Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

EFFECTIVE DESIGN, DEVELOPMENT AND EVALUATION OF MENINGITIS VACCINES

Summary of the impact:
Research performed by the University of Oxford has led to increased protection against meningococcal meningitis, through childhood immunisation in the UK and internationally. Around 600,000 infants each year receive meningococcal vaccines, which prevent up to 1,000 cases of meningitis per annum. Research into the immune responses to polysaccharide conjugate vaccines has changed policy by leading to the introduction of new meningococcal C vaccines in early childhood and booster vaccination in adolescents. Oxford University research has also led to the planned use of vaccines against serogroup B meningococcal disease, which have been licensed and recommended for the prevention of disease in high-risk individuals, and broader use is under consideration.

Underpinning research:
Meningococcal disease is the leading infectious cause of death in children in the UK, and its prevention is a major objective of the Oxford Vaccine Group, directed by Professor Andrew Pollard. During the period from 2001-2013 more than 10,000 volunteers were enrolled in clinical studies in Oxford, mainly children, and the research provided new insight into the design, development and evaluation of novel vaccines for meningitis and specifically meningococcal disease.

Clinical Trials of New Meningitis Vaccines
The University of Oxford has been at the forefront of the evaluation of novel meningitis candidates in infants and young children. The first global clinical trials in infants of a quadrivalent meningococcal vaccine (MenACYW, Menveo, Novartis vaccines)[1], a combination *Haemophilus influenzae* type b-serogroup C meningococcal vaccine (Menitorix, GSK vaccines)[2] and the first trials of the leading serogroup B meningococcal candidate vaccine (MenB, Bexsero, Novartis vaccines)[3] were undertaken in Oxford and Professor Pollard was the chief investigator for the pan-European phase 3 study of the MenB vaccine (1,885 infants enrolled)[4]. These studies showed that the vaccines were safe and highly immunogenic in infants and toddlers. Oxford researchers have also led the development of novel vaccine candidates for the prevention of serogroup B meningococcal disease. Several different vaccine approaches were evaluated through preclinical development including vaccines that use viral vectors to deliver candidate bacterial proteins, purified protein vaccines, and outer membrane vesicle vaccines. All of these candidates have been designed and produced by the University and tested in preclinical studies and one is in Phase I evaluation.

Laboratory Evaluation of Immune Responses
New understanding of the development of immunity to bacterial polysaccharide and protein-polysaccharide conjugate vaccines was obtained by the Oxford Vaccine Group, including a major contribution to the understanding of immunological hyporesponsiveness using B cell ELISPOT assays developed by the University. In these studies it was found that antigen-specific B cells were depleted by plain polysaccharide vaccines but not conjugate vaccines[4], reducing responsiveness to subsequent vaccine doses. In studies of conjugate vaccines, a strong relationship between germinal centre priming in infants and the magnitude of the immune response was found, suggesting that strategies favouring production of memory B cells might lead to better magnitude and persistence of immune responses[6]. Evaluation of the serogroup C meningococcal vaccine (introduced in the UK in 1999) demonstrated that immunity after early childhood vaccination does not persist and that the population immunised before 6 years of age have now become susceptible again. Further data collected in Oxford indicate that adolescent booster doses of vaccine appear to

overcome this and that adolescents produce far more persistent immune responses leading to new vaccine strategies[7].

References to the research:

1. Snape MD et, al. A randomized controlled trial of a novel tetravalent meningococcal glycoconjugate vaccine in infants. JAMA 2008 Jan 9;299(2):173-84. http://www.ncbi.nlm.nih.gov/pubmed/18182599. ***This was the pivotal study of the quadrivalent ACYW vaccine demonstrating immunogenicity in infants that supported its licensure and policy recommendations.***

2. Pace D, Snape M, Westcar S, Oluwalana C, Yu LM, Begg N, Wysocki J, Czajka H, Maechler G, Boutriau D, **Pollard** AJ. A novel combined Hib-MenC-TT glycoconjugate vaccine as a booster dose for toddlers: a phase 3 open randomised controlled trial. Arch Dis Child. 2008 Nov; 93(11):963-70.

3. Findlow J et, al. Multicentre, open-label, randomised phase II controlled trial of an investigational recombinant meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy, Clin Infect Dis, 2010 Nov 15;51(10):1127-37. Epub 2010 Oct 18 http://www.ncbi.nlm.nih.gov/pubmed/20954968. ***The first study ever study in infants of the leading serogroup B meningococcal vaccines.***

4. Gossger N, et, al. European MenB Vaccine Study Group. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. ***JAMA***. 2012 Feb 8;307(6):573-82.***The Oxford led European phase III trial of the leading serogroup B meningococcal vaccine.***

5. Kelly DF et, al. CRM197-conjugated serogroup C meningococcal capsular polysaccharide, but not the native polysaccharide, induces persistent antigen-specific memory B cells. Blood 2006;108(8):2642-7 http://www.ncbi.nlm.nih.gov/pubmed/16675705. ***The first study to indicate the immunological basis for differences in responses to polysaccharide and conjugate meningococcal vaccines.***

6. Blanchard-Rohner G, et, al. The magnitude of germinal center priming with a protein-polysaccharide conjugate vaccine in human infants determines the persistence of antibody and the intensity of booster response. Journal of Immunology 2008;180(4):2165-73. http://www.ncbi.nlm.nih.gov/pubmed/18250423. ***First evidence for a link between early B cell priming in infancy with booster responses in the second year of life.***

7. Snape MD, et, al. Sero-protection against serogroup C meningococcal disease in adolescents in the United Kingdom: an observational study. BMJ 2008 Jun 28;336(7659):1487-91. Epub 2008 Jun 5. http://www.ncbi.nlm.nih.gov/pubmed/18535032. ***The first study to show that protection against meningitis C had waned among teenagers in the UK leading to calls for boosters to be added.***

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Details of the impact:

Meningitis C:

The studies on meningitis vaccines led by the University of Oxford have had a direct impact on national and international immunisation policy. Trials of the combination Haemophilus influenzae type b-Serogroup C meningococcal meningitis vaccine (Menitorix, GSK vaccines)[2] supported recommendations for its use in several countries including the UK and Australia[7] as a booster dose for toddlers. The quadrivalent meningococcal vaccine (MenACYW, Menveo, Novartis Vaccines)[1] is now recommended for high-risk groups and travellers by the UK Department of Health following

the study in infants conducted by the Oxford Vaccine Group. These recommendations were widely reported[8] and led to the vaccines' licensure[9], and are cited in the US recommendations. In areas where meningitis C vaccines are used, serious disease caused by the targeted bacteria has essentially ceased. Over the past 5 years there have been just 2 deaths in people under 20 years of age, in comparison to 78 deaths in the UK in the year prior to the Department of Health's introduction of these Meningitis C vaccines[10]. The phase 4 studies designed and conducted at the University of Oxford, which showed that those vaccinated with serogroup C meningococcal vaccine in early childhood can lose immunity, together with data from the Health Protection Agency, led to widespread changes in immunisation policy in those countries using the vaccine[11]. This also led to widespread media coverage. Adolescent booster doses have been recommended in many countries including the UK[11], Canada[12] and the USA[13], with national recommendations citing studies by the University of Oxford as primary evidence.

Meningitis B:

Studies on serogroup B meningococcal vaccines have led to major media interest following conference presentations of trials conducted in Oxford including numerous newspaper reports, front page coverage by the Independent (2008), Daily Mail and extensive BBC News reporting. The first infant studies of a new serogroup B vaccine (Bexsero) were conducted in Oxford and have been extensively cited. Professor Pollard was asked to give evidence to the World Health Organization in April 2011 on serogroup B meningococcal vaccines[14]. In addition, the first phase 3 infant study in Europe, led by Oxford University investigators, assembled with data from other global studies, led to licensure of the vaccine by the European Medicines Agency in early 2013. A recommendation in the UK for use of the vaccine among high risk groups and laboratory workers has been made[15], and its routine use for children is being considered by the Department of Health[16]. The design and development of new vaccines for serogroup B meningococcus by Oxford University have led to a number of patents on the candidate vaccines (based on various surface proteins including Opa, PorA and FetA[17]), which provide a licensing position for the University as these vaccines progress through early phase clinical trials.

Conduct of Trials:

Studies on plain polysaccharide meningococcal and pneumococcal vaccines provided the first direct demonstration that these vaccines do not induce memory B cells, explaining the phenomenon of hyporesponsiveness (where "booster" doses of vaccines do not induce an immune response). This led to a change in policy for vaccine trials, which had previously used plain polysaccharides to test immunological memory. This outcome was cited in a commentary from Novartis Vaccines in 2009[18].

Sources to corroborate the impact:

7. The Australian Immunisation Handbook, 10th Edition 2013. Meningococcal disease. http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/handbook10-4-10 [Accessed 4/11/13]. ***Recommendations for the use of the combination Haemophilus influenzae type b-Serogroup C meningococcal meningitis vaccine as a booster dose for toddlers. Supported by Oxford research.***

8. Combined meningitis vaccine hope http://news.bbc.co.uk/1/hi/health/7096522.stm [Accessed 4/11/13]. ***Media reporting on the importance of work in Oxford on a quadrivalent meningitis vaccine.***

9. Recommendations on meningococcal vaccine policy for the UK Dept. Health: Green Bk, Ch 22, Meningococcal https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/223749/Green_Book_Chapter_22_v2_3.pdf [Accessed 4/11/13]. ***Evidence that studies in Oxford have been used to support UK policy on monovalent serogroup C meningococcal vaccine and quadrivalent ACYW meningococcal vaccines.***

10. Agency, H. P. (n.d.). Vaccination for Meningococcal disease. hpa.org.uk. Health Protection

Agency, 7th Floor, Holborn Gate, 330 High Holborn, London, WC1V 7PP, 020 7759 2700 / 2701 http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1296682977081 [Accessed 4/11/13]. ***Health Protection Agency (UK) fact sheet featuring information about the decrease in lives lost since the introduction of Meningitis C vaccines.***

11. UK Joint Committee on Vaccines and Immunisation, Meningococcal Sub-Committee, Minute of the meeting held on Friday 18 February 2011. http://webarchive.nationalarchives.gov.uk/20120907090205/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_128724.pdf [Accessed 4/11/13]. ***Evidence that work on serogroup C meningococcal vaccines in Oxford was used in determining UK immunization policy.***

12. Canadian immunisation Advisory Committee Statement (ACS): National Advisory Committee on Immunization (NACI) Update on the Invasive Meningococcal Disease and Meningococcal Vaccine Conjugate Recommendations. April 2009 http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-3/index-eng.php [Accessed 4/11/13]. ***Evidence that work on serogroup C meningococcal vaccines in Oxford underpinned policy decisions in the Canada.***

13. United States vaccine policy: Updated Recommendations for Use of Meningococcal Conjugate Vaccines --- Advisory Committee on Immunization Practices (ACIP), 2010. January 28, 2011 / 60(03); 72-76. www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a3.htm. [Accessed 4/11/13]. ***Evidence that work on serogroup C meningococcal vaccines in Oxford underpinned policy decisions in the USA.***

14. Evidence to WHO provided by Professor Pollard www.who.int/immunization/sage/DRAFT_AGENDA_Apr_SAGE_with_timings_10_Feb_2011.pdf. [Accessed 4/11/13]. ***Evidence that the expertise in Oxford on meningococcal vaccines is of special interest to WHO.***

15. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK July 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224896/JCVI_interim_statement_on_meningococcal_B_vaccination_for_web.pdf [Accessed 4/11/13]. ***JCVI interim statement recommending the use of the meningococcal B vaccine among high risk groups and laboratory workers in the UK. This statement directly cites the Gossger N, et, al 2012 paper from Oxford.***

16. Joint Committee on Vaccination and Immunisation (JCVI). Update on the outcome of consultation about use of Bexsero® meningococcal B vaccine in the UK. Published October 2013. https://www.gov.uk/government/publications/jcvi-update-on-the-use-of-bexsero-meningococcal-b-vaccine [Accessed 4/11/13]. ***Documentation confirming the Department of Health's ongoing consideration for the routine use of the meningococcal B vaccine among children in the UK.***

17. International Patent Application PCT/GB2005/005014, which was filed on 22nd December 2005 and entitled "Compositions". Patent applications directly related to PCT/GB2005/005014 are: GB 0428381.8, EP 05843720.3, US 11/722300, JP 2007-547652. ***Patent application information for vaccine.***

18. Commentary from Novartis vaccines on hyporesponsiveness: By Michael Broker, Keith Veitch - Quadrivalent meningococcal vaccines: Hyporesponsiveness as an important consideration when choosing between the use of conjugate vaccine or polysaccharide vaccine. http://ipac.kacst.edu.sa/eDoc/2010/190189_1.pdf [Accessed 4/11/13]. ***Evidence that work to document and characterize the mechanisms of polysaccharide induced hypo-responsiveness has influenced industry perspectives on vaccine development.***