

Institution: London School of Hygiene & Tropical Medicine (LSHTM)		
Unit of Assessment: 2		
Title of case study: The Zika virus emergency: informing the international response		
Period when the underpinning research was undertaken: 2016-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Laura Rodrigues Elizabeth Brickley Hannah Kuper Rosanna Peeling & associated research teams	Role(s) (e.g. job title): Professor Assistant Professor Professor Professor	Period(s) employed: 01/07/1986-29/06/2018 02/10/2017-present 01/05/2002-present 01/10/2008-present
Period when the claimed impact occurred: 2016-2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words) Research led by LSHTM during the 2015-16 Zika virus outbreak in Brazil formally identified the link between Zika virus and microcephaly and defined the clinical presentation of Congenital Zika Syndrome (CZS). The discoveries made an immediate impact, informing the national and international response and outbreak surveillance. Researchers provided expert advice to UK government departments, NGOs, academic organisations and industry on how to control the mosquito vectors and avoid the disease. The researchers also rapidly developed a free online course, with over 18,000 people participating in more than 189 countries. Since the epidemic ended, LSHTM staff have been building capacity to manage future outbreaks, developing new control methods, and assessing the impact of CZS on affected families and communities.		
2. Underpinning research (indicative maximum 500 words) In early 2015, a widespread epidemic of Zika fever, caused by the Zika virus, occurred across South and Central America. In January 2016, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC). This was in response to the growing body of evidence that mother-to-child transmission of Zika resulted in birth defects such as microcephaly and other neurological problems, and Guillain-Barré syndrome in adults. Research by LSHTM staff played a key role during the outbreak, and continued to provide evidence to guide support to those affected afterwards. Defining Congenital Zika Syndrome (CZS) and neurological complications, including impact on families and communities The Microcephaly Epidemic Research Group (MERG), originally led by Rodrigues and Brazilian partners and at the request of the Brazilian Ministry of Health, demonstrated the association between Zika virus infection and microcephaly in Brazil in 2016. In collaboration with maternity hospitals across Pernambuco state, a case-control study in 8 public hospitals confirmed the scientific view that the microcephaly epidemic was a result of congenital Zika infection (3.1). MERG subsequently led the Brazilian Consortium of Cohorts on Pregnant Women and Children, which enabled teams in Recife, Rio de Janeiro and London to collaborate with a wide range of institutions throughout Brazil. The consortium worked with 4,000 pregnant women in Pernambuco, who had experienced a rash during pregnancy since January 2016, to measure the risk of microcephaly and other manifestations, find out when in pregnancy infection with Zika put women at most risk, and monitor babies' development as they grew. This work, continued by Brickley, established 2 cohorts of children with prenatal exposure to Zika virus. Through follow-up, MERG staff estimated the absolute and relative risks associated with Zika infection among the cohort of pregnant women, describing the range of adverse outcomes		

detected in affected children. They also identified at-risk children for adverse neurodevelopment as a result of Zika exposure. This work provided the clinical definition of CZS, including associated signs and symptoms in early childhood, and prognosis of those with severe effects including microcephaly (3.2, 3.3). Studies explored patterns in the growth, brain development and experiences of epilepsy of the babies born with CZS following the outbreak. The cohort size enabled researchers to identify other related symptoms that might not otherwise have been considered, including urinary tract infections, dysphagia (swallowing problems), and epilepsy.

Kuper led LSHTM research in Brazil in 2016 and 2017 to address the effects of the CZS and microcephaly epidemic on families and communities, including economic impact, health service use, mental health of carers, and sexual and reproductive health (3.4, 3.5). Funded by the Wellcome Trust and DFID (now FCDO), Kuper co-developed and piloted a community-based intervention to support carers, the Juntos programme.

Developing a platform for diagnosis innovation and evaluation

The overlap in the epidemiological distribution of dengue, chikungunya and Zika, and their non-specific clinical manifestations, presented a challenge for accurate diagnosis and reporting. The ZikaPLAN platform for diagnostics innovation and evaluation, led by LSHTM's Peeling, developed and validated tools for diagnosis, surveillance and research. The group established a specimen biobank and a network of laboratory and clinical sites, pre-approved for clinical trial protocols, and novel Zika virus diagnostic tests in accordance with the WHO Target Product Profile. UNICEF selected the network to run evaluations of products they were looking to procure for Zika diagnostics. The prototype of the antigen test successfully detected virus strains and the serological test performed better than current tests on the market and antibody-measuring laboratory tests (3.6).

3. References to the research (indicative maximum of six references)

3.1 de Araújo TVB, **Rodrigues LC**, de Alencar Ximenes RA, de Barros Miranda-Filho D, Montarroyos UR, de Melo APL, Valongueiro S, de Albuquerque MFPM, Souza WV, Braga C, Filho SPB, Cordeiro MT, Vazquez E, Di Cavalcanti Souza Cruz D, Henriques CMP, Bezerra LCA, da Silva Castanha PM, Dhalia R, Marques-Júnior ETA, Martelli CMT; investigators from the Microcephaly Epidemic Research Group; Brazilian Ministry of Health; Pan American Health Organization; Instituto de Medicina Integral Professor Fernando Figueira; State Health Department of Pernambuco. 2016. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. *Lancet Infectious Diseases*. (12):1356-1363. doi: [10.1016/S1473-3099\(16\)30318-8](https://doi.org/10.1016/S1473-3099(16)30318-8).

3.2 Ximenes RAA, Miranda-Filho DB, **Brickley EB**, Montarroyos UR, Martelli CMT, Araújo TVB, **Rodrigues LC**, de Albuquerque MFPM, de Souza WV, Castanha PMDS, França RFO, Dhália R, Marques ETA; Microcephaly Epidemic Research Group (MERG). 2019. Zika virus infection in pregnancy: Establishing a case definition for clinical research on pregnant women with rash in an active transmission setting. *PLoS Neglected Tropical Diseases*. 13(10): e0007763. doi: [10.1371/journal.pntd.0007763](https://doi.org/10.1371/journal.pntd.0007763)

3.3 Ramond A, Lobkowicz L, Sanchez Clemente N, Vaughan A, Turch MD, **Wilder-Smith A**, **Brickley E**. 2020. Postnatal symptomatic Zika virus infections in children and adolescents: a systematic review. *PLoS Neglected Tropical Diseases*. 14(10): e0008612. doi: [10.1371/journal.pntd.0008612](https://doi.org/10.1371/journal.pntd.0008612)

3.4 Duttine A, Smyhthe T, Calheiros de Sa MR, Ferrite S, Moreira ME, **Kuper H**. 2020. Juntos: a support program for families impact by congenital Zika syndrome in Brazil. *Global Health: Science and Practice*. 8(4):846-857. doi: [10.9745/GHSP-D-20-00018](https://doi.org/10.9745/GHSP-D-20-00018)

3.5 Albuquerque M, Lyra TM, Melo A, Valongueiro SA, Araújo TVB, Pimentel C, Moreira MCN, Mendes CHF, Nascimento M, **Kuper H**, **Penn-Kekana L**. 2019. Access to healthcare for children with Congenital Zika Syndrome in Brazil: perspectives of mothers and health professionals. *Health Policy and Planning*, 34;7:499-507. doi: [10.1093/heapol/czz059](https://doi.org/10.1093/heapol/czz059)

3.6 Wilder-Smith A, Preet R, **Brickley EB**, de Alencar Ximenes RA, Miranda-Filho D, CM Turchi, de Araújo T, Montarroyos U, Moreira ME, Turchi MD, Solomon T, Jacobs BC, Villamizar C, Osorio L, de Filippis AM, Neyts J, Kaptein S, Huits R, Ariën KK, Willison HJ, Edgar JM, Barnett SC, **Peeling R**, Boeras B, Guzman MG, de Silva AM, Falconar AK, Romero-Vivas C, Gaunt MW, Sette A, Weiskopf D, Lambrechts L, Dolk H, Morris JK, Orioli IM, **O'Reilly KM**, **Yakob L**, Rocklöv J, Soares C, Ferreira ML, de Oliveira Franca RF, Precioso RF, **Logan J**, Lang T, Jamieson N, Massad E. 2019. ZikaPLAN: addressing the knowledge gaps and working towards a research preparedness network in the Americas. *Global Health Action*. 12:1. doi: [10.1080/16549716.2019.1666566](https://doi.org/10.1080/16549716.2019.1666566)

We believe this body of research meets the 'at least 2*' definition given its reach, significance and rigour.

4. Details of the impact (indicative maximum 750 words)

Spread by *Aedes aegypti* mosquitoes, and sexual transmission, the Zika outbreak caused several countries to issue travel warnings, and heightened concern about the safety of athletes and tourists visiting the 2016 Summer Olympic Games in Rio de Janeiro. Research and impact occurred almost simultaneously; as the outbreak progressed and symptoms emerged, researchers continually provided new data and insights that underpinned interventions, and informed the national and international response and surveillance of the outbreak.

Defining congenital Zika virus

The initial description of the full clinical definition of congenital Zika syndrome, provided by Rodrigues' work, underpinned the August 2016 WHO rapid advice guidelines for screening and management of affected children (5.1). These guidelines formalised recommendations for families of babies with congenital Zika virus syndrome and provided advice to women of reproductive age and pregnant women about the risks. The work of MERG informed the Zika-related guidance of WHO and the Brazilian Ministry of Health in formulating additional interim guidance for surveillance, care and support for those affected by Zika and the associated conditions (5.2). In part due to efforts by individuals in MERG, the cluster of microcephaly and other neurological disorders was recognised as a National Health Emergency in Brazil and a PHEIC by the WHO (5.3).

By formally establishing the link between Zika virus and microcephaly, LSHTM provided the evidence base for increased risk communication to reduce the chance of being exposed to the virus. For example, WHO advised that pregnant women should not travel to areas of ongoing Zika outbreaks, and that women whose sexual partners lived in or travelled to Zika areas should ensure safe sexual practices or abstain from sex while they were pregnant.

LSHTM staff rapidly acted on research results to improve outcomes for communities affected by microcephaly. In monitoring the cohort of infants with CZS, then aged 3-5 years old, they collected valuable information, including long-term health outcomes and how to support affected families while preparing for future outbreaks. MERG collaborated with the advocacy group, Movimento Zika, to produce and disseminate guides on Zika for mothers of children with CZS. Weekly support groups were held in the local community to allow parents to share knowledge and tips.

In addition, the patient support programme 'Juntos' ('together'), piloted from 2017 to 2018, allowed parent groups in the community to meet regularly to share stories, provide emotional support, and learn about different aspects of Zika, and how they could fight for their rights. Juntos, a programme co-developed by Kuper in the non-profit research and educational hub based in the International Centre for Disability at LSHTM, included training, supervision and mentoring of facilitators, with materials available in English and Portuguese. A short film featuring Juntos, with a focus on setting up parent groups, was completed in collaboration with Medical Aid Films and screened in medical centres across Brazil and Colombia. The researchers have written a facilitator manual and developed a range of resources, available in English, Portuguese and Spanish (5.4).

Evaluating diagnostics

An international virtual biobanking system of Zika-positive clinical samples was developed through the ZikaPLAN diagnostic package in collaboration with UNICEF and WHO, and used as positive controls for evaluation of new diagnostic tests. UNICEF contracted LSHTM in 2017 to assess Zika and other arbovirus tests via lab-based validation, which led to the approval of 2 Zika tests, made by Chembio Diagnostic Systems and SD Biosensor, for UNICEF procurement in 2019 (5.5). UNICEF committed to buying USD1.5million worth of tests and possible further purchases for a total amount of up to USD3.5million for the Chembio product (5.5).

Advising governments, international organisations and the public on risk

The WHO Emergency Committee was chaired by LSHTM's Heymann (5.3). Its PHEIC declaration mobilised global responses in risk communication, awareness and increased efforts to control the spread of *Aedes* mosquitoes. LSHTM's infectious disease experts (including via the inter-disciplinary Centres) addressed this new epidemic from multiple perspectives. Briefed by their colleagues, Logan and Whitworth provided expert input on *Aedes* control and Zika infection respectively to the Parliamentary and Scientific Committee meeting in 2016, and clinical and travel guidance to the UK government (5.6). Logan, Rodrigues, Watts and Rowland served as members of the Department of Health's Scientific Advisory Group for Emergencies (SAGE) during the Zika outbreak, which was chaired by Whitty (LSHTM 2001-2019, now Chief Medical Officer for England) (5.7).

LSHTM experts were at the forefront of providing information to the media and general public, with more than 9,000 articles on Zika mentioning LSHTM in 2016 including The Telegraph, Washington Post, Globo and New Scientist. Staff also provided televised expert comment for BBC News, Channel 4 News, ITV News, CNN and many more (5.8). The annual Bug Off campaign, launched by LSHTM in 2016, provides advice to travellers for avoiding vector-borne diseases, including Zika and other infections transmitted by *Aedes*. Backed by Dame Kelly Holmes, the campaign has reached a global audience of 25 million since its inception, capturing and reflecting sustained interest in minimising risk of overseas travel (5.9).

LSHTM developed the Massive Online Open Course (MOOC): 'Preventing the Zika virus: understanding and controlling the *Aedes* mosquito,' and ran it quarterly from 2016 to 2018, attracting 18,396 students in total. The MOOC was used internationally within academic institutions, governments, control programmes and companies. The course materials remain accessible via the LSHTM Open Educational Resources platform. The International Centre for Disability at LSHTM also launched a MOOC for healthcare professionals, 'Integrated healthcare for children with developmental disabilities', with course material drawing on Zika examples from Brazil. The course ran twice in 2019, attracting approximately 7,318 learners (5.10).

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 World Health Organization. Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero. Rapid Advice Guideline. 30 August 2016. WHO/ZIK/MOC/16.3/Rev3.

- Underpinned by Rodrigues initial clinical description of CZS

5.2 Brazilian Ministry of Health. Integrated guidelines on surveillance in the context of a public health emergency of national importance. (in Portuguese)

- Rodrigues listed as collaboration expert

World Health Organization. Surveillance for Zika virus infection, microcephaly and Guillain-Barre syndrome. Interim guidance. 7 April 2016. WHO/ZIKV/SUR/16.2 Rev.1

- Rodrigues listed as key advisor

World Health Organization. WHO toolkit for the care and support of people affected by complications associated with Zika virus. ISBN 978-92-4-151271-8

- Rodrigues technical reviewer

5.3 Members of, and Advisers to, the International Health Regulations Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations.

- statements of recommendations and actions accessed at: <https://www.who.int/groups/zika-virus-ihr-emergency-committee>
- Heymann Chair

WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. 1 February 2016. Accessed at: [https://www.who.int/news/item/01-02-2016-who-statement-on-the-first-meeting-of-the-international-health-regulations-\(2005\)-\(ihr-2005\)-emergency-committee-on-zika-virus-and-observed-increase-in-neurological-disorders-and-neonatal-malformations](https://www.who.int/news/item/01-02-2016-who-statement-on-the-first-meeting-of-the-international-health-regulations-(2005)-(ihr-2005)-emergency-committee-on-zika-virus-and-observed-increase-in-neurological-disorders-and-neonatal-malformations)

- PHEIC declaration

5.4 Ubuntu 'Juntos' programme manuals and resources available for download. Accessed at: <https://www.ubuntu-hub.org/resources/juntos/>

5.5 UNICEF. Innovation case study: Zika virus diagnostics for testing at point-of-care. November 2019.

- States LSHTM engaged to complete clinical evaluation of two products for Unicef tendering, pg 7, 41.

Chembio Diagnostics awarded UNICEF contract to supply point-of-care Zika/ Chikunguna/ Dengue tests and micro readers Press release, 2019. Accessed at: <https://www.globenewswire.com/news-release/2019/03/07/1750120/0/en/Chembio-Diagnostics-Awarded-UNICEF-Contract-to-Supply-Point-of-Care-Zika-Chikungunya-Dengue-Tests-and-Micro-Readers.html>

5.6 Parliamentary and Scientific Committee Zika Meeting 10/3/16. Event held as a contribution to British Science Week. Accessed at: <https://www.scienceinparliament.org.uk/wp-content/uploads/2013/09/P-and-SC-Zika-Breifing.pdf>

- Whitworth and Logan contributors

5.7 Minutes of the Scientific Advisory Group for Emergencies (SAGE) meetings on the Zika outbreak in 2016. Accessed at: <https://www.gov.uk/government/publications/sage-minutes-zika-outbreak-2016>

3 February 2016: Logan, Rowland, Rodrigues, Watts

23 February 2016: Logan, Watts, Rowland, Whitty

7 March 2016: Whitty, Watts, Rowland

8 June 2016: Rodrigues, Watts, Whitty

5.8 LSHTM 2016 media highlights, accessed at: <http://blogs.lshtm.ac.uk/inthenews/2016/12/21/in-the-news-media-highlights-2016/#more-1814>

5.9 Arctec: Freedom to explore blog post, accessed at: <http://arctec.lshtm.ac.uk/bug-off/#:~:text=campaign%20has%20reached%20a%20global,staying%20safe%20whilst%20travelling%20abroad>
<https://www.bug-off.org/>

5.10 FutureLearn: Preventing the Zika virus: understanding and controlling the *Aedes* mosquito. Accessed at: <https://www.futurelearn.com/courses/preventing-zika>

FutureLearn: Integrated healthcare for children with developmental disabilities. Accessed at: <https://www.futurelearn.com/courses/children-with-developmental-disabilities>