Institution: University of Oxford		
Unit of Assessment: 5 – Biological Sciences		
Title of case study: More effective immunisation policies to prevent hyperinvasive meningococcus infections through genomic epidemiology		
Period when the underpinning research was undertaken: 2000 – 2015		
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:**
Martin C.J. Maiden	Professor of Molecular Epidemiology	1997 – present
Keith Jolley	Postdoctoral researcher	1998 – present
Holly Bratcher	Research Assistant	2008 – present
Christoph Tang	Professor of Cellular Pathology	August 2011 – present
Period when the claimed impact occurred: 2014 – July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

From 2009 onwards there was a sharp rise in the incidence of invasive meningococcal disease (IMD) in the UK and other countries, caused by a strain of serogroup W *Neisseria meningitidis* (W:cc11). Whole genome sequence (WGS) analysis tools developed by University of Oxford researchers were instrumental in allowing the rapid identification and characterisation of the W:cc11 strain as an aggressive strain that had originated in South America, providing an early indication that it had the potential to cause a serious UK outbreak. This research directly influenced a major change in UK national immunisation policy: the introduction in 2015 of the MenACWY vaccine targeted at teenagers and young adults, resulting in the first use of this vaccine in Europe as part of a routine national immunisation schedule. At least 2,500,000 doses of the MenACWY vaccine were given in the first 4 years of the programme. An estimated 6,000 cases of serogroup W disease have been prevented by the vaccine over 5 years, with an estimated 720 lives saved. Following the success in the UK, the Netherlands, Canada and Ireland also added MenACWY vaccination to their immunisation schedules, supported by use of the WGS tools developed at the University of Oxford.

2. Underpinning research

Researchers at the University of Oxford have studied the population biology and evolution of bacterial pathogens, with a particular focus on *Neisseria meningitidis*, the bacterium that causes invasive meningococcal disease (IMD). The group has pioneered the development of web-based platforms for open-access, sequence and whole genome sequence (WGS)-based analyses for public health implementation. The increase in the capacity and reduction in cost of WGS methods enabled the routine use of these data in real time for epidemiological surveillance and investigations of bacterial disease outbreaks. Research using WGS defines the outbreak strains and compares the data to a library of previously characterised strains, reveals the relationship to previous outbreaks or epidemics; how aggressive the new strain is likely to be; whether existing vaccines will protect against it; and the likelihood of antimicrobial resistance. The information from this research then informs the public health response.

For this to be realised, the Oxford researchers developed generic, portable, publicly -available and robust analysis frameworks, which can be readily interpreted and used in real-time by microbiologists, clinicians, and public health epidemiologists. In 2010, Maiden and Jolley published the Bacterial Isolate Genome Sequence Database (BIGSdb) which enables phenotype and sequence data, ranging from a single sequence read to whole genome data, to be efficiently and effectively linked for a limitless number of bacterial specimens [1]. These software tools were integrated into the existing PubMLST website (https://PubMLST.org) and since then have been used to run all the databases on the site, which now covers 127 different organisms, over 500,000 genomes and over 800,000 isolates. In 2012, the Maiden group

conducted research to demonstrate how the PubMLST *Neisseria* database (https://PubMLST.org/neisseria) could be used to analyse and characterise real disease outbreaks. By collecting and assembling WGS data from a meningococcal disease outbreak that had previously occurred at the University of Southampton, and depositing it in the database, they were able to show that multiple closely related but distinct strains were simultaneously present in asymptomatic carriage and disease, with two causing disease and one responsible for the outbreak itself [2]. The Maiden Laboratory went on to apply WGS to systematically characterise hyperinvasive meningococcal strains [3] and established the relationship between meningococcal lineage (referred to as the clonal complex or cc) with the serogroup, which is defined by the nature of the capsule expressed by bacteria; the capsule is also an important vaccine antigen [3]. A crucial step was the use of WGS techniques to characterise and differentiate cc11 strains causing epidemics of IMD, in particular the genomic identification of the serogroup W:cc11 strain [4].

The Oxford researchers were also the first to demonstrate the remarkable effect of herd immunity conferred by conjugate meningococcal vaccines, through extensive carriage studies led over a number of years before and during implementation of the serogroup C vaccine in the UK in 1999. By studying meningococcal carriage, they determined the effect the vaccine had on the meningococcal bacteria population. Maiden's studies showed that after the MenC vaccine was introduced, there was a dramatic fall in carriage of meningococcal bacteria, leading to protection even of people who had not been vaccinated, and with no evidence for an increase in other meningococcal serogroups. Moreover, serogroup C strains were particularly affected, resulting in a dramatic reduction of their transmission, including in teenagers and university freshers [5].

In 2011, the Meningitis Research Foundation, a major UK funder of meningococcal research, commissioned the establishment of the Meningococcus Genome Library (MRF-MGL). The University of Oxford research and expertise in WGS tools formed the key part of the MRF-MGL collaboration that also included Public Health England (PHE) and the Wellcome Trust Sanger Institute. The MRF-MGL remains the principal publicly accessible research data source of WGS for every disease isolate of *Neisseria meningitidis* in the UK. MRF-MGL provides the complete genetic blueprint of every meningococcus that was isolated as a cause of meningitis or septicaemia in England, Wales and Northern Ireland between July 2010 and June 2013, and from Scotland between 2009 and 2013. Oxford research using the MRF-MGL demonstrated its key role in the real-time genomic surveillance of meningococcal strains, and revealed information crucial to effective deployment and assessment of vaccines against *Neisseria meningitidis* [6].

3. References to the research (Oxford employees in bold, students in italics)

1. **KA Jolley** and **MC Maiden** (2010), BIGSdb: Scalable analysis of bacterial genome variation at the population level. *BMC Bioinformatics* **11**(1): p. 595. DOI: 10.1186/1471-2105-11-595 (Google Scholar 1312 citations).
2. **KA Jolley**, *DM Hill*, **HB Bratcher**, **OB Harrison**, IM Feavers, J Parkhill, and **MC Maiden** (2012), Resolution of a meningococcal disease outbreak from whole genome sequence data with rapid web-based analysis methods. *J. Clin. Microbiol.,* **50**(9): p. 3046-53. DOI: 10.1128/jcm.01312-12 (Google Scholar 74 citations).
3. **HB Bratcher**, C Corton, **KA Jolley**, J Parkhill, and **MC Maiden** (2014), A gene-by-gene population genomics platform: de novo assembly, annotation and genealogical analysis of 108 representative Neisseria meningitidis genomes. *BMC Genomics*, **15**:1138. DOI: 10.1186/1471-2164-15-1138 (Google Scholar 108 citations).
4. J Lucidarme, *DM Hill,* **HB Bratcher**, SJ Gray, M du Plessis, RS Tsang, JA Vazquez, MK Taha, M Ceyhan, AM Efron, MC Gorla, J Findlow, **KA Jolley**, **MC Maiden**, and R Borrow (2015), Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. *J. Infect.*, **71**(5):544-52. DOI:10.1016/j.jinf.2015.07.007.
5. **MC Maiden**, **AB Ibarz-Pavón**, **R Urwin**, SJ Gray, NJ Andrews, SC Clarke, AM Walker, MR Evans, JS Kroll, KR Neal, DAA Ala'Aldeen, **DW Crook**, **K Cann**, S Harrison, R

Cunningham, D Baxter, E Kaczmarski, **J MacLennan**, JC Cameron, JM Stuart (2008), Impact of Meningococcal Serogroup C Conjugate Vaccines on Carriage and Herd Immunity. *The Journal of Infectious Diseases,* **197**:737–743. DOI: 10.1086/527401

6. *DMC Hill***,** J Lucidarme, SJ Gray, LS Newbold, R Ure, **C Brehony**, OB Harrison, **JE Bray**, **KA Jolley**, **HB Bratcher**, J Parkhill, **CM Tang**, R Borrow, and **MCJ Maiden** (2015), Genomic epidemiology of age-associated meningococcal lineages in national surveillance: an observational cohort study. *Lancet Infect Dis*, 2015. **15**(12): p. 1420-8. DOI: 10.1016/S1473-3099(15)00267-4

Funding included Wellcome Trust Senior Research Fellowship 'Population genomics of the Neisseria' total GBP2,404,296 (087622/Z/08, 2009-2016) and for PubMLST GBP637,098 (104992/Z/14, 2014-19), both to M. Maiden and held at the University of Oxford.

4. Details of the impact

The research has led to a major change in immunisation policy in the UK, and other countries, and is an exemplar of the public health benefits of publicly-available libraries of genomic information for control of bacterial and other microbial pathogens.

Pathway to impact: the rise of MenW in the UK and the public health response

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* represents a serious public health concern. More than 1,000,000 cases are estimated to occur worldwide every year. The bacterium causes a range of serious, life-threatening diseases including septicaemia and meningitis, particularly in children and teenagers. In the UK mortality rates are around 5%, with about 20% of survivors suffering from life-altering sequelae such as limb amputations and brain damage. Some aggressive epidemic strains have much higher mortality rates.

Historically, the incidence of serogroup W strains causing IMD had been low in the UK (1%–2% of total cases annually). However, from 2009 onwards there was a significant rise in cases of IMD caused by serogroup W strains in England from 22 in 2009-10 (2 deaths) to 55 in 2012-13 (9 deaths). Even though case numbers were low, infections were associated with severe outcome, atypical clinical presentations (e.g. septic arthritis and severe respiratory tract infections), and a case fatality rate of 12-13% [A].

By late 2013 Public Health England (PHE, at that time the Health Protection Agency) was concerned about the increase in serogroup W cases. The Oxford research played a key part in guiding the appropriate actions of PHE's Vaccine Preventable Invasive Bacterial Diseases Forum, of which Maiden was a member [B]. An international collaboration led by the Maiden Laboratory and PHE was established to characterise the strain responsible for the increase in cases and determine whether it posed a serious public health risk. Isolates sequenced by PHE and by the Maiden group were analysed using the PubMLST *Neisseria* database (incorporating the BIGSdb tools [1]), and also using the MRF-MGL. This allowed the rapid identification and characterisation of the serogroup W strain (W:cc11) and its relationship to other circulating meningococcal strains.

Crucially, information on previously characterised strains contained in the databases established that the serogroup W strain was derived from hyperinvasive strains that had caused recent major outbreaks in South America with high mortality rates, and was related to the serogroup C strain which had caused global outbreaks of IMD in the 1990s, with thousands of cases and hundreds of deaths in the UK every year. The results [4] were shared with PHE in real time.

Introduction of a MenACWY vaccine into the UK's routine immunisation schedule

The strain identification [4] was one of the first exemplars of the application of genomic data to drive a population-level public health intervention, and led to a change in the UK immunisation policy. At the October 2014 meeting of the Joint Committee on Vaccination and Immunisation (JCVI), the independent body which advises the Department of Health and Social Care on immunisation, PHE stated that '*…Of particular concern was the fact that most cases of MenW disease in England and Wales were caused by W:cc11, the same clonal complex as the outbreak MenC strain which struck the UK during the 1990s, which was associated with*

increased virulence, increased fatality rates and disease in younger age groups.' [C]. Based on the findings of [4], JCVI were seriously concerned that the W:cc11 strain could cause a nationwide outbreak, leading to their recommendation that a MenACWY vaccine should be introduced into the routine UK immunisation schedule [D].

In summer 2015, the monovalent MenC vaccine given to teenagers in school year 9 was replaced with a single dose of a quadrivalent MenACWY vaccine. The MenACWY vaccine continued to be given routinely to this age group through a schools-based programme. At the same time, an emergency MenACWY catch-up programme began through GP surgeries, targeted at all teenagers aged 14-18 (since they have high carriage rates of meningococci and are a source of infection for susceptible children and adults) and those up to the age of 25 attending university for the first time (since there are high rates of meningococcal disease in this population) [E].

This was the first use of the quadrivalent MenACWY vaccine in Europe as part of a national routine immunisation schedule and arose directly from knowledge of the genomic epidemiology of the serogroup W strain provided by the Maiden laboratory, and the use of the publicly available resources his laboratory developed. Prior to this, the MenACWY vaccine had been only used in the UK for high-risk individuals, travellers to endemic regions and for controlling sporadic outbreaks.

Impact of the MenACWY vaccine on cases of serogroup W disease in England

At the point the MenACWY vaccine was introduced, serogroup W cases were rising at a rate of around 80% a year across all age groups (55 cases in 2012-13, 95 in 2013-14, 176 in 2014-15) [A,F]. In the first year of vaccination (2015 - 16) there were 211 serogroup W cases in England instead of a projected 317, representing an estimated 106 cases prevented. Over the next 3 years the incidence of serogroup W disease in the UK fell by more than 60%, with 225 cases in 2017-18, 113 cases in 2018-19 and 79 cases in 2019-20 [F].

PHE data indicate that if case numbers had continued to rise by 80% a year, in the 5 years to 2019 – 20, an additional 6,000 serogroup W cases would be expected in the UK, with 720 deaths (based on a 12% mortality rate) and a further 1,200 people (20%) of survivors left with life-changing disabilities which seriously affect quality of life and also have a significant economic impact for the sufferers, their families, and the NHS [F]. Whilst these figures are based on an assumption of a steady increase, the epidemic of the related serogroup C strain in the 1990s had shown that the serogroup W strain could cause thousands of cases and hundreds of deaths if left unchecked (there were nearly 1,000 cases and 78 deaths before the MenC vaccine was introduced in 1999), and that JCVI experts were seriously concerned about the potential for this aggressive MenW strain to do the same [C].

The rapid decline in MenW cases in all age groups, not just those immunised, corroborates the remarkable effect of herd immunity conferred by conjugate meningococcal vaccines that had been first recognised by Maiden's laboratory through carriage studies he led during the implementation of the MenC vaccine in the UK during 1999-2000 [5].

Between 83% and 88% of each year 9 group received the MenACWY vaccine in UK schools in the 4 academic years from 2015-16 to 2018-19 (approximately 500,000 teenagers a year; each yearly birth cohort is approximately 600,000 according to ONS). In addition, in the same period, several hundred thousand of those aged up to 25 were vaccinated as part of the catch-up programme through GP surgeries. Overall, approximately 2,500,000 doses of MenACWY vaccine were given in the UK over the first 4 years of the programme [G].

Influence on MenACWY immunisation schedule changes in other countries

The subsequent rise of serogroup W cases in other countries including France, Italy, Netherlands, Canada, Ireland and Australia led to them introduce the MenACWY vaccine into their national schedules [H]. In the case of the Netherlands, Canada and Ireland, the national research that prompted immunisation schedule changes used the PubMLST *Neisseria* database and the MRF-MGL to identify and characterise the strain; the Netherlands and Ireland directly referenced the research [4]. Cases in these three countries were confirmed to be related to the strain first identified in the UK. The Netherlands added MenACWY vaccination to their national

schedule in 2018. From 2014-15 to 2015-16, serogroup W cases had increased more than fourfold in The Netherlands, particularly in adults over 65 years old [I]. The Public Health Agency of Canada used the *Neisseria* databases to characterise the strain affecting Canada and argue for the introduction of the MenACWY vaccine [J]. By 2019, individual provinces and territories in Canada had almost all had implemented MenACWY immunisation [H]. From 2013, Ireland experienced a similar rise in serogroup W cases; work by Irish public health authorities in collaboration with the Maiden group identified that this was the same serogroup W strain that was affecting the UK. Data from the study informed Ireland's National Immunisation Advisory Committee, which made the decision to introduce MenACWY vaccination in Ireland in 2019 [K]. The latest recommendations in Australia also include MenACWY [L].

5. Sources to corroborate the impact

A. Journal article: Ladhani SN et al. (2015). *Increase in endemic Neisseria meningitidis capsular Group W sequence type 11 complex associated with severe invasive disease in England and Wales.* Clin Infect Dis. 60(4), 578-85. DOI: 10.1093/cid/ciu881. Corroborates the background to the MenW IMD outbreak, symptoms and severity, and cases and deaths 2008-09 to 2013-14.

B. Minutes of the HPA Vaccine Preventable Invasive Bacterial Diseases Forum, 20 November 2013, corroborating Prof Maiden's role in the response to the increase in MenW cases.

C. Minutes of the Joint Committee on Vaccination and Immunisation (JCVI), October 2014. Paras 37-47 corroborate the discussion and recommended response to the MenW outbreak. https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/229171787772

D. Corroborator 1: Senior Clinical Scientist, Immunisation and Countermeasures, National Infection Service, Public Health England, who can corroborate the link between the underpinning research, the collaboration for [4] and the PHE recommendations to JCVI [C].

E. Letter from the NHS and PHE to Clinical Commissioning Groups, GPs and others to announce the implementation of the new MenACWY programme, June 2015.

F. PHE Invasive meningococcal disease laboratory annual reports for 2014-15 to 2019-20, corroborating cases of MenW IMD and providing data on which projected figures are based. E.g. https://www.gov.uk/government/publications/meningococcal-disease-laboratory-confirmed-cases-in-england-in-2019-to-2020

G. PHE vaccine coverage estimates for the MenACWY vaccine, 2018-19 report, confirming coverage estimates for 2015-19. https://www.gov.uk/government/publications/meningococcal-acwy-immunisation-programme-vaccine-coverage-estimates

H. Journal article: Presa J et al. (2019) Epidemiologic Trends, Global Shifts in Meningococcal Vaccination Guidelines, and Data Supporting the Use of MenACWY-TT Vaccine: A Review. *Infect Dis Ther.* **8**(3): 307–333. DOI: 10.1007/s40121-019-0254-1.

I. Journal article: Knol MJ et al. (2018) 'Implementation of MenACWY vaccination because of ongoing increase in serogroup W invasive meningococcal disease, the Netherlands'. *Euro Surveill.* **23**(16):18-00158 DOI: 10.2807/1560-7917.ES.2018.23.16.18-00158. Corroborates the use of PubMLST and the MRF-MGL to characterise the MenW strain in the Netherlands, leading to implementation of MenACWY vaccination; references [3].

J. Tsang RS et al. (2019) 'Increase in ST-11 serogroup W Neisseria meningitidis invasive meningococcal disease in Canada, 2016–2018'. *Canada Communicable Disease Report*, Vol. 45-6. DOI: 10.14745/ccdr.v45i06a04. Corroborates the use of the PubMLST Neisseria database and the MRF-MGL in Canada, which influenced MenACWY introduction.

K. Journal article: Mulhall RM et al. (2019) 'cgMLST characterisation of invasive Neisseria meningitidis serogroup C and W strains associated with increasing disease incidence in the Republic of Ireland.' *PLoS One.* 14(5):e0216771. DOI: 10.1371/journal.pone.0216771. Includes corroboration that this contributed to the decision to introduce MenACWY in Ireland.

L. Summary of the Meningococcal immunisation service, Australian Government Department of Health, webpage, last updated 23 June 2020, including specification of ACWY. https://www.health.gov.au/health-topics/immunisation/immunisation-services/