Journal of Infection (2015) 71, 544—552

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage

Jay Lucidarme [a,*], Dorothea M.C. Hill [b], Holly B. Bratcher [b], Steve J. Gray [c], Mignon du Plessis [d], Raymond S.W. Tsang [e], Julio A. Vazquez [f], Muhamed-Kheir Taha [g], Mehmet Ceyhan [h], Adriana M. Efron [i], Maria C. Gorla [j], Jamie Findlow [a], Keith A. Jolley [b], Martin C.J. Maiden [b], Ray Borrow [a,c]

[a] *Vaccine Evaluation Unit, Public Health England, Manchester Medical Microbiology Partnership, Second Floor, Clinical Sciences Building II, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WZ, UK*
[b] *Department of Zoology, University of Oxford, Oxford, UK*
[c] *Meningococcal Reference Unit, Public Health England, Manchester Medical Microbiology Partnership, Second Floor, Clinical Sciences Building II, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WZ, UK*
[d] *Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, National Health Laboratory Service, 1 Modderfontein Road, Sandringham, Johannesburg, 2131, South Africa*
[e] *National Microbiology Laboratory, Public Health Agency of Canada, 1015 Arlington Street, Winnipeg, MB R3E 3R2, Canada*
[f] *Reference Laboratory for Meningococci, Institute of Health Carlos III, Majadahonda, Spain*
[g] *Institut Pasteur, Unité des Infections Bactériennes invasives, Département Infection et Epidémiologie, Paris, France*
[h] *Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[i] *Servicio Bacteriología Clínica, Departamento de Bacteriología, Instituto Nacional de Enfermedades Infecciosas-ANLIS «Dr. Carlos G. Malbrán», Ciudad Autónoma de Buenos Aires, Argentina*
[j] *Division of Medical Biology, Bacteriology Department, Adolfo Lutz Institute, São Paulo 01246-902, Brazil*

Accepted 17 July 2015
Available online 28 July 2015

* Corresponding author. Tel.: +44 0 161 276 6791.
E-mail addresses: jay.lucidarme@phe.gov.uk (J. Lucidarme), dorothea.hill@zoo.ox.ac.uk (D.M.C. Hill), holly.bratcher@zoo.ox.ac.uk (H. B. Bratcher), Steve.Gray@phe.gov.uk (S.J. Gray), mignond@nicd.ac.za (M. du Plessis), Raymond.Tsang@phac-aspc.gc.ca (R.S.W. Tsang), julioavazquez@gmail.com (J.A. Vazquez), muhamed-kheir.taha@pasteur.fr (M.-K. Taha), mceyhan@hacettepe.edu.tr (M. Ceyhan), amefron@anlis.gov.ar (A.M. Efron), mcgorla@ial.sp.gov.br (M.C. Gorla), Jamie.Findlow@phe.gov.uk (J. Findlow), keith.jolley@zoo.ox.ac.uk (K.A. Jolley), martin.maiden@zoo.ox.ac.uk (M.C.J. Maiden), Ray.Borrow@phe.gov.uk (R. Borrow).

http://dx.doi.org/10.1016/j.jinf.2015.07.007

KEYWORDS
Meningococcal;
ST-11 clonal complex;
Genome;
Serogroup W;
Serogroup C

Summary *Objectives: Neisseria meningitidis* is a leading cause of meningitis and septicaemia. The hyperinvasive ST-11 clonal complex (cc11) caused serogroup C (MenC) outbreaks in the US military in the 1960s and UK universities in the 1990s, a global Hajj-associated serogroup W (MenW) outbreak in 2000–2001, and subsequent MenW epidemics in sub-Saharan Africa. More recently, endemic MenW disease has expanded in South Africa, South America and the UK, and MenC cases have been reported among European and North American men who have sex with men (MSM). Routine typing schemes poorly resolve cc11 so we established the population structure at genomic resolution.
Methods: Representatives of these episodes and other geo-temporally diverse cc11 meningococci (n = 750) were compared across 1546 core genes and visualised on phylogenetic networks.
Results: MenW isolates were confined to a distal portion of one of two main lineages with MenB and MenC isolates interspersed elsewhere. An expanding South American/UK MenW strain was distinct from the 'Hajj outbreak' strain and a closely related endemic South African strain. Recent MenC isolates from MSM in France and the UK were closely related but distinct.
Conclusions: High resolution 'genomic' multilocus sequence typing is necessary to resolve and monitor the spread of diverse cc11 lineages globally.

Introduction

The Gram-negative bacterium *Neisseria meningitidis*, the meningococcus, is principally a commensal that colonises the nasopharynx of approximately 10% of humans. It is also a leading cause of meningitis and septicaemia, being associated with sporadic cases, outbreaks and epidemics throughout the world.[1] The principal meningococcal virulence factor is the polysaccharide capsule which also defines the serogroup. Serogroups A, B, C, W, X and Y are responsible for most disease and vaccines are currently available against serogroups A, C, W and Y.[1,2] Bexsero, a recently licensed vaccine against serogroup B organisms, targets subcapsular antigens[2] and was developed in response to safety and efficacy concerns surrounding the B polysaccharide. Reference laboratories conventionally identify serogroups and also type/subtype meningococci on the basis of outer membrane proteins (OMPs). Meningococcal population structure has been studied with multilocus sequence typing (MLST) which classifies meningococci into clonal complexes (ccs). Most invasive isolates belong to a limited number of ccs, which correspond to the hyperinvasive lineages first identified by multilocus enzyme electrophoresis (MLEE).[3]

Meningococci belonging to the ST-11 clonal complex (cc11; also known as the ET-37 complex and lineage 11) are hyperinvasive and may express serogroups C (MenC:cc11) or W (MenW:cc11) and, less frequently, B (MenB:cc11) or Y. They are associated with high rates of morbidity and mortality[4] and have a propensity to cause outbreaks and epidemics. For example: cc11 meningococci were responsible for serogroup B and C outbreaks in the US military in the 1960s, leading to the implementation of the first generation of meningococcal polysaccharide vaccines.[5] Epidemics caused by MenC:cc11 in North America, Europe and Australia in the 1990s/2000s, prompted the first use of serogroup C glycoconjugate vaccines[6] and in 2000 a Hajj-associated outbreak of MenW:cc11 disease swept the globe, persisting for several years.[7] Since 2001, MenW:cc11 has caused epidemics in the meningitis belt of Sub-Saharan Africa.[8] North America and Europe have recently experienced several high-profile cases and outbreaks of MenC:cc11 disease among men who have sex with men (MSM), the first being identified in Toronto in 2001.[9] From 2003, endemic MenW:cc11 disease increased in South Africa, Brazil and, subsequently, several other South American countries where case fatality rates reached 28%.[10,11] England and Wales have also seen a year-on-year increase in endemic MenW:cc11 disease since 2009.[12]

Beyond the serogroup, currently used typing schemes offer limited resolution among cc11 meningococci. PorB OMP serotypes 2a or NT (non-typable using antisera available from the National Institute for Biological Standards and Control, Potters Bar, UK) are broadly distributed within the cc, whilst almost all MenW:cc11 organisms and a large proportion of MenC:cc11 organisms express the PorA OMP subtype P1.5,2. MLEE was instrumental in identifying the 'ET-15' subpopulation responsible for the elevated MenC:cc11 disease of the 1990s/2000s, as well as among MSM cases.[9] This labour intensive and poorly portable scheme was superseded in late 1998 by MLST[13]; however, the majority of cc11 disease isolates exhibit a single sequence type (ST-11). PorA also poorly resolves these meningococci as, although subtypes P1.5-1,10-8 and P1.5-1,10-4 are the most common, a large proportion exhibit the widespread P1.5,2 subtype.[14] Consequently, research groups and reference laboratories have targeted individual ET-15 markers such as the genomic presence of the insertion sequence IS*1301* or the fumerase (*fumC*) gene mutation responsible for the characteristic electropherotype.[15,16] As none of the typing markers employed to date are satisfactory, there is uncertainty as to the relatedness of current and historical cases and the provenance of emerging cc11 strains. Isolates typed as MenW:cc11, for example, are often described as 'the Hajj strain' with no direct evidence that they are closely related.[17]

Whole genome sequencing (WGS) of meningococcal genomes is currently the most cost effective method for