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

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Controlling the hepatitis B virus in Africa and preventing unnecessary expenditure

1. Summary of the impact

Research conducted by LSHTM has informed the delivery of a 30-year WHO strategy aimed at reducing the devastating burden of liver cancer in Africa and least developed countries in other regions. Studies evaluating the effectiveness of the Gambia Hepatitis Intervention Study (GHIS) – the only randomised trial of a hepatitis B vaccine with a disease endpoint in Africa – have shaped current WHO policy recommendations for vaccinations against the virus, enabling WHO to advise against the need for a booster programme, and protecting governments in the less developed world from significant additional expenditure.

2. Underpinning research

Around 600,000 people die each year from the acute or chronic consequences of hepatitis B with 25% of adults chronically infected during childhood later dying from liver cancer or cirrhosis. The GHIS, beginning in 1986, was designed to evaluate the effectiveness of administering a hepatitis B vaccine to infants in one of the worst affected countries in sub-Saharan Africa – an estimated 10% of adults in West Africa die prematurely from the virus. The GHIS is a collaboration between WHO's International Agency for Research on Cancer (IARC), the Gambian government and the Medical Research Council Unit The Gambia.

As an IARC employee, Andrew Hall, Professor of Epidemiology, was principal investigator on the project at its inception before moving to LSHTM in 1990 (then Senior Lecturer). Since 1993, Hall has published more than 20 papers in leading journals, analysing the efficacy of the vaccination programme as the trial cohorts grow older.

Around 126,000 children were recruited to the study and, in the first phase from 1986 to 1990, half were randomised to receive hepatitis vaccination at birth, 2, 4 and 9 months of age in addition to vaccines delivered under the Gambian Expanded Programme on Immunisation (EPI). In Phase II (1991–1997), the efficacy of the vaccine was evaluated and Phase III (1998–present) continues to follow up the children in the trial. A national cancer register was set up in 1986 and continues to be updated, enabling linkages to be drawn between cancer cases and vaccination.

Hall was co-author of a paper published in *The Lancet* in 1993[3.1] that demonstrated the protection conferred by the hepatitis B vaccine. Through examining 3- and 4-year-old children who had received the vaccine in infancy, the paper showed it to be 84% effective against infection and 94% effective against chronic carriage. Hall was lead author on a paper that showed universal hepatitis B immunisation was cost effective,[3.2] offering a replicable model for other African countries.

Hall was subsequently involved in a number of subgroup studies to measure, at regular intervals in childhood and adolescence, immune response and infections, generating data on antibody decay and vaccine efficacy against hepatitis B infection.[3.3] Funded by the IARC and the Italian and Swedish governments, the ultimate aim was to determine whether there was a need to implement a hepatitis B booster programme. A paper in *Vaccine* in 1999 demonstrated vaccine efficacy at the age of 9,[3.4] supporting WHO recommendations to introduce hepatitis B vaccination into the EPI across Africa.

Research published in 2007 demonstrated, through serological assessments of vaccines aged up to 15, that hepatitis B vaccination early in life confers long-lasting protection against carriage of the virus despite decreasing antibody levels, highlighting the need for further research to evaluate the necessity of a booster.[3.5] Subsequent studies found that good levels of protection existed in 18- and 22-year-olds following vaccination in infancy, leading to the conclusion that a costly booster programme was not required.[3.6]

3. References to the research

3.1 Fortuin, M, Chotard, J, Jack, AD, Maine, NP, Mendy, M, Hall, AJ, Inskip, HM, George, MO and Whittle HC (1993) Efficacy of hepatitis B vaccine in the Gambian Expanded Programme of Immunisation, *Lancet*, 341(8853): 1129–1131, doi:10.1016/0140-6736(93)93137-P. Citation count: 55

3.2 Hall, AJ, Robertson, RL, Crivelli, PE, Lowe, Y, Inskip, HM, Snow, SK and Whittle, H (1993) Cost-effectiveness of hepatitis B vaccine in The Gambia, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 87(3): 333–336, doi: 10.1016/0035-9203(93)90154-I. Citation count: 39

3.3 Jack, AD, Hall, AJ, Maine, N, Mendy, M and Whittle HC (1999) What level of hepatitis B antibody is protective?, *Journal of Infectious Diseases*, 179(2): 489–492, doi:10.1086/314578. Citation count: 85

3.4 Viviani, S, Jack, A, Hall, AJ, Maine, N, Mendy, M, Montesano, R and Whittle, HC (1999) Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age, *Vaccine*, 17(23–24): 2946–2950, doi:10.1016/S0264-410X(99)00178-4. Citation count: 92

3.5. van der Sande, MAB, Waight, PA, Mendy, M, Zaman, S, Kaye, S, Sam, O, Kahn, A, Jeffries, D, Akum, AA, Hall, AJ, Bah, E, McConkey, SJ, Hainaut, P and Whittle, HC (2007) Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence, *PLoS One*, 2(8): e753, doi:10.1371/journal.pone.0000753. Citation count: 6

3.6. Mendy, M, Peterson, I, Hossin, S, Peto, T, Jobarteh, ML, Jeng-Barry, A, Sidibeh, M, Jatta, A, Moore, SE, Hall, AJ and Whittle, H (2013) Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: no need for a booster dose, *PLoS One*, 8(3): e58029, doi:10.1371/journal.pone.0058029. Citation count: 0

Key grants

This work was funded from core funding of the IARC (WHO) and the Medical Research Council Unit The Gambia. Professor Hall was employed by IARC from 1986 to 1990 and subsequently has been a consultant to IARC to maintain the project.

4. Details of the impact

Research carried out by LSHTM's Andrew Hall in collaboration with the GHIS team has been central to informing WHO's current recommendations on controlling the hepatitis B virus, a disease estimated to have infected 2bn people worldwide, through an infant vaccination programme. Crucially WHO guidelines explicitly state that there is no evidence to support the need for a booster dose following three doses of hepatitis B vaccine in infancy, a recommendation drawn directly from the conclusions of Hall's body of research that the vaccine confers adequate protection up to 15 years of age – since extended to 22 years.

The WHO position paper on hepatitis B vaccine,[5.1] published in 2009 and replacing previous guidelines issued in 2004, cites six papers co-authored by Hall between 1995 and 2008. The position paper recommends that all infants in highly endemic areas like Africa should receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours. It advises governments that delivery of the vaccine within this 24-hour time period, as advocated by the GHIS research study, should be a 'performance measure for all immunisation programmes'. Unless vaccinated at birth, the majority of children born to contagious mothers become chronically infected. The WHO paper noted that 2006 data showed the first dose was administered within 24 hours of birth in only 27 per cent of cases.

As of 2008, 177 countries had incorporated a hepatitis B vaccine into their routine national EPI programmes as a result of the success of the Gambia study.[5.2] During the impact period, at least five further countries in the African WHO region have added infant hepatitis B vaccination to their

EPI, providing virtually universal coverage in the African region. These countries are Liberia, Niger, Central African Republic, Chad and Namibia. In 2012, given numbers of babies born in these countries and hepatitis B third dose coverage from the most recent coverage surveys (for Liberia, Central African Republic, Chad), and from official reports (for Niger and Namibia),[5.3] this means that approximately an additional 1.2m infants per year are being protected against developing liver cancer later in life in these predominantly highly disadvantaged countries which introduced the vaccine during the impact period. The majority of remaining countries globally not to have introduced universal vaccination are in north-west Europe.

A series of follow-up studies by Hall into vaccine efficacy provided the evidence underlying the WHO 2009 recommendation that no booster programme for the hepatitis B vaccine is required if the vaccine is correctly administered at birth. The consequences of adding a booster programme on the budget of Ministries of Health in the less developed world would have been significant. In order to formulate the 2009 position paper, WHO's Strategic Advisory Group of Experts (SAGE) on immunisation, the principal advisory group to WHO for vaccines and immunisation, assessed the available scientific evidence to review the need for booster doses of the vaccine.[5.4,5.5] Hall was a member of the SAGE sub-committee that used the GRADE system of assessing evidence.[5.6] The Gambia study was judged the only 'high-quality' study and therefore played a critical role in the final formulation of the booster policy recommendation.

Professor Hall was knighted in the Queen's Birthday Honours for 2013 for services to public health. His citation notes his seminal contribution to hepatitis B vaccination: 'He is leading the single most important validation of the hepatitis B vaccine outside the Far East, in which over 125,000 infants in The Gambia have been enrolled. A world authority on hepatitis vaccines and viruses, he is in international demand for his knowledge of infectious disease control'.[5.7]

5. Sources to corroborate the impact

5.1 WHO (2009) Hepatitis B vaccines: WHO position paper, *WHO Weekly Epidemiological Record*, 84(40): 405–420, http://www.who.int/entity/wer/2009/wer8440.pdf (accessed 7 November 2013).

5.2 François, G, Dochez, C, Jeffrey M, Burnett, R, Van Hal, G and Meheus, A (2008) Hepatitis B vaccination in Africa: mission accomplished? *The Southern African Journal of Epidemiology and Infection*, 23(1): 24–28.

5.3 WHO vaccine-preventable diseases: monitoring system, 2013 global summary http://apps.who.int/immunization_monitoring/globalsummary (accessed 7 November 2013).

5.4 The role of the evidence in the SAGE process of policy formulation can be verified by the Executive Secretary to the SAGE committee, WHO.

5.5 The role of the evidence in the SAGE process of policy formulation can be verified by the former head of the WHO Hepatitis Section, WHO.

5.6 The Grade document of the SAGE committee can be found at http://www.who.int/immunization/hepb_grad_duration.pdf (accessed 7 November 2013).

5.7 Knighthood: https://www.gov.uk/government/publications/birthday-honours-lists-2013 (accessed 7 November 2013).