

# Meningococcal Disease Section 1: Microbiology And Historical Perspective

**MeningoNI Forum** (see page 87(2) 83 for full list of authors)

Provenance: externally peer reviewed

Accepted: 5th March 2018

## INTRODUCTION

There are few infectious diseases than can strike fear into parents, the public and healthcare professionals, as much as meningococcal meningitis. Over the past five years, there has been renewed interest in vaccine prevention of meningococcal meningitis mainly through the development of two new vaccination programmes, namely (i) the 4CMenB vaccine to cover meningococcal serogroup B strains<sup>1</sup> and (ii), the introduction of the MenACWY vaccination, in adolescents and the university population<sup>2</sup>. In 2016, public interest in this disease and its prevention through vaccination was demonstrated by an unprecedented number of petition signatures from the public (> 823,349), calling on the UK government to extend the meningococcal B vaccination programme to those older than 1 year old<sup>3</sup>. In addition, the recently revised National Institute for Health and Care Excellence (NICE) guidelines on Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management<sup>4</sup> coupled with decision making within the devolved Northern Ireland context, make it timely to review meningococcal meningitis. This review examines aspects of epidemiology, laboratory diagnosis, treatment/management, post-disease complications, vaccination and prevention, as well as exploring the various support structures and resources offered by the meningitis charities to patients and healthcare professionals, currently operating in Northern Ireland.

## MICROBIOLOGY OF NEISSERIA MENINGITIDIS

Meningitis in its broadest form has a variety of different aetiological causes, including viral<sup>5</sup>, bacterial<sup>6,7</sup>, fungal<sup>8,9</sup> and parasitic (eosinophilic)<sup>10</sup> and we attach citations to seminal reviews on each of these aetiologies to help guide readers to additional reading resources. Of these, meningococcal infection is the most common cause of bacterial meningitis in the UK and Ireland, accounting for approximately 2,000 cases per year, of which about 1,600 cases have a laboratory confirmation. The common aetiological bacterium is *Neisseria meningitidis* (*N. meningitidis*) – the so-called “meningococcus”, which is a major pathogen of meningitis and septicaemia in humans, but not in animals. This Gram-negative bacterium belongs to the genus *Neisseria*, which currently comprises 29 species described within, including

*N. meningitidis*. Of the other 28 species, eight including *N. cinerea*<sup>11</sup>, *N. flava*<sup>12</sup>, *N. flavescens*<sup>13</sup>, *N. lactamica*<sup>14</sup>, *N. mucosa*<sup>15</sup>, *N. perflava*<sup>16</sup>, *N. sicca*<sup>17</sup> and *N. subflava*<sup>18</sup> have been reported to occasionally cause meningitis, but not with the same frequency as *N. meningitidis*. In addition, the other major human pathogen within this genus, *N. gonorrhoeae*, has infrequently been associated with disseminated infection from the urogenital tract although there have been 24 reported cases of this species causing meningitis<sup>19</sup>. Both *N. meningitidis* and *N. gonorrhoeae* are human host-restricted pathogens. In the case of meningococcus, the only natural reservoir of this bacterium is due to oropharyngeal “carriage” by otherwise healthy humans. Carriage rates vary dramatically with age – an important factor that affects transmission dynamics and vaccination strategies for meningococcal disease<sup>20</sup>. Most of the other *Neisseria* species are harmless commensals of humans and animals.

Gaspard Vieusseux<sup>21</sup> gave the first clinical description of meningococcal disease in 1805, during an outbreak with 33 deaths in the vicinity of Geneva, Switzerland, however the causative agent was not cultivated and named “*Diplokokkus intracellularis meningitidis*” until approximately 80 years later by Anton Weichselbaum, in the CSF of six of eight patients with bacterial meningitis.<sup>22</sup> It is now known that the Gram-negative *Proteobacterium*, *N. meningitidis* has twelve capsular serogroups (A, B, C, E, H, I, K, L, W, X, Y and Z), which are characterised by their polysaccharide capsule, which is the organism’s principal virulence factor, however six serogroups, namely A, B, C, W, X and Y account for most cases of meningococcal disease worldwide, with different seroprevalance.<sup>23</sup> Meningococci are further classified into type and subtype on the basis of their outer membrane proteins (OMPs), and porins (porB and porA, respectively)<sup>24</sup>. Molecular methods, such as multilocus sequence typing (MLST), in conjunction with eBurst (Based upon related sequence types) software, are used in the classification of meningococci. Sequence types (ST) are based on the variants observed in the nucleotide sequences of 400 - 500bp long

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fragments of seven housekeeping genes. Subsequently, clonal complexes (ccs), which differ substantially in their pathogenic potential, are identified as closely related groups of isolates in which all STs are linked to a single locus variant of at least one other ST<sup>25</sup>. With increasing availability and reducing costs, whole genome sequencing, is currently providing further insights into the characterisation and accurate typing of isolates<sup>26</sup>. Of significance is the “The Meningitis Research Foundation Meningococcus Genome Library (MRF-MGL)”, which commenced in 2012 and contains the whole genome sequences of invasive meningococcal isolates, in entire epidemiological years, from England, Wales and Northern Ireland which were received by the Public Health England Meningococcal Reference Unit from July 2010 to June 2013. The MRF-MGL is freely available to researchers worldwide and is an excellent resource of quality data which can be used to study surveillance, outbreaks, epidemiology, evolution, development and evaluation of new vaccines. Additionally, data from the MRF-MGL can be used in conjunction with PubMLST, another open access repository of Neisserial isolate data, in order to compare current data with historical and international cases (<http://pubmlst.org/neisseria/>)<sup>27</sup>.

### HISTORICAL PERSPECTIVE

“Within the last few years a peculiar inflammatory affection has been discovered, attacking the base of the brain and superior part of the spinal cord, to which the name of cerebro-spinal meningitis has been given. This, although an acute inflammation, appears to prevail at times as an epidemic, and did so some years ago in the Belfast Workhouse. It most frequently attacks boys, or young men recently subjected to the vicissitudes of a military life.” Professor Seaton Reid, President, Belfast Clinical and Pathological Society, and taken from the Presidential Opening Address of the 7th Session of the Belfast Clinical and Pathological Society, Saturday 29 October, 1859<sup>28</sup>. This oration was one of the earliest reports of meningococcal disease in Northern Ireland and was given approximately 54 years after its first description by Vieusseux in 1805.<sup>21</sup> Reid’s description of the disease was approximately 25 years before the first microbiological description of the aetiological agent of the infection, namely the meningococcus. This was first described as intracellular oval micrococci by the Italian pathologists, Marchiafava and Celli, in a sample of CSF<sup>29</sup>.

Reid’s early description of meningococcal disease alluded to an important epidemiological component of the disease, namely transmission from person-to-person, exacerbated by infected patients living and working in close proximity to each other and affecting inhabitants of a Belfast Workhouse, as well as in young military recruits. The association between this disease and the military continued with an eloquent report of a meningococcal meningitis outbreak in a military camp in Randalstown, Co. Antrim in the *British Medical Journal*, in December 1916, relating to an on-going outbreak, dating back to 17th February 1915, totalling 129 cases<sup>30</sup>. Of these 129 cases, 44 were from the military, of whom 25 recovered

and 19 died. We know from this report by Captain James Wilson, Royal Army Medical Corps and colleagues, that there had been an “extensive” outbreak in the community in Belfast in 1907-1908 and in the surrounding towns and villages, with a few sporadic cases occurring each year after that<sup>30</sup>. This report cites the index case originating from the Randalstown camp, where the 14th Battalion Royal Irish Rifles were training in preparation for deployment to the Somme, after a period of final training in Liphook in Hampshire<sup>30</sup>. These troops would later form part of the 36th (Ulster) Division, in Kitchener’s New Volunteer Army. It was believed that meningococci were not transmitted from England or Scotland to the troops, but that these bacteria were the legacy of carriage from the 1907-1908 outbreak in Belfast<sup>30</sup>. Most of the military recruits were volunteers, coming from a variety of backgrounds and their billets in Randalstown was their first experience of communal living. Wilson’s paper describes their living conditions in a positive manner, including the state of the huts that the recruits were housed in (Figure 1), but we can see from this photograph, that each hut had a high occupancy rate. Subsequently, in 1918, Captain Glover published his paper in the *BMJ* entitled “Spacing-out in the prevention of military epidemics of cerebro-spinal fever”, whereby he advocated that military personnel should have at least two and a half feet spacing between each bed, in order to reduce meningococcal carriage, particularly amongst recruits during the first three months of service<sup>31</sup>.



Fig 1. Kit Inspection in Hut.

A slide from lecture derived from Jim Maultsaid’s War Book showing soldiers standing to attention in Randalstown hut, kit laid out for inspection; 1915.

Photograph courtesy of the Ulster Museum (BELUM.Y15526)

Paradoxically, 95 years later, replication of the scenario of young people living together and in close proximity with each other for the first time, allows for the transmission of the meningococcus from person-to-person and the recurrence of disease, as was tragically witnessed by the death a fresher business studies student at the University of Ulster, Jordanstown campus in September 2010 (<http://www.bbc.co.uk/news/uk-northern-ireland-11418804>).

In 1952 in the *Ulster Medical Journal*, Dr Sarah Campbell

described 47 cases of meningococcal meningitis occurring predominantly in neonates and babies (n=24), toddlers and infants (n=17), children [5-10 years] (n=2) and older children/adolescents/teenagers/young adults (n=4). Treatment options had evolved to using antibiotics as the mainstay of treatment, including i.m. penicillin and i.v. sulphamezathine<sup>32</sup>.

In 1974, Dr Maurice Savage described 29 confirmed cases of meningococcal meningitis at the Royal Belfast Hospital for Sick Children and an additional 12 unconfirmed cases based on typical findings consistent with meningococcal disease at post mortem, characterised by presence of a purpuric rash or close contact with a proven case<sup>33</sup>. Savage's paper highlighted the difference in the spectrum of disease presentation, comparing a simple case of meningitis with slow progression and a classical presentation, to a rapidly fatal form of the disease. It is also interesting to note from Savage's paper emerging descriptions of antibiotic resistance with the sulphonamides, which were the mainstay of antibiotic management, 21 years earlier in the Campbell paper<sup>32,33</sup>.

From 1995-1998, data on meningococcal disease in Northern Ireland, based on laboratory reports of *N. meningitidis* were published by Public Health officials and data from 1999-present has been based on enhanced surveillance of meningococcal disease notifications validated by laboratory reports. Both "Acute Encephalitis/Meningitis Bacterial" and "Meningococcal septicaemia" are now formally recognised Notifiable Infectious Diseases in Northern Ireland.

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