Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA1 – Clinical Medicine

Title of case study: Preventing newborn mortality due to syphilis

1. Summary of the impact

Research conducted by LSHTM has played a key role in supporting the global elimination of congenital syphilis. Two studies providing evidence of the health burden of congenital syphilis in Africa and the effectiveness of benzathine penicillin treatment form a pillar upon which WHO established its new syphilis elimination initiative. Further research has resulted in the adoption of new point-of-care tests for screening pregnant women for syphilis in 30 countries. As a result, more women are diagnosed and fewer babies die of syphilis.

2. Underpinning research

Syphilis causes 500,000 stillbirths and newborn deaths every year. Research conducted by the LSHTM has been responsible for putting congenital syphilis back on the global agenda, focusing on the evaluation and dissemination of effective screening and treatment programmes.

In 2001–2002 Deborah Watson-Jones (then LSHTM's Wellcome Trust Clinical Research Fellow) undertook two landmark studies in Mwanza, Tanzania, documenting for the first time since the 1950s the incidence of adverse pregnancy outcomes in women with untreated syphilis. First, 380 previously unscreened women were recruited into a retrospective cohort at delivery and tested for syphilis. Results showed that, in this setting, syphilis was responsible for 50% of stillbirths.[3.1] Watson-Jones' second study – a comparison of birth outcomes for 1,688 women – showed convincingly, for the first time, that single-dose treatment of benzathine penicillin given before 28 weeks' gestation prevented adverse pregnancy outcomes attributable to maternal syphilis.[3.2] Subsequent research led by Fern Terris-Prestholt (Lecturer in Health Economics, at LSHTM since 2000) compared the cost-effectiveness of on-site antenatal syphilis screening and treatment in Mwanza with other antenatal and child health interventions. Findings showed that in this setting screening was one of the most cost effective health interventions, at US$10.5 per disability-adjusted life year (DALY) saved if stillbirths are included.[3.3]

In 2004, these studies were heavily cited in a special issue of the *Bulletin of the WHO* (Vol. 82-6, June), stimulating a resurgence of interest in congenital syphilis and shifting the focus onto barriers to effective control and treatment of the disease – the subject of concurrent research led by David Mabey (Professor of Communicable Diseases since 1994) and Dr Rosanna Peeling (at that time employed by WHO, joined LSHTM as Professor of Diagnostics Research in 2009). Their review of antenatal screening services in developing countries highlighted the poor integration of HIV and syphilis programmes. Further interviews with stakeholders revealed that because rapid plasma reagin syphilis screening tests require laboratory equipment and time to produce results, many women, particularly in remote areas, who tested positively for syphilis, never received treatment as they did not return for test results.[3.4]

Following these findings, in 2003, Mabey and Peeling led an evaluative study of four new point of care tests (POCTs) in four countries. They found that these rapid serological tests were an acceptable diagnostic alternative to conventional laboratory tests. Further, because POCTs require neither laboratory equipment nor electricity and can be performed on a finger-prick blood sample, with results in 15 minutes, these tests could increase coverage of syphilis screening and enable treatment to be given at the first clinic visit.[3.5]

Between 2008 and 2012, Mabey and Peeling led further research to assess the feasibility and cost effectiveness of scaling up the use of syphilis POCTs in rural health facilities in China, Brazil, Tanzania, Uganda, Zambia, Peru and Haiti, in close collaboration with country programmes. Their findings indicated POCTs could be used even in the most remote settings at an affordable cost.[3.6]

3. References to the research

3.1 Watson-Jones, D, Changalucha, J, Gumodoka, B, Weiss, H, Rusizoka, M, Ndeki, L, Whitehouse, A, Balira, R, Todd, J, Ngeleja, D, Ross, D, Buvé, A, Hayes, R and Mabey, D (2002) Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy, *Journal of Infectious Diseases,* 186(7): 940–947, doi: 10.1086/342952. Citation count: 88

3.2 Watson-Jones D, Gumodoka B, Weiss H, Changalucha, J, Todd, J, Mugeye, K, Buvé, A, Kanga, Z, Ndeki, L, Rusizoka, M, Ross, D, Marealle, J, Balira, R, Mabey, D and Hayes, R (2002) Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes, *Journal of Infectious Diseases,* 186(7): 948–957, doi: 10.1086/342951. Citation count: 64

3.3 Terris-Prestholt, F, Watson-Jones, D, Mugeye, K, Kumaranayake, L, Ndeki, L, Weiss, H, Changalucha, J, Todd, J, Lisekie, F, Gumodoka, B, Mabey, D and Hayes, R (2003) Is antenatal syphilis screening still cost effective in sub-Saharan Africa?, *Sexually Transmitted Infections*, 79(5): 375–381, doi: 10.1136/sti.79.5.375. Citation count: 57

3.4 Peeling, R, Mabey, D, Fitzgerald, DW and Watson-Jones, D (2004) Avoiding HIV and dying of syphilis, *Lancet,* 364(9445): 1561–1563, doi:10.1016/S0140-6736(04)17327-3. Citation count: 26

3.5 Mabey, D, Peeling, RW, Ballard, R, Benzaken, AS, Galbán, E, Changalucha, J, Everett, D, Balira, R, Fitzgerald, D, Joseph, P, Nerette, S, Li, J and Zheng, H (2006) Prospective, multi-centre clinic-based evaluation of four rapid diagnostic tests for syphilis, *Sexually Transmitted Infections*, 82(Suppl. 5): v13–v16, doi: 10.1136/sti.2006.022467. Citation count: 19

3.6 Mabey, DC, Sollis, KA, Kelly, HA, Benzaken, AS, Bitarakwate, E, Changalucha, J, Chen, X-S, Yin, Y-P, Garcia, PJ, Strasser, S, Chintu, N, Pang, T, Terris-Prestholt, F, Sweeney, S and Peeling, RW (2012) point-of-care tests to strengthen health systems and save newborn lives: the case of syphilis, *PLoS Medicine*, 9(6): e1001233, doi: 10.1371/journal.pmed.1001233. Citation count: 12

Key grants

Watson-Jones, The Impact of Syphilis on the Outcome of Pregnancy and Evaluation of Syphilis Screening Strategies for the Reduction of Adverse Pregnancy Outcomes in Mwanza, Tanzania, Wellcome Trust Clinical Training Fellowship, 1/1997–8/2000, £492,237.

Bill & Melinda Gates Foundation sub contracts to LSHTM via WHO:
- (PI Croft as Dean of Faculty), Accessible Quality-Assured Diagnostics Tests for Sexually Transmitted Diseases, WHO, 2008-2011, $1,163,505
- (PI Croft as Dean of Faculty), Introduction of rapid syphilis tests in developing countries, WHO, 2010-2011, $2,147,011
- Mabey, Evaluation of rapid tests for sexually transmitted infections in developing countries, WHO, 2011-12, $248,935

4. Details of the impact

As a direct result of the dissemination of LSHTM's Mwanza research, international momentum to eliminate syphilis gained pace, leading to WHO's launch of a major new initiative for the global elimination of congenital syphilis in 2007,[5.1] marked by the publication of a special supplement of the journal *Sexually Transmitted Diseases* in which Watson-Jones' research was cited 12 times. Although these predate the REF 'impact period', they have resulted in ongoing and new impacts ever since. These include the publication, in 2010, of the Centres for Disease Control and Prevention (CDC) and WHO 'road map' for the global elimination of congenital syphilis which cites four publications by Watson-Jones with particular emphasis on the effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes.[5.2] In 2012, based on consultations involving LSHTM researchers (2007–2011), WHO published its *Investment Case for Eliminating Mother-to-child Transmission of Syphilis*, drawing on LSHTM research to make the economic case for screening.[5.3]

As a direct result of Mabey's and Peeling's POCT evaluation study, The Global Fund for AIDS, TB and Malaria announced it would fund the purchase of syphilis POCT by country programmes beginning in 2007/2008. Mabey and Peeling's close collaboration with national policy-makers for this study directly resulted in the incorporation of POCT for syphilis into the prenatal screening programmes and official health care strategies of six countries between 2010 and 2012: China, Brazil, Tanzania, Uganda, Zambia and Peru. Impacts are detailed in WHO's *Research for Universal Health Coverage* 2013 report which notes that over 150,000 individuals were screened as a result of the LSHTM study and states: 'in all participating countries, the study achieved significant increases in coverage of diagnostic testing for syphilis. This reduced the prevalence of syphilis and the risk of HIV infection'.[5.4] The research also helped to strengthen health services in some of the participating countries. In Brazil, for instance, it has provided a model for the provision of health services to indigenous populations, as well as a template for the introduction of new technologies. Impact was made at the highest level of government: at a Chinese meeting of the State Council in November 2010, Premier Wen Jiabao announced that the state would fund syphilis screening in Chinese antenatal clinics[5.5] and, in 2012, Brazil's Minister of Health declared syphilis screening for remote populations would be one of three main national priorities to combat sexually transmitted disease.[5.6]

Dr Lori Newman, who leads syphilis research at WHO said: 'The public health impact of this study is clearly documented in the dramatic increase in syphilis testing coverage of pregnant women in the participating countries … the tools and lessons learned from that work have been used to scale-up syphilis testing coverage in other countries as well.'[5.7] These 'other countries' include six African and 19 South American countries whose policy-makers participated in jointly sponsored LSHTM/WHO meetings in Dar es Salaam and Lima during 2011. During these meetings a 'rapid syphilis toolkit' was launched. Developed at LSHTM, this free online resource is designed to help national health programme managers introduce and scale-up the use of POCTs.

In March 2012, Peeling established the Global Congenital Syphilis Partnership.[5.8] Hosted by LSHTM, the Partnership includes global leaders in health and development such as the Bill & Melinda Gates Foundation, Save the Children, WHO and CDC. Since its formation it has provided technical support for the use and evaluation of a new generation of 'duplex' POCTs for HIV and syphilis now being developed by two major diagnostics companies (Standard Diagnostics and Chembio). When the Partnership was launched, Peeling was interviewed about LSHTM research by BBC Radio 4's *Today* programme (over 7m listeners/week), *The Guardian, Metro* (2m readership), Reuters news and the *British Medical Journal* with additional coverage appearing, among others, in the *Huffington Post*, *The Chicago Tribune, The Globe and Mail* (Canada) and on Fox News.

Definitive diagnosis of congenital syphilis is difficult, however WHO estimates suggest that in the four years following the publication of LSHTM's Mwanza research, the global prevalence of syphilis dropped to less than half of what it was.[5.9] Reports from the Americas note that since LSHTM's local POCT projects there has been an expansion in syphilis testing among pregnant women, with 10 out of 29 countries now reporting 95% of those attending antenatal care having been tested.[5.10]

5. Sources to corroborate the impact

5.1 WHO (2007) *The Global Elimination of Congenital Syphilis: Rationale and Strategy for Action*. Geneva: WHO, http://whqlibdoc.who.int/publications/2007/9789241595858_eng.pdf (accessed 27 September 2013).

5.2 Kamb, ML, Newman, LM, Riley, PL, Mark, J, Hawkes, SJ, Malik, T and Broutet, N (2010) A road map for the global elimination of congenital syphilis, *Obstetrics and Gynecology International*, 312798, doi: 10.1155/2010/312798.

5.3 WHO (2012) *Investment Case for Eliminating Mother-to-child Transmission of Syphilis*. Geneva: WHO, http://apps.who.int/iris/bitstream/10665/75480/1/9789241504348_eng.pdf (accessed 27 September 2013) (School staff Cousens, Goodman, Hanson, Peeling, Sicuri, Vickerman acknowledged on p. v; references by School staff on p. 35 are 2, 11, 14).

5.4 WHO (2012) *The World Health Report 2013: Research for Universal Health Coverage*. Geneva: WHO, p. 109, http://apps.who.int/iris/bitstream/10665/85761/2/9789240690837_eng.pdf (accessed 27 September 2013).

5.5 GOV.cn (Chinese Government official web portal) (2010) Chinese government vows to step up HIV-AIDS control ahead of World AIDS Day, press release, 29 November, http://www.gov.cn/english/2010-11/29/content_1755901.htm (accessed 27 September 2013).

5.6 Ministério de Saúde (Brazilian Ministry of Health) (2012) Saúde reforça importância do teste rápido de sífilis, press release, 3 October, http://portalsaude.saude.gov.br/portalsaude/noticia/7555/162/saude-reforca-importancia-do-teste-rapido-de-sifilis.html (accessed 27 September 2013), (Portuguese).

5.7 Corroborating statement by Medical Officer, Sexually Transmitted Infections Team, Department of Reproductive Health and Research, WHO.

5.8 LSHTM (2012) New health partnership tackles congenital syphilis, podcast, 1 March 2012, http://www.lshtm.ac.uk/newsevents/multimedia/podcasts/2012/new_health_partnership_tackles.html (accessed 27 September 2013).

5.9 Newman, L, Kamb, M, Hawkes, S, Gomez, G, Say, L, Seuc, A and Broutet, N (2013) Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data, *PLoS Medicine,* 10(2): e1001396, doi: 10.1371/journal.pmed.1001396.

5.10 Pan American Health Organization (2013) *2012 Progress Report: Elimination of mother-to-child transmission of HIV and Congenital Syphilis in the Americas*. Washington, DC: PAHO, http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=20942&Itemid (accessed 27 September 2013).