liverpool, UK, and University of Texas Medical Branch, Galveston, USA.

2005 – 2007. **Gates Japanese Encephalitis Control Fellowship** (funded through PATH,

Seattle). £206,982

4. Details of the impact

Solomon's research at the UoL has been pivotal in changing the way a life threatening illness is understood, diagnosed and prevented across Asia. Through a partnership with a consortium of Governments, Academic Partners, and Health agencies, facilitated by a series of meetings ranging from WHO small working groups to large international conferences, critical information on the prevalence, diagnostics, treatment and prevention of Japanese Encephalitis has been disseminated to at risk populations supported by guidelines and awareness campaigns. For example, the UoL Team developed the online e-learning tools for Clinical Assessment of Children, and for using the disease outcome score UoL developed (now known as the Liverpool Outcome Score). By tackling each of the core issues relating to the lack of vaccine uptake, the impacts of Solomon's research have been felt throughout the entire REF period; this has benefited individuals in at risk areas by massively limiting the number of cases, which has in turn, benefited governments by significantly reducing the economic burden of caring for individuals disabled by this devastating disease.

The JE surveillance guidelines that the UoL developed on the back of its clinical-epidemiological research, have been used across Asia since 2008, and are helping with disease recognition. In 2012, 18 (75%) of the 24 countries with JE virus transmission risk conducted at least some JE surveillance [8].

The UoL rapid diagnostic kit for diagnosing JE was the prototype for kits developed by the UoL, and others, some of which have gone through to commercialisation, such as that produced by Venture Technologies, Singapore, and since 2008, Pan Bio, Australia, and Excyton Diagnostics, India [9]. Such kits are now widely used across Asia, through the JE laboratory diagnostic network that the UoL helped establish [10]. This is playing an essential role in helping recognition of JE so that the disease burden can be ascertained.

The Liverpool Outcome Score has been disseminated widely through the WHO and PATH partners, and the biannual WHO JE Regional meetings in Southeast Asia. It is publicly available (www.path.org/vaccineresources/details.php?i=677) and is used in many Asian countries to help quantify the disease burden of JE [11,12,13].

In the 1990s, other than China which had developed its own vaccine, sustained JE vaccination programmes were restricted to wealthier Asian countries. The UoL work on establishing the disease burden through improved surveillance, diagnosis and quantification of disability has played a major role in helping Governments decide on JE vaccination programmes. The UoL team had a leading role in the JE control partnership which included other HEIs, Governments across Asia, WHO, and non-governmental organisations. Together, with US$ 14m funding from the Bill and Melinda Gates Foundation, the partnership supported vaccine roll out [14]. The UoL research was disseminated by way of participation in all the main WHO working groups, committees, meetings and conferences, advising, for example on vaccine development, and surrogate markers of vaccine efficacy [15].

The impact of this research can be examined through the new vaccination programmes across Asia, which the UoL has catalysed and supported. In the summer of 2006, 19 million children were immunised in India, and by the end of 2013, 88 million Indian children had been vaccinated. By 2013 vaccination had begun in 11 countries outside China (eight of them since 2008), and the vaccine had reached more than 200 million people; approximately 170 million since Jan 2008.
The public health benefits can be estimated from a health economic modelling study: in a cohort of 100 000 unvaccinated children followed up from birth to 30 years of age, the model predicted 488 cases and 122 deaths associated with JE [16]. In the absence of JE immunization it was estimated that the treatment of acute JE would cost US$ 483,672 and that 7,441 Disability Adjusted Life Years (DALYs) would be lost because of JE. Relative to the no-vaccination strategy, the use of the vaccine would result in 427 fewer JE cases, 107 fewer deaths, and 6556 fewer DALYs lost. For the 170 million people vaccinated since 2008, this equates to 660,000 cases and 165,000 deaths

avoided. The estimated total direct costs associated with the treatment of JE and disability during the 30-year follow-up of 100 000 neonates who were not vaccinated is US$ 738,315, and the corresponding costs of using the vaccine are US$ 225,859 [16]. The savings per 100 000 neonates are thus US$ 512 456, or US$ 791m for the 170 million people vaccinated since 2008.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

8. Centers for Disease C, Prevention. Japanese encephalitis surveillance and immunization--Asia and the Western Pacific, 2012. MMWR Morbidity and Mortality Weekly Report. 2013;62:658-62.

9. Khalakdina A, Shrestha SK, Malla S, Hills S, Thaisomboonsuk B, Shrestha B, Gibbons RV, Jacobson J. Field evaluation of commercial immunoglobulin M antibody capture ELISA diagnostic tests for the detection of Japanese encephalitis virus infection among encephalitis patients in Nepal. International Journal of Infectious Diseases 2010;14 Suppl 3:e79-84.

10. World Health Organization. Japanese encephalitis laboratory network - overview; accessed June 2013 at http://www.wpro.who.int/immunization/laboratory/je/overview/en/index.html.

11. Ma J, Jiang L. Outcome of children with Japanese encephalitis and predictors of outcome in southwestern China. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2013;107:660-5.

12. Maha MS, Moniaga VA, Hills SL, Widjaya A, Sasmito A, Hariati R, Kupertino Y, Artastra IK, Arifin MZ, Supraptono B, Syarif I, Jacobson JA, Sedyaningsih ER. Outcome and extent of disability following Japanese encephalitis in Indonesian children. International Journal of Infectious Diseases. 2009;13:e389-93.

13. Hills SL, Van Cuong N, Touch S, Mai HH, Soeung SC, Lien TT, Samnang C, Sovann L, Van Diu P, Lac LD, Heng S, Huong VM, Grundy JJ, Huch C, Lewthwaite P, Solomon T, Jacobson JA. Disability from Japanese encephalitis in Cambodia and Viet Nam. Journal of Tropical Pediatrics. 2011;57:241-4.

14. Solomon T. Control of Japanese encephalitis--within our grasp? New England Journal of Medicine. 2006;355:869-71.

15. Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine. 2005;23:5205-11.

16. Ding D, Kilgore PE, Clemens JD, Wei L, Zhi-Yi X. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. Bulletin of the World Health Organization. 2003;81:334-42.