Institution: St George's, University of London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Driving strategies to prevent neonatal Group B streptococcal infection

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:
Paul T. Heath	Senior Lecturer, then Reader, Professor	1999 – 2020 (present)
Kirsty Le Doare	Senior Lecturer, Reader, then Professor	2018 – 2020 (present)
Shamez Ladhani	Honorary Senior Lecturer, Honorary Reader, Professor	2014 – 2020 (present)
Christine Jones	Clinical Lecturer, then Honorary Senior Lecturer	2012 – 2020 (present)
Ifeanyichukwu Okike	Clinical Lecturer	2009 – 2010

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Heath and colleagues have defined the epidemiology of neonatal sepsis and meningitis in the UK since 2000, including the risk factors for Group B Streptococcus (GBS), the most important cause. The work led directly to national guidelines for GBS prevention, major clinician and patient education, and also recognition of the need and potential for prevention through maternal vaccination. Heath and Le Doare have addressed the critical components in the pathway toward vaccine implementation on a global scale, including definition of serocorrelates of protection to enable licensure, optimal assessment of safety in pregnancy, cost effectiveness, and public acceptability. These have led to regulatory, WHO, and government endorsement, and major charitable and commercial investment.

2. Underpinning research (indicative maximum 500 words)

Defining the epidemiology and disease burden related to Group B Streptococcus

Group B streptococcus (GBS) causes 90,000 infant deaths per year. Heath and colleagues have defined the epidemiology of neonatal sepsis and meningitis in the UK. They undertook the first national surveillance study between 2000 and 2001 that established the burden of GBS disease, demonstrating that 53% of cases and 73% of fatal early-onset cases had identifiable risk factors, including prolonged rupture of membranes and known maternal carriage of GBS [1]. The work led to a new national risk-based intrapartum antibiotic prophylaxis prevention strategy for early onset GBS (see impact below), and the establishment of a unique national neonatal infection surveillance network (www.neonin.org.uk). The St George's-led national surveillance of neonatal meningitis between 2010 and 2011 confirmed GBS as the commonest cause accounting for 50% of cases [2]. Repeat surveillance of GBS between 2014 and 2015 [3] identified further risk factors and preterm birth was incorporated into guidelines. In addition, the need for an alternative maternal vaccine-based approach that would address both early and late onset disease was clearly established and the serotypes needed for 95% coverage defined [3].

Driving the strategy for maternal vaccine implementation

The group have led internationally in developing maternal vaccination strategies against a range of serious infant infections. Having established the limitations of current GBS prevention, Heath

and Le Doare, with collaborators across the world, developed a pathway to maternal vaccination [4], and elicited support and funding from the WHO and The Bill and Melinda Gates Foundation. The evidence for and guidance on maternal vaccination safety; cost-effectiveness; maternal vaccine acceptability, and assay standardisation in order to facilitate vaccine licensure has been provided:

i) The safety of vaccination is paramount. Based on the largest UK experience of maternal vaccination (St George's has done more pregnancy vaccine trials than any other centre), Heath has developed guidelines and standards for the assessment of safety of maternal vaccination through the international Brighton Collaboration GAIA project (https://brightoncollaboration.us/gaia/)[5].

ii) The group demonstrated the cost-effectiveness of maternal vaccination in a UK-based assessment, providing an impetus for ongoing vaccine development and facilitating decision making for vaccine manufacturers, and national and international policy makers [6]. Data from this analysis were considered at the Department of Health GBS expert advisory group in 2018.

iii) The group has worked to establish parent and healthcare workers' acceptability of maternal vaccination as a strategy for prevention of disease. They have done this through collaborations with relevant partners and public presentations (i.e. SGUL Spotlight on Science events: vaccines for babies before birth, 28 June 2016). Their patient partner initiative is consulted on all maternal and neonatal vaccine-related studies nationally and they work closely with the national support charities: GBSS, Meningitis Now and Meningitis Research Foundation.

Pathway to licensure of maternal GBS vaccines

The large sample sizes required for trials to assess maternal GBS vaccine efficacy constitute a significant obstacle on the pathway to vaccine licensure. Le Doare systematically reviewed evidence of protection based on immunologic data from vaccine and sero-epidemiological studies, and was able to establish evidence for strong correlates of protection. Immune correlates are now considered to be pivotal for licensure, negating the need for very large sample size trials. Le Doare leads an international Bill & Melinda Gates Foundation (BMGF) - funded consortium (GASTON) to derive new standards for assessing the immunological responses to GBS and to develop standardised assays to assess serocorrelates of protection [7]. They are conducting UK (MRC-funded), European and Ugandan (EDCTP and BMGF-funded) studies to define serocorrelates of protection in the field.

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

1. Group B streptococcal disease in UK and Irish infants younger than 90 days. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, O'Connell LAF, Cafferkey M, Verlander NQ, Nicoll A, McCartney AC, PHLS Group B Streptococcus Working Group. Lancet 2004; 363: 292-4. DOI: 10.1016/S0140-6736(03)15389-5. Journal article cited 167 times (WOS 11.02.2021).

2. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United Kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, Anthony M, Ninis N, Heath PT; neoMen Study Group. Clin Infect Dis. 2014; 59(10):e150-7. DOI: 10.1093/cid/ciu514. Journal article cited 74 times (WOS 11.02.2021)

3. Group B streptococcal disease in UK and Irish infants younger than 90 days, 2014-15: a prospective surveillance study. O'Sullivan CP, Lamagni T, Patel D, Efstratiou A, Cunney R, Meehan M, Ladhani S, Reynolds AJ, Campbell R, Doherty L, Boyle M, Kapatai G, Chalker V, Lindsay D, Smith A, Davies E, Jones CE, Heath PT. Lancet Infect Dis. 2019 Jan;19(1):83-90. DOI: 10.1016/S1473-3099(18)30555-3. Journal article cited 19 times (WOS 11.02.2021).

4. Group B streptococcus and respiratory syncytial virus immunisation during pregnancy: a landscape analysis. Heath PT, Culley FJ, Jones CE, Kampmann B, Le Doare K, Nunes MC, Sadarangani M, Chaudhry Z, Baker CJ, Openshaw PJM. Lancet Infect Dis. 2017;17(7):e223. DOI: 10.1016/S1473-3099(17)30232-3. Journal article cited 44 times (WOD 11.02.2021).

5. Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women. Jones CE, Munoz FM, Spiegel HM, Heininger U, Zuber PL, Edwards KM, Lambach P, Neels P, Kohl KS, Gidudu J, Hirschfeld S, Oleske JM, Khuri-Bulos N, Bauwens J, Eckert LO, Kochhar S, Bonhoeffer J, Heath PT; Brighton Collaboration Immunization in Pregnancy Working Group. Vaccine. 2016 Dec 1;34(49):5998-6006. DOI: 10.1016/j.vaccine.2016.07.032. Journal article cited 24 times (WOS 11.02.2021).

6. Cost-effectiveness analysis of maternal immunisation against group B Streptococcus (GBS) disease: A modelling study. Giorgakoudi K, O'Sullivan C, Heath PT, Ladhani S, Lamagni T, Ramsay M, Al-Janabi H, Trotter C. Vaccine. 2018 Oct 3, 36(46):7033-7042. DOI: 10.1016/j.vaccine.2018.09.058. Journal article cited 5 times (WOS 11.02.2021).

7. Serocorrelates of protection against infant group B streptococcus disease Le Doare K, Kampmann B, Vekemans J, Heath PT, Goldblatt D, Nahm MH, Baker C, Edwards MS, Kwatra G, Andrews N, Madhi SA, Ter Meulen AS, Anderson AS, Corsaro B, Fischer P, Gorringe A. Lancet Infect Dis. 2019 May;19(5):e162-e171. DOI: DOI: 10.1016/S1473-3099(18)30659-5. Journal article cited 18 times (WOS 11.02.2021).

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

National guidelines, practice, and policy

Heath's work in defining the national GBS-disease burden and risk factors resulted in formulation and implementation of the first and then updated national guidelines for the prevention of early onset neonatal GBS disease based on intrapartum prophylactic antibiotics given to women with defined risk factors [A (RCOG Greentop guidelines 2017), B]. Prior to this, there were no agreed national policies to reduce GBS infection in infants.

The updated guidelines resulted in changes to the UK screening pathway, enabling more mothers to receive antibiotics during pregnancy and the likely prevention of many cases of GBS disease. Based on risk factors including mode of delivery, rupture of membranes and known carriage of GBS, 25% of live births were originally targeted for prophylaxis. In 2017, the addition of preterm infants as a risk group, resulted in an additional 7% of all live-births being added to the screening pathway [A]. These numbers equate to approximately 160,000 mothers being eligible to receive antibiotics in labour in the UK per year, potentially preventing many cases of early onset GBS disease.

While the relative incidence of early vs. late onset disease, and the case fatality rate of early onset disease both decreased between 2014 and 2015 compared with surveillance between 2000 and 2001(case fatality decreased from 10.6% to 5.2%), the work also clearly established the need for a new strategy to address both early and late onset GBS disease.

This work culminated in Professors Heath and Le Doare's membership of the UK Department of Health GBS research steering committee, which made recommendations for future research to prevent GBS in the UK [C]. These made clear the critical need for a new strategy focused on maternal vaccination, a body of work that the group is now leading.

Impact on practitioners and patients: Educating clinicians and parents about neonatal meningitis

The group's work to educate clinicians and parents about neonatal infection, meningitis and, specifically, GBS, has directly informed guidance nationally and internationally. The RCPCH, Meningitis Now and Meningitis Research Foundation have developed tools for the recognition and management of neonatal meningitis via online tools [Da (with over 1,000 hits)], clinical

algorithms [Db] and patient information [Dc], which are all derived from this research (please see testimonial letter from MRF) [E].

Global Policy and Regulatory body endorsement of maternal vaccinations
Based on their contributions, both Professors Heath and Le Doare sit on the World Health Organisation (WHO) subcommittee addressing GBS vaccine development issues and have contributed to critical reports on the Preferred Product Characteristics and Vaccine Value Proposition, culminating in the WHO scientific advisory group of experts on immunisation (SAGE) agreement to prioritise GBS vaccine licensure for global use [F, G].

Furthermore, they instigated a pivotal meeting between the GASTON consortium (led by Le Doare, and funded by BMGF) and the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in 2018. This resulted in acceptance of the principle of a pathway based on correlates of protection toward licensure of GBS vaccines, providing the support needed for policy makers to recommend its implementation [H].

As a result, the US FDA, the Medicines and Healthcare products Regulatory Agency (MHRA)/ EMA and WHO have endorsed the group's proposed route to facilitate GBS vaccine licensure, representing a step change in the way that vaccines are licenced and facilitating potential accelerated licensure for other maternal vaccines.

Impact on maternal vaccine safety
Professor Heath's work with the Brighton Collaboration GAIA project resulted in the development of standards for assessing vaccine safety in pregnancy [6 (in research above)]. Professor Heath presented guidelines to the WHO Global advisory Committee on Vaccine Safety in June 2016. The committee then recommended their widespread use [I]. These guidelines have been implemented as the gold standard for assessing maternal vaccine safety in clinical trials, facilitating maternal vaccine development for other important indications (e.g. respiratory syncytial virus (RSV), pertussis [I]), as well as GBS.

Commercial impact
The group's work to develop a pathway to a maternal GBS vaccine, endorsed by regulatory and global policy bodies, and backed by cost effectiveness data, has led to significant charitable and commercial investment. Funding for studies in the UK (MRC), Europe (EDCTP), South Africa (BMGF) and Uganda (BMGF) has been secured. Pfizer and Minervax, the two leading vaccine candidate manufacturers, are also undertaking phase 2b trials of their products, within the St George's led EDCTP-funded PREPARE consortium with results available by 2024 [J]. It is anticipated that these vaccine trials with immunological endpoints, known from the serocorrelate work to be protective, can lead to a vaccine being licenced by 2025.

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

A. Hughes RG, Brocklehurst P, Steer PJ, Heath P, Stenson BM on behalf of the Royal College of Obstetricians and Gynaecologists. Prevention of early-onset neonatal group B streptococcal disease. Green-top Guideline No. 36. BJOG 2017;124:e280–e305. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg36 please see Exec Summary, page 4, and evidence in section 7.3, page 14, citing O'Sullivan et al (Ref 39 in document, Ref [3] in research above)
B. National Institute for Health and Care Excellence (NICE) Neonatal infection (early onset): antibiotics for prevention and treatment Clinical guideline [CG149]: https://www.nice.org.uk/guidance/cg149/resources
C. Uncertainties in screening and prevention of Group B Streptococcus disease. Le Doare K, Heath PT, Plumb J, Owen N, Brocklehurst P, Chappell L. Clin Infect Dis 2018 Dec 17.
D. a. http://neonatal.meningitis.org/
b. https://www.meningitis.org/getmedia/75ce0638-a815-4154-b504-b18c462320c8/Neo-Natal-Algorithm-Nov-2017

c. https://www.meningitis.org/getmedia/e37b3e16-49e0-4676-937e-e46f563ab749/Lumbar-Puncture-January-2018?disposition=attachment

E. MRF Testimonial Letter

F. https://www.who.int/immunization/research/development/ppc_groupb_strepvaccines/en/ and https://www.who.int/publications/i/item/WHO-IVB-17.09

G. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vekemans J, Moorthy V, Friede M, Alderson MR, Sobanjo-Ter Meulen A, Baker CJ, Heath PT, Madhi SA, Mehring-Le Doare K, Saha SK, Schrag S, Kaslow DC. Vaccine. 2018 Feb 2. pii: S0264-410X(17)31359-2.

H. https://www.fda.gov/media/113260/download

I. https://www.who.int/vaccine_safety/committee/reports/wer9128_29.pdf?ua=1 and https://clinicaltrials.gov/ct2/show/NCT03614676, and https://clinicaltrials.gov/ct2/show/NCT04589312

J. https://clinicaltrials.gov/ct2/show/NCT04596878 and www.GBSPREPARE.org