Original article

Rise in invasive serogroup W meningococcal disease in Australia, 2013-2015

Nicolee V Martin, Katherine S Ong, Benjamin P Howden, Monica M Lahra, Stephen B Lambert, Frank H Beard, Gary K Dowse, Nathan Saul on behalf of the Communicable Diseases Network Australia MenW Working Group

Abstract

Since 2013, there has been an increase in the number of notified cases of invasive meningococcal disease (IMD) due to serogroup W (MenW) in Australia. In response to this observed increase, the Communicable Diseases Network Australia convened a working group in 2015 to collate and analyse the epidemiology of MenW disease nationally. Enhanced surveillance data collected by jurisdictions were collated and analysed, and whole genome sequencing (WGS) of MenW isolates assessed the genomic relatedness of strains between 2012 and 2015. This report describes that epidemiology. Since 2013, the incidence and proportion of MenW has increased in Australia, rising from an average of 2% of all IMD cases annually (range 0% to 5%) between 1991 and 2012; to 8% (12/149) of cases in 2013, 10% (17/169) in 2014, and 19% (34/182) in 2015. Victoria has been the main affected state, with 50% (17/34) of national cases in 2015. MenW has affected older populations, with a median age between 2003 and 2015 being 44 years. During this period, case fatality was 10.7% (17/159), 2.3 times higher than for all IMD serogroups combined (4.7%, 173/3720). There were 7 deaths due to MenW in 2015 (CFR 21%). WGS has found the majority of Australian isolates cluster within a group of W:P1.5,2:F1-1:ST11 isolates from the United Kingdom and South America, regions where rapid spread and endemic transmission has occurred since 2009. The recent increase in incidence of MenW in Australia is evolving and is being closely monitored. Lessons learned from the international experience will be important in informing the public health response. *Commun Dis Intell* 2016;40(4):E454–E459.

Keywords: meningococcal disease; Australia, *Neisseria meningitidis*

Introduction

Invasive meningococcal disease (IMD) is caused by the bacterium *Neisseria meningitidis*. Meningitis and septicaemia are the most common clinical presentations of IMD, and infection can lead to serious outcomes including death.[1] Historically, most IMD in Australia has been caused by serogroups B (MenB) and C (MenC). The national rate of IMD notification has declined since the introduction of the MenC vaccine on the National Immunisation Program in 2003 but total numbers of IMD have been increasing since 2013.[2,3] The incidence of IMD due to serogroup W (MenW) in Australia has been low. However, since 2013 there has been an increase in both the incidence and proportion of MenW relative to all IMD cases, notably in Victoria.[4,5] There are international reports of a hypervirulent strain of MenW that began circulating in the United Kingdom and Chile in 2009 and has since become endemic in these countries. In this context the epidemiology of IMD in Australia was investigated, with a particular focus on MenW.

Methods

Notifications of IMD in Australia have been routinely collected in the National Notifiable Diseases Surveillance System (NNDSS), a collation of surveillance data collected locally in the 8 states and territories, since 1991. The NNDSS was used to compare the epidemiology of IMD due to non-MenW serogroups with that of MenW during the period 1991 and 2015. A sub-set of these data from 2003 were used to calculate case fatality ratios by serogroup and Indigenous status. Prior to this time, although these fields were available, they were not consistently complete.

Laboratory surveillance of IMD, including phenotypic and genotypic characteristics of invasive strains, has been conducted in Australia by reference laboratories in each state and territory (the Australian National Neisseria Network) since 1984, and these data supplement the NNDSS data.

Additional enhanced data (clinical presentation, hospitalisation status, co-morbidities, complications, risk factors, travel history) provided by states and territories were collated and analysed retrospectively, for MenW cases notified between 2012 and 2015. This period was selected to represent the time-frame in which MenW cases began to increase and for which enhanced clinical and whole genome sequencing (WGS) data were available.

WGS was performed by the Microbiological Diagnostic Unit (MDU) at the University of Melbourne or at the University of Western Australia (Western Australian isolates only), to determine the genomic relatedness of 34 Australian isolates of MenW between 2006 and 2015. Genomic DNA extraction and phylogenomic analysis was performed according to previously established methods within the MDU public health laboratory[6] including the Nullarbor bioinformatic pipeline (https://github.com/tseemann/nullarbor). These 3 data sources were merged in a single Microsoft Excel dataset for this descriptive analysis.

Results

Epidemiology

Australian IMD notifications reached an annual peak of 688 cases in 2002 (rate of 3.5 per 100,000 population), with a decreasing trend evident since then (Figure 1).

Between 1991 and 2015, MenB and MenC were the most common serogroups causing IMD in Australia comprising 49% (4520/9269) and 16% (n=1503) of all cases, respectively. The remaining serogroups have accounted for a very small proportion of cases overall, including MenW, 3% (n=234); serogroup Y, 2% (n=218); and serogroups A, X, and Z each less than 0.1%. Thirty per cent of cases during this time were not grouped (n=2,714) or non-groupable (n=68), with this proportion decreasing from 90% of cases in 1991 to 3% of cases in 2014 (Figure 1).

In 2015, MenB remained the predominant serogroup, comprising 61% (111/182) of all notified IMD cases. MenC decreased from a high of 33% (225/688) of cases in 2002 to approximately 1% (2/182) of cases in 2015 (Figure 1). In contrast, MenW represented an average of 2% of cases annually (range 0% to 5%) between 1991 and 2012, but has been increasing since then: 8% (12/149) of all cases in 2013, 10% (17/169) in 2014, and 19% (34/182) in 2015 (Figure 1).

The largest increase in MenW notifications has occurred in Victoria, accounting for 50% (17/34) of all MenW cases reported nationally in 2015, and nearly 6 times the annual Victorian average of 2.9 cases between 1991 and 2011 (Figure 2).

Figure 2: Notifications of invasive meningococcal disease serogroup W, Australia, 2012 to 2015, by state and territory and month

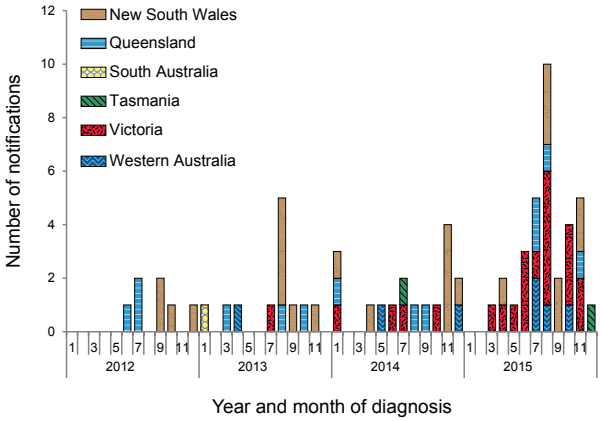
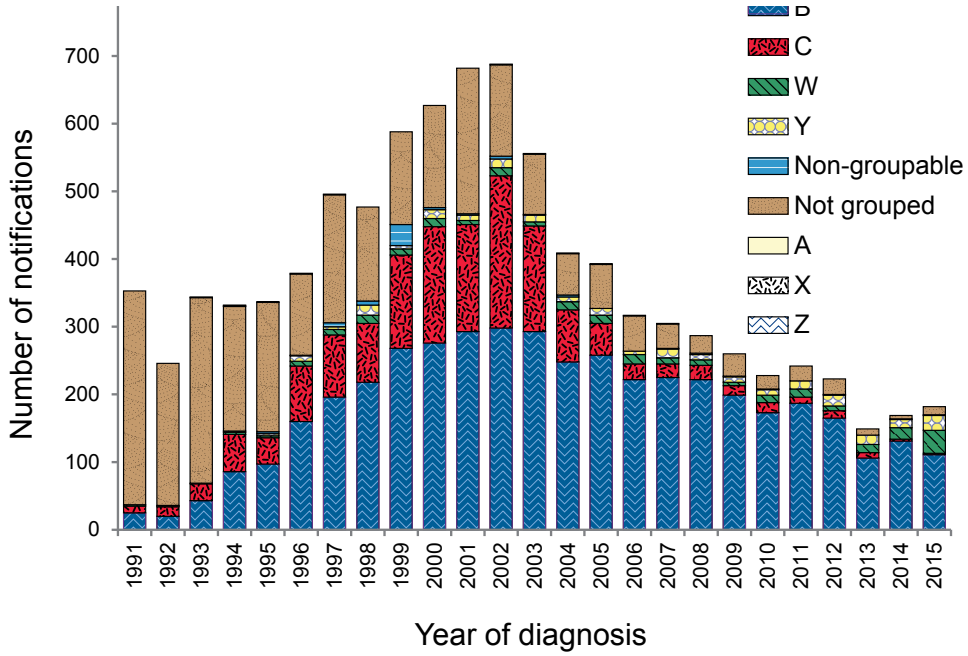


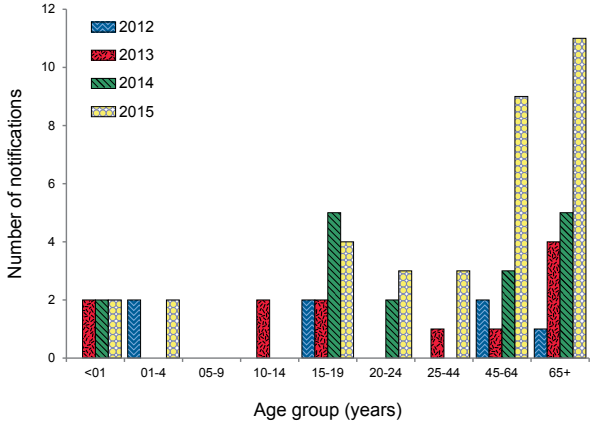
Figure 1: Notifications of invasive meningococcal disease, Australia, 1991 to 2015, by serogroup and year



The age distribution of IMD notifications has a bimodal pattern, strongly influenced by the predominance of MenB notifications, with peaks in children less than 5 years of age, and in adolescents and young adults aged between 15 and 24 years. Between 1991 and 2015, males represented 53% of all IMD cases and predominated in all age groups less than 45 years of age, while females predominated in age groups 45 years or over.

While MenW had similar peaks in the 0–4 and 15–24 age groups, there were also a relatively larger proportion of cases among adults aged 45 years or over, as reflected in the older median age of MenW cases compared with IMD generally (Table 1). Increases in MenW notifications since 2013 were confined to those 15 years of age or over with children less than 10 years of age relatively unaffected to date (Figure 3). Males represented 53% (123/234) of all MenW cases between 1991 and 2015, and represented 60% of cases (75/126) in those less than 35 years of age. Females represented 67% (72/108) of MenW cases aged 35 years or over.

Figure 3: Notifications of invasive meningococcal disease serogroup W, Australia, 2012 to 2015, by age group



Of the 3,720 cases of IMD notified between 2003 and 2015, 4.7% (n=173) were reported as having died with an annual case fatality ratio (CFR) ranging from 3% to 7% (Table 2). MenB has accounted for the majority of deaths in all years except 2003 when MenC had the highest proportion (73%, 19/26) and 2015 when MenW had the highest proportion (58%, 7/12).

Between 2003 and 2011, 11% of all MenW cases were fatal compared with the lower CFR for other serogroups (Table 2). There were 7 deaths due to MenW (CFR 21%) in 2015, accounting for 58% of all IMD deaths for that year. The median age of death for MenW cases between 2012 and 2015 was 26 years, nearly half the median age of death for this serogroup between 2003 and 2011, but older than for all non-MenW cases during this period (Table 1).

Enhanced surveillance data

Enhanced data was collected for all 70 MenW cases notified between 2012 and 2015: New South Wales (n=25), Victoria (n=22), Queensland (n=13), Western Australia (n=7), Tasmania (n=2) and South Australia (n=1).

Eighty per cent (56/70) of the MenW cases had a typical clinical presentation of septicaemia, meningitis, or both while 20% (14/70) had an atypical presentation, including: septic arthritis (n=6), pneumonia (n=4), epiglottitis (n=3) and other (n=1). All 69 cases that had information available on their hospitalisation status were hospitalised. Twenty-three per cent (16/69) of hospitalised cases were admitted to an intensive care unit.

Information on complications was available for 29% (20/70) of cases: 15 had no complications reported, 3 had minor complications, and 2 had major complications (excluding death).

There was no medical or behavioural risk factor information available for 22 cases. Of the remaining cases, 48% (23/48) had at least 1 risk factor identified: 25% (n=12) had a chronic disease; 31% (n=15) reported smoking either current (n=8) or previous (n=7); and 13% (n=6) had an immunological condition. Eight cases (17%) had 2 or more risk factors.

Vaccination against MenW is currently not routinely recommended in Australia excepting for those with medical conditions associated with an increased risk of meningococcal disease, for persons travelling overseas to areas in which MenW is endemic, or for those at occupational risk. Information on vaccination status was available for 35 (50%) of MenW cases, none of whom were vaccinated.

Travel history in the preceding 2 weeks was known for 84% (59/70) of cases for overseas travel and 54% (38/70) for interstate travel. Only 2 cases (3%) reported overseas travel (to England and Papua New Guinea, respectively), and 2 (5%) reported interstate travel (to New South Wales and Queensland respectively).

Genomic relatedness of Australian strains of invasive meningococcal disease serogroup W

Of the 70 MenW cases reported between 2012 and 2015, 51 isolates had typing available at the time of this report, and of these 65% (33/51) were strain type

Table 1: Summary table of invasive meningococcal disease cases, deaths and median age at onset

	Number of cases	Median age at onset	Age at onset range in years	Number of deaths	Median age of death	Age of death range in years	Case fatality rate (%)
All IMD 2003–2015	3,720	17	0–102	173	20	0–95	4.7
MenW 2003–2015	159	44	0–93	17	40	0–89	10.7
MenW 2003–2011	89	40	0–93	10	49	0–89	11.2
MenW 2012–2015	70	48	0–89	7	26	18–78	10
IMD (excluding W) 2012–2015	653	18	0–98	30	17	0–94	4.6
MenW 2015	34	51	0–85	7	26	18–78	20.6
All IMD Indigenous 2003–2015	353	3	0–72	15	3	0–72	4.2
MenW Indigenous 2003–2015	12	1	0–48	0	–		–

Table 2: Notifications, rates, deaths and case fatality ratio of invasive meningococcal disease, Australia, 2003 to 2015, by serogroup

	Serogroup B				Serogroup C				Serogroup W				Serogroup Y				All serogroups			
	Cases	Rate	Deaths	CFR (%)	Cases	Rate	Deaths	CFR (%)	Cases	Rate	Deaths	CFR (%)	Cases	Rate	Deaths	CFR (%)	Cases	Rate	Deaths	CFR (%)
2003	293	1.49	6	2.0	156	0.79	19	12.2	6	0.03	0	0	10	0.05	0	0.0	556	2.82	26	4.7
2004	248	1.24	12	4.8	77	0.39	4	5.2	12	0.06	2	16.7	7	0.04	0	0.0	409	2.05	19	4.6
2005	258	1.28	13	5.0	47	0.23	4	8.5	12	0.06	2	16.7	10	0.05	1	10.0	393	1.95	21	5.3
2006	222	1.09	8	3.6	23	0.11	1	4.3	14	0.07	3	21.4	5	0.02	0	0.0	317	1.55	12	3.8
2007	225	1.08	5	2.2	20	0.10	3	15.0	9	0.04	0	0.0	13	0.06	0	0.0	305	1.46	9	3.0
2008	222	1.04	9	4.1	21	0.10	1	4.7	8	0.04	0	0.0	8	0.04	0	0.0	287	1.35	10	3.5
2009	199	0.92	8	4.0	14	0.06	1	7.1	5	0.02	1	20.0	8	0.04	0	0.0	260	1.20	10	3.8
2010	173	0.79	10	5.8	15	0.07	1	6.7	11	0.05	1	9.1	8	0.04	0	0.0	228	1.03	14	6.1
2011	187	0.84	12	6.4	9	0.04	0	0.0	12	0.05	1	8.3	12	0.05	2	16.7	242	1.08	15	6.2
2012	165	0.73	10	6.1	11	0.05	2	18.2	7	0.03	0	0.0	16	0.07	0	0.0	223	0.98	12	5.4
2013	106	0.46	2	1.9	8	0.03	1	12.5	12	0.05	0	0.0	14	0.06	1	7.1	149	0.64	5	3.4
2014	131	0.56	7	5.3	3	0.01	0	0.0	17	0.07	0	0.0	12	0.05	1	8.3	169	0.72	8	4.7
2015	111	0.47	4	3.6	2	0.01	0	0.0	34	0.14	7	20.6	22	0.09	1	5.0	182	0.77	12	6.6
Total	2,540		106	4.2	406		37	9.1	159		17	10.7	145		6	4.1	3,720		173	4.7

CFR Case fatality rate.

Rate = rate per 100,000 population.

W:P1.5,2:F1-1:ST11 (or close variants) 35% (18/51) were not ST11 based on *in silico* typing (MDU, unpublished data), and results were pending for the remaining 19 cases. All but 1 of the 33 ST11 and close variant isolates clustered with a group that has been identified in the United Kingdom (UK) and South America in recent years.[7–9] The ST11 variant was the dominant strain of MenW identified in 2015 representing 86% (25/29) of MenW strains with results so far available in that year, a 46 percentage point increase from 2014 when 4 of the 10 MenW isolates with results available were ST11.

WGS of the 33 ST11 (and close variants) identified 2 main phylogenetic clusters of MenW, cluster 1 comprised 14 cases (12 from Victoria and 2 from New South Wales), which were all genetically closely related. Meanwhile, Cluster 2 comprised 18 cases (including 5 from Queensland, 6 from Western Australia, 5 from New South Wales, 2 from Victoria) and were not closely related.

Discussion

This analysis was prompted by the recent increase in incidence of MenW in Australia, with this serogroup comprising 19% of all IMD notifications in 2015. As at 5 October 2016, 39% (67/174) of all IMD notifications and 6 of the 8 deaths (CFR of 9%) due to IMD in 2016 were due to MenW.

MenW appears on average to cause more severe disease than other circulating IMD serogroups, with the CFR over the period 2003 to 2015 being 10.7% (20.6% in 2015), compared with 4.7% for all IMD over the same period. Between 2003 and 2015 the median age of onset for MenW (44 years) was higher than that of IMD generally (17 years) and the median age of death for MenW (40 years) was twice that of all IMD. The older age of MenW cases generally may at least partially explain the increased CFR for this serogroup. However, in the more recent period between 2012 and 2015, while the median age of MenW remained older (48 years) the median age of death was younger at 26 years. Victoria has had the highest number of cases of MenW (50% of all cases in 2015), and the most marked increase in incidence, and WGS suggests most isolates from Victoria, and some from New South Wales, may be genetically related, suggesting the possibility of transmission within this region.

There are no contemporary data on nasopharyngeal carriage of meningococci in Australia. Carriage studies might help to inform understanding of the underlying prevalence and transmission dynamics of MenW strains in Victoria and other states and territories, although sample size considerations make such studies difficult to undertake.

WGS has also identified that MenW in Australia is the same hypervirulent strain that has been circulating in the UK and South America since 2009.[7,8] This is consistent with a previous review of Australian meningococcal epidemiology, which identified that intercontinental spread of clonal strains was responsible for the pattern of hypersporadic invasive disease.[10]

Cases due to this strain have rapidly increased to now comprise 25% of IMD cases in the UK in 2014 to 2015, and 59% of all cases in Chile in 2012. MenW is now considered to be endemic in these countries. The initial increase was seen in older adults, but rapidly spread across all age groups within 2 years, particularly in adolescents and infants.[11] Disease severity has been high, and in response to this hypervirulent strain of MenW, targeted vaccination programs have been initiated in the UK and Chile.[7,12]

Conjugate MenC vaccine is part of the funded National Immunisation Program for all children at the age of 12 months. A multi-component MenB vaccine is registered for use in Australia, but is not part of the funded vaccination program. However, the Australian Technical Advisory Group on Immunisation has recommended it for use in children (particularly those <24 months of age) and adolescents aged 15–19 years.[13] A number of safe and effective quadrivalent conjugate meningococcal vaccines(covering serogroups A, C, W and Y) are also registered for use in Australia, and *The Australian Immunisation Handbook* recommends their use in individuals of any age who have predisposing medical conditions associated with increased risk of IMD or who are planning travel to parts of the world where epidemics of group A, C, W or Y meningococcal disease occur.[13] It is notable that based on WGS of the Australian MenW isolates to date, there has been no evidence of Hajj-related outbreak strains, suggesting that vaccination strategies for Hajj attenders may have been successful in preventing importation of these strains.[4] Australian guidelines also recommend post-exposure vaccination of unimmunised household and other higher risk contacts of cases of IMD caused by serogroups C, A, W or Y.[1] Individuals or parents who wish to protect themselves or their children against MenW could discuss receipt of a quadrivalent conjugate vaccine with their immunisation provider, via a private prescription.

The situation in Australia with regards to IMD due to MenW is evolving and continues to be closely monitored. A national working group has been formed under the auspices of the Communicable Diseases Network of Australia to further assess the situation and ensure consistent collection of enhanced data. Lessons learned from the international experience will be important in informing the public health response.

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Members of the Communicable Diseases Network Australia

The Department of Health, Canberra

Author details

Ms Nicolee V Martin, Epidemiologist, Assistant Director, Immunisation Branch, Office of Health Protection, Australian Government Department of Health, Canberra, Australian Capital Territory

Dr Katherine S Ong, Senior Medical Advisor, Department of Health and Human Services, Victoria

Prof Benjamin P Howden, Director, Microbiological Diagnostic Unit Public Health Laboratory, Medical Director, Doherty Applied Microbial Genomics, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Victoria

Professor Monica M Lahra, Director, WHO Collaborating Centre for STD and Neisseria Reference Laboratory, Microbiology Department, South Eastern Area Laboratory Services, the Prince of Wales Hospital, Sydney, New South Wales

Associate Professor Stephen B Lambert, Senior Medical Officer, Communicable Diseases Branch, Prevention Division, Queensland Health and UQ Child Health Research Centre, Faculty of Medicine and Biomedical Sciences, The University of Queensland, Queensland

Dr Frank H Beard, Staff Specialist, Public Health Physician, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, the Children's Hospital at Westmead, New South Wales

Dr Gary K Dowse, Medical Epidemiologist, Communicable Disease Control Directorate, Department of Health, Western Australia

Dr Nathan Saul, Epidemiologist, Vaccine Preventable Diseases, Communicable Disease Branch, Health Protection NSW, Sydney New South Wales

Corresponding author: Ms Nicolee Martin, Epidemiologist, Immunisation Branch, Office of Health Protection, MDP 13, GPO Box 9848, CANBERRA ACT 2601. Telephone: +61 2 6289 2708. Email: nicolee.martin@health.gov.au

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