ORIGINAL ARTICLE

The epidemiology of invasive meningococcal disease and the utility of vaccination in Malta

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Abstract

Invasive meningococcal disease (IMD) is a vaccine-preventable devastating infection that mainly affects infants, children and adolescents. We describe the population epidemiology of IMD in Malta in order to assess the potential utility of a meningococcal vaccination programme. All cases of microbiologically confirmed IMD in the Maltese population from 2000 to 2017 were analysed to quantify the overall and capsular-specific disease burden. Mean overall crude and age-specific meningococcal incidence rates were calculated to identify the target age groups that would benefit from vaccination. Over the 18-year study period, 111 out of the 245 eligible notified cases were confirmed microbiologically of which 70.3% had septicaemia, 21.6% had meningitis, and 6.3% had both. The mean overall crude incidence rate was 1.49/100,000 population with an overall case fatality rate of 12.6%. Meningococcal capsular groups (Men) B followed by C were the most prevalent with W and Y appearing over the last 6 years. Infants had the highest meningococcal incidence rate of 18.9/100,000 followed by 6.1/100,000 in 1–5 year olds and 3.6/100,000 in 11–15 year old adolescents. The introduction of MenACWY and MenB vaccines on the national immunization schedule in Malta would be expected to reduce the disease burden of meningococcal disease in children and adolescents in Malta.

Keywords Meningococcus · Epidemiology · Malta · Conjugate vaccination · MenB vaccination

Introduction

Invasive meningococcal disease (IMD) manifests predominantly as meningitis and/or septicaemia with most affected individuals having a sudden presentation and rapid deterioration. Although rare, IMD affects all ages, and the brunt of the disease burden is highest in infants, children below 4 years of age and adolescents [1, 2]. Compared with other age groups, there is also a relatively increased incidence of IMD in the elderly who suffer the highest case fatality rates of all [1–3]. Despite advances in medical care, around 10% of individuals with IMD die, and up to 20–36% of survivors sustain permanent disabilities such as sensorineural hearing loss, neurodevelopmental problems, seizures and amputations [4–7].

IMD is a worldwide disease, but the epidemiology of the meningococcal capsular groups (Men) is unpredictable and varies by geographical regions and over time. MenB still causes the majority of IMD within Europe, followed by MenC and more recently MenW [1]. In the USA, MenB, MenC and MenY are each responsible for around one third of the IMD cases [2]. Classically, MenA was a major cause of epidemics within countries in the meningitis belt of sub-Saharan Africa [8], with recent emergence of MenW, C and X disease [9, 10]. Nasopharyngeal carriage provides a continuous reservoir making eradication of the disease difficult. Migration and international travel poses a risk of transmission of Men capsular groups especially to family members within hosting countries [11].

The introduction of meningococcal conjugate vaccines on national immunization programmes has resulted in significant reductions in the corresponding burden of IMD. Control of IMD at a population level by meningococcal conjugate vaccines is not only a direct effect of protection of the vaccinated individuals but also is largely a result of their ability to

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interrupt transmission through reduction in meningococcal carriage rates, thus inducing a herd immune effect. This effect is only seen when adolescents, who are the main transmitters of the meningococcus, are included in meningococcal immunization strategies. Drastic reductions in IMD in all ages, including unvaccinated groups, have been observed with immunization programmes that included adolescents in catch-up or routine campaigns for MenC in Europe and Salvador in Brazil and MenA in Africa [12–16]. In contrast, exclusive vaccination of at-risk children < 5 years old against MenW disease with a MenACWY conjugate vaccine in Chile and with a MenC conjugate vaccine in Bahia, Brazil, without immunizing adolescents did not impact MenW and MenC disease in unvaccinated age groups, including the elderly, in the respective countries [15, 17]. The recent introduction of protein-based vaccines against MenB in developed countries holds promise for control of the most prevalent meningococcal capsular group although up until now their effect is only envisaged to result from direct protection since impact on nasopharyngeal carriage has not been demonstrated [18, 19].

The Maltese archipelago is a small group of islands situated in the Southern Mediterranean area having a population of around 475,000 people, around 2.5 million tourists per year and a population density of 1325 persons per square kilometre, the highest in Europe [20, 21]. As yet, meningococcal vaccines have never been introduced on the national immunization schedule in Malta although such vaccines are available privately for individuals wishing to protect themselves or their children against IMD. We aimed to study the population epidemiology of IMD in the Maltese islands in order to assess the utility of a meningococcal vaccination programme.

Methodology

Cases of invasive meningococcal disease

All microbiological confirmed cases of IMD over an 18-year period, from 2000 to 2017, were collected from the bacteriology laboratory at Mater Dei Hospital (MDH) which provides care for all patients suffering from IMD. Cases were included if they satisfied the European Centre for Disease Prevention and Control (ECDC) laboratory criteria for IMD which consisted of (a) identification of the meningococcus through culture or molecular methods from usual sterile sites (blood, cerebrospinal fluid (CSF), synovial fluid and any other usually sterile fluid) or from purpuric lesions or (b) detection of Gram-negative diplococci from direct visualization of the CSF or through a positive meningococcal rapid antigen screen (RAS) [22]. Subsequently, isolates were classified according to the capsular group, if

groupable. Identification of the serogroups was performed by slide agglutination tests using specific capsular antisera (Remel Europe Ltd., Kent, UK). All isolates were sent to the Public Health England (PHE) Meningococcal Reference Unit (previously Health Protection Agency Meningococcal Reference Unit) in Manchester, UK, where the capsular group was reconfirmed and phenotyping was performed by identification of the serotypes and serosubtypes with monoclonal antibodies as described by Gray et al. [23]. Multilocus sequence typing (MLST) was not carried out. From 2012 to 2013, a polymerase chain reaction assay (PCR) amplifying the specific capsular genes was performed at the PHE laboratory on CSF and/or blood of patients whose cultures were negative. In 2014, a meningococcal screening PCR was introduced at the microbiological laboratory in MDH, and any positive samples were sent to the PHE laboratory for capsular gene identification. Meningococcal capsular gene detection was performed at MDH in 2017. Meningococcal isolates identified from non-sterile sites such as throat or nasopharyngeal swabs and sputum were excluded.

Notification of IMD is statutory obligatory in Malta. All notified cases of IMD, identified through passive surveillance, were collected from the Infectious Disease Prevention and Control Unit (IDCU) in Malta. The criteria for reporting adopted by the IDCU were in accordance with the case definitions for confirmed IMD set by the European Union Commission Decisions in 2002, 2008 and subsequently in 2012 [22, 24, 25] which also included possible cases of IMD as defined by the presence of one of the clinical criteria of meningitis, haemorrhagic rash, septic shock or septic arthritis or probable cases, as defined by the presence of clinical criteria with an epidemiological link to a case of IMD, in the absence of laboratory confirmation of the infecting pathogen. Cases were notified to the IDCU by clinicians when a patient was clinically suspected to have IMD and subsequently by the laboratory when the meningococcus was identified in clinical specimens. When microbiological results did not reveal an invasive pathogen, IDCU contacted the clinicians to ascertain that the clinical picture, investigations and progress of the cases still satisfied the set case definitions of IMD. These data were used to calculate the total number of IMD cases per year in Malta over the study period.

The results of microbiological investigations of all notified cases were validated against electronic results and/or written case records. Individuals with a foreign hospital number or whose laboratory results showed an alternative diagnosis were excluded from the analysis. Population data were obtained from the National Statistics Office in Malta. This study was approved by the Faculty of Medicine and Surgery University of Malta Research Ethics Committee (Ref No: FRECMDS_1819_38).

Statistical analysis

The primary objective of this study was to perform population-based descriptive statistics on IMD in order to quantify the disease burden caused by the meningococcus in the Maltese population. The median was used in preference to the mean to describe the age demographics as in view of the relative rarity of IMD, it was expected to have a small number of cases with a wide age range. The proportion of laboratory-confirmed IMD cases was calculated per year from the total number of reported IMD cases. The disease burden caused by the different meningococcal capsular groups was calculated for each year from the number of laboratory confirmed isolates. The distribution of cases was analysed according to prespecified age groups as follows: < 1, 1–5, 6–10, 11–15, 16–20, 21–25, 26–45, 46–64 and ≥ 65+ years. A cut-off of < 16 years was taken to indicate the paediatric population as determined by the hospital admission policy for children in MDH, Malta. This enabled calculation of the age-specific incidence rates of meningococcal disease, and the corresponding 95% CI using a Poisson regression analysis, in Maltese children and identification of the target groups that would benefit from vaccination. Fisher's exact test was used to analyse differences in the disease burden between the capsular groups. A p value < 0.05 for all analyses was taken as being statistically significant. The software STATA 13 was used for the analyses.

Results

Demographics

A total of 290 cases of meningococcal disease were identified over the 18-year study period: 286 were notified, whilst additional 4 cases had not been notified but were identified from the bacteriology lab from the results of their cultures. Of these, 245 individuals resident in Malta were eligible to be included in the analysis, of whom 53.9% were male (132/245). Of the 45 excluded cases, 33 were tourists, and 12 were found to have an alternative diagnosis on review of their electronic results or case records (either because CSF was suggestive of viral meningitis in culture negative cases or a different pathogen was noted during validation of the electronic records). Only 45.3% (111/245) of cases were confirmed microbiologically, of which 80.2% (89/111) were confirmed on culture (Fig. 1). Meningococcal PCR, introduced in 2012, confirmed 8 of the culture negative cases from 2012 to 2017 all of which were in children, although testing was performed at the request of the caring doctor rather than routinely on all suspected cases. The median age of the laboratory-confirmed cases was 14.9 years (range, 0.10–83.27 years). Out of the 111 microbiologically confirmed cases of IMD,

70.3% (78/111) had confirmed septicaemia (confirmed from blood or petechial scrapings), 21.6% (24/111) had confirmed meningitis, 6.3% (7/111) had confirmed septicaemia and meningitis, 0.9% had arthritis, and 0.9% had pericarditis.

*These 4 cases were picked up by the microbiological laboratory but were not notified. PCR, polymerase chain reaction assay. RAS, rapid antigen screen; Men meningococcus.

Meningococcal incidence rates

The variation of the annual total number of confirmed cases generally followed the variation of the total number of notified cases except for 2006 when only 6 out of a total of 34 notified cases (17.6%) were confirmed microbiologically (Fig. 2).

The mean overall crude incidence rate of confirmed IMD from 2000 to 2017 (Table 1) was 1.49/100,000 (95% CI, 1.09 to 1.90) population. Although the mean crude incidence rate decreased from 1.78/100,000 (95% CI, 1.11 to 2.45) population in 2000–2008 to 1.21/100,000 (95% CI, 0.70–1.71) population from 2009 to 2017, this was not statistically significant (difference 0.57; $p = 0.13$).

The mean age-specific incidence rate of IMD was significantly higher in infants (18.9/100,000; median age 7 months; range, 1.2–11.5 months), 1–5-year-old children (6.1/100,000; median age 3.5 years; range, 1.0–5.9 years) and 11–15-year-old adolescents (3.6/100,000, median age 14.7 years; range, 11.0–15.9 years) than the rest of the population (Fig. 3) with the highest burden being in infants.
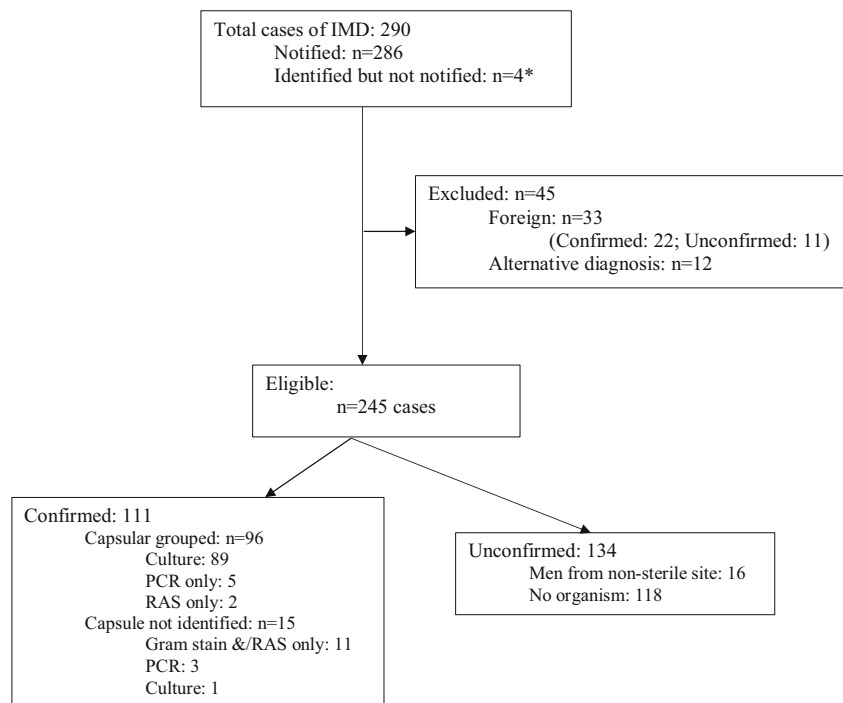
Case fatality rate

There were 14 deaths caused by confirmed IMD (Table 1), of which 8 (57.1%) were in children < 16 years old. The overall case fatality rate (CFR) was 12.6% (14/111). In children < 16 years of age, the highest age-specific CFR was in 1–5-year-olds (4/24; 16.7%), 6-10-year-olds (1/8; 12.5%) and 11–15-year-olds (2/17; 11.8%), whilst in adults, the highest risk of dying was in 46–64-year-olds (3/17; 17.6%) and in ≥ 65-year-olds (2/12; 16.7%).

Seasonal variation

The months with the highest total and similarly confirmed number of IMD cases were January, February, March and August, whilst the lowest numbers were recorded in April and from October to December. No epidemics of meningococcal disease occurred during the study period.

In view of the unexpected peak of IMD in August, the cases of IMD in tourists who became unwell whilst in Malta were looked at (these had been excluded from the primary analysis). A peak in IMD in tourists was also noted in August when 8/22 (36.4%; median 16.9 years, range, 14.8–21.2 years) confirmed cases occurred.

Fig. 1 Flow diagram of analysed cases

Total cases of IMD: 290
    Notified: n=286
    Identified but not notified: n=4*

Excluded: n=45
    Foreign: n=33
        (Confirmed: 22; Unconfirmed: 11)
    Alternative diagnosis: n=12

Eligible:
    n=245 cases

Confirmed: 111
    Capsular grouped: n=96
        Culture: 89
        PCR only: 5
        RAS only: 2
    Capsule not identified: n=15
        Gram stain &/RAS only: 11
        PCR: 3
        Culture: 1

Unconfirmed: 134
    Men from non-sterile site: 16
    No organism: 118

*These 4 cases were picked up by the microbiological laboratory but were not notified
PCR: polymerase chain reaction assay; RAS: rapid antigen screen, Men: meningococcus

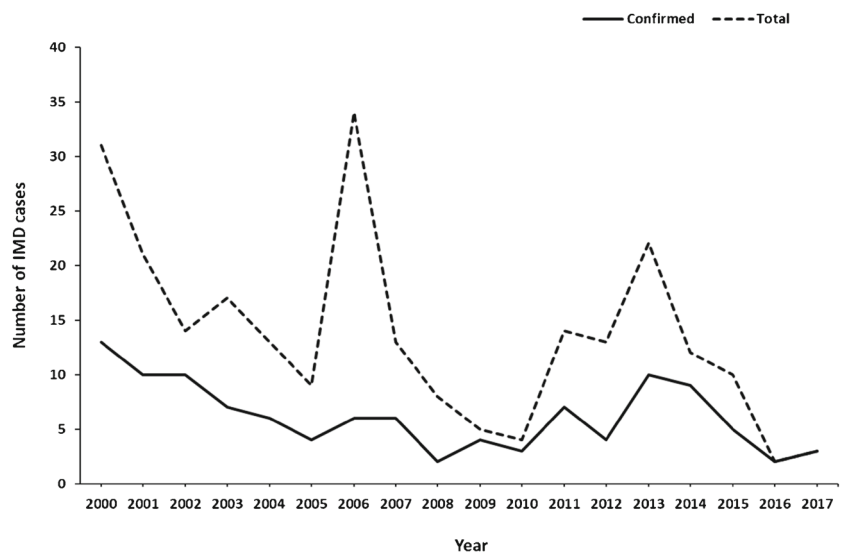## Distribution of capsular groups

Identification of the meningococcal capsule was successful in 96/111 cases, 89 of which were isolated by culture (Fig. 1). The most frequent isolated capsular groups were MenB (63.5%; 61/96) and MenC (24.0%; 23/96). Capsular groups W and Y and non-groupable meningococci collectively constituted a minor proportion of cases (12.5%; 12/96), although capsular group Y became prevalent from 2011 to 2013 (28.6%; 6/21 cases) and capsular group W became more frequent from 2014 to 2017 (21.1%; 4/19 cases) (Fig. 4).

Age-specific incidence rates

MenB disease was significantly more prevalent than other capsular groups in children < 16 years of age.

**Fig. 2** Number of IMD cases per year

Total: Total number of notified cases; *Confirmed*: Number of microbiologically confirmed cases only

Table 1 Distribution of confirmed invasive meningococcal capsular groups and deaths by age and year in Malta (2000–2017)

Year	Age/years										Capsular Group					
	<1	1–5	6–10	11–15	16–20	21–25	26–45	46–64	>65	Total	B	C	W	Y	NG	NI
2000	1 B	7 7**B**	1 B	2 B, C	0 0	0 0	1 B	1 B	0 0	13	12	1	0	0	0	0
2001	0 0	5 4B, NG	1 B	2 2B	1 B	0 0	1 B	0 0	0 0	10	9	0	0	0	1	0
2002	0 0	0 0	1 **B**	3 2B, NI	1 NI	0 0	0 0	5 3B, 2C	0 0	10	6	2	0	0	0	2
2003	0 0	2 2B	1 B	2 B, NI	0 0	0 0	1 B	1 C	0 0	7	5	1	0	0	0	1
2004	0 0	2 2B	1 B	2 2**B**	1 B	0 0	0 0	0 0	0 0	6	6	0	0	0	0	0
2005	1 C	2 B, C	0 0	0 0	0 0	1 C	0 0	0 0	1 C	4	1	3	0	0	0	0
2006	1 B	0 0	1 NI	2 2B	0 0	1 C	1 B	0 0	0 0	6	4	1	0	0	0	1
2007	1 B	1 B	0 0	0 0	0 0	0 0	0 0	2 2B	2 B, W	6	5	0	1	0	0	0
2008	0 0	0 0	0 0	0 0	0 0	0 0	0 0	2 **B**, C	0 0	2	1	1	0	0	0	0
2009	1 B	2 B, C	0 0	0 0	0 0	0 0	0 0	1 C	0 0	4	2	2	0	0	0	0
2010	1 B	0 0	0 0	0 0	1 NI	0 0	0 0	1 B	0 0	3	2	0	0	0	0	1
2011	0 0	0 0	0 0	1 C	1 Y	1 NI	1 B	1 C	2 2**Y**	7	1	2	0	3	0	1
2012	0 0	0 0	0 0	0 0	2 B, Y	0 0	1 NI	1 NI	0 0	4	1	0	0	1	0	2
2013	3 B, 2C	0 0	0 0	2 B, Y	1 B	0 0	1 NI	1 NI	2 C, Y	10	3	3	0	2	0	2
2014	2 **C**, W	1 NI	0 0	1 NI	1 C	0 0	0 0	1 C	3 C, **W**, NI	9	0	4	2	0	0	3
2015	1 C	1 B	1 NI	0 0	0 0	0 0	0 0	0 0	2 2C	5	1	3	0	0	0	1
2016	0 0	0 0	1 NI	0 0	1 **W**	0 0	0 0	0 0	0 0	2	0	0	1	0	0	1
2017	2 **B**, W	1 **B**	0 0	0 0	0 0	0 0	0 0	0 0	0 0	3	2	0	1	0	0	0
Total	14 7B, 5C, 2W	24 20B, 2C, NG, NI	8 5B, 3NI	17 11B, 2C, Y, 3NI	10 4B, C, W, 2Y, 2NI	2 C, NI	7 5B, 2NI	17 8B, 7C, 2NI	12 B, 5C, 2W, 3Y, NI	111	61	23	5	6	1	15
Deaths	1 C	4 3B, C	1 B	2 B, C	1 W	0 0	0 0	3 2B, C	2 W, Y	14	7	4	2	1	0	0

Meningococcal capsular groups marked in bold indicate a fatal outcome with the corresponding number of deaths shown in the bottom row. *NI* not identified: meningococcal capsule identification was not done.

Fig. 3 Mean age-specific incidence rate of IMD in Malta from 2000 to 2017. Error bars represent 95% Confidence Intervals
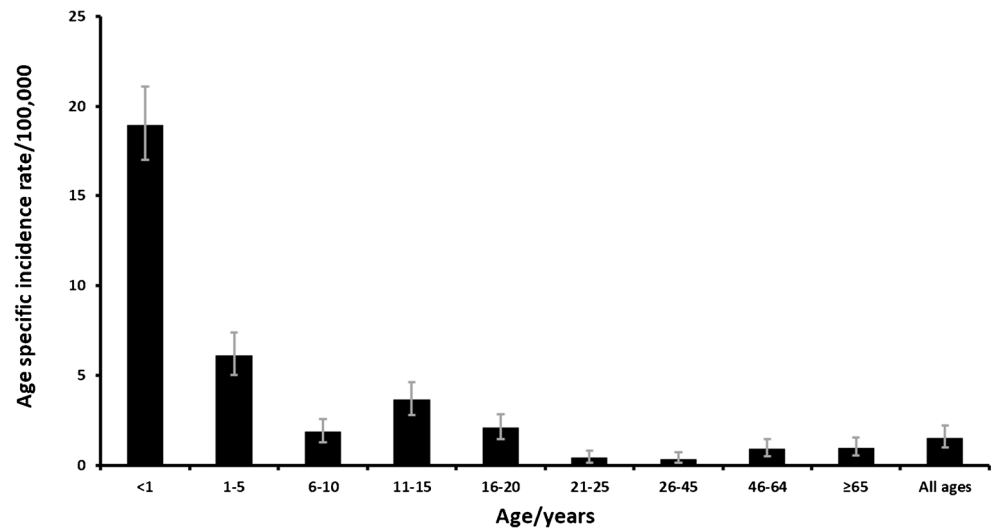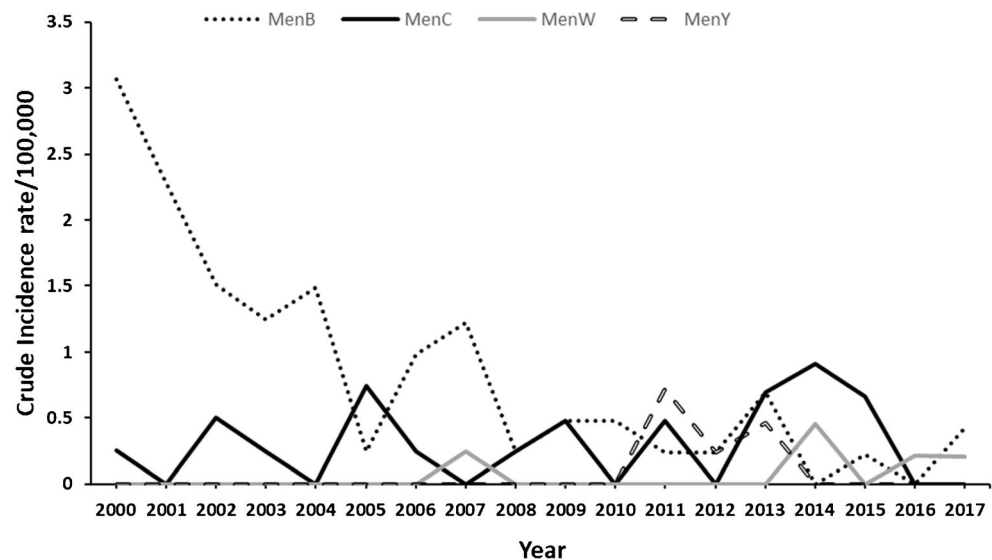

Infants suffered the highest incidence of MenB, MenC and MenW disease compared with all other age groups (Fig. 5). MenY disease was only observed in 11–20-year-olds, whilst MenW affected teenagers and infants. The incidence rates of MenB, C, W and Y disease were not significantly different in elderly people ≥ 65 years old.

Capsular group B meningococcus

The overall mean crude incidence rate of MenB in Malta was 0.84/100,000 (95% CI, 0.42 to 1.25) population with an overall case fatality rate of 11.5% (7/61). A statistically significant downward trend from 1.37/100,000 population, 95% CI 0.68 to 2.06, over 2000–2008, down to 0.31/100,000 population, 95% CI 0.13 to 0.49, over 2009–2017, (difference 1.06; $p = 0.004$) was observed (Fig. 4).

The highest disease burden of MenB disease was in infants (9.66/100,000; 95% CI, 8.28–11.20) with a median age of 5.3 months, followed by 1–5-year-olds (5.02/100,000; 95% CI: 4.02–6.14), median age 3.5 years, and 11–15-year-olds (2.22/100,000; 95% CI, 1.59–3.03), median age 14.2 years (Fig. 5). Only PorA phenotyping was performed, with 68% (36/53) of the typed isolates having PorA subtypes P1.19,P1.15 (Table 2).

Capsular group C meningococcus

The overall mean crude MenC incidence rate in the whole population reached 0.28/100,000 (95% CI, 0.09 to 0.65) individuals over 2000–2017 with a CFR of 17.4% (4/23). The mean crude incidence rate for MenC remained stable from 2000 to 2008 (0.25/100,000 population; 95% CI, 0.06 to 0.44) compared with 2009–2017 (0.33/100,000 population;

Fig. 4 Crude incidence rate of MenB, C, W and Y disease (2000–2017)

Fig. 5 Distribution of meningococcal capsular groups by age (2000–2017)
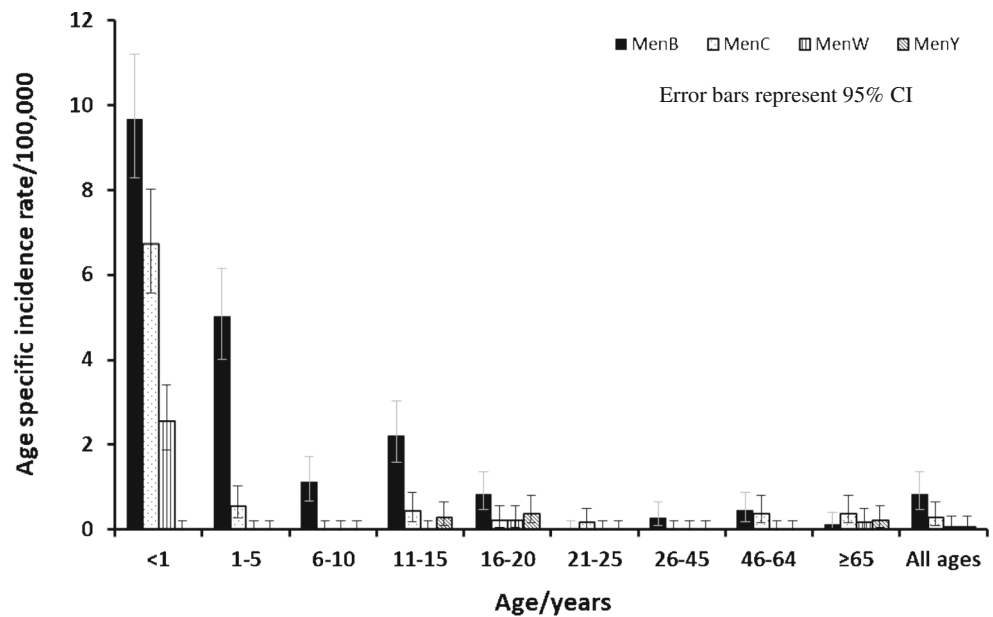
15 isolates which did not undergo capsule identification and 1 isolate which was not groupable were not included in figure

95% CI, 0.08 to 0.58), difference 0.08, $p = 0.56$ (Fig. 4). The mean age-specific incidence rate of MenC disease was significantly higher in infants (6.72/100,000 infants; 95% CI, 5.58–8.03; median age 7.5 months, range, 6.24–10.7 months) compared with all other age groups (Fig. 5). Fatalities from MenC disease were more common in children, with 3 of the 4 deaths occurring in children aged 6 months, 2 years and 15 years.

Of the 23 MenC cases, three were confirmed by detection of the sia D gene by PCR, whilst 20 were confirmed by culture. Phenotyping of the cultured MenC strains was performed on 13 isolates, since 6 of the meningococcal cultures did not remain viable in storage and could not be shipped to the PHE laboratory in the UK for further identification (Table 3). Out of the 4 cases who succumbed to MenC disease, 3 were phenotyped, and all had the PorA subtypes P1.5,P1.2.

Capsular group W and Y meningococcus

The overall mean crude incidence rate of MenW and Y disease was 0.06/100,000 (95% CI, 0.001–0.31) each, with an associated CFR of 40% (2/5) and 17% (1/6), respectively. Deaths occurred predominantly in > 65-year-olds although MenW

Table 2 Distribution of MenB phenotypes

MenB phenotype	Number	Year
B:1:NT	1	2013
B:1:P1.14	1	2005
B:4:NT	1	2000
B4:P1.12,P1.15	1	2000
B:4:P1.19,P1.15	*32	2000–2004; 2006–2009
B:14:P1.4	*1	2004
B15:P1.14	1	2001
B:NT:P1.3,1.19	2	2004
B:NT:P1.4	4	2009, 2012, 2013
B:NT:P1.5	1	2010
B:NT:P1.14	2	2009–2012
B:NT:P1.15	1	2000
B:NT:P1.19,P1.15	4	2000, 2004
B:NT:P1.16	*1	2000
Not typed	*8	2000, 2003, 2010, 2011, 2013, 2015, 2017

*Fatal outcome, 4 with B:4:P1.19,1.15; 1 each from the rest

Table 3 Phenotype of capsular MenC strains isolated from 2000 to 2017

MenC phenotype	ST-11 strain	Number	Year/s
C2a:P1.5,P1.2,NT	Probable	1	2013
C2a:P1.5,NT,NT	Probable	3	2003, 2006, 2011
C:NT:P1.5,P1.2,NT	Probable	*2	2008, 2009
C:2b:P1.5,P1.2	No	*1	2000
C:NT:NT,P1.10,NT	No	2	2002, 2005
C:NT:NT,P1.14,NT	No	2	2005
C:NT:NT,NT,NT	No	2	2002, 2009

*Fatal outcome

caused 1 death in a 19-year-old adolescent. MenW disease appeared in infants and 16–20-year-old adolescents since 2014 to 2017 (mean age specific incidence rate 11.5/100,000 [95% CI, 8.42–15.34] and 1.0/100,000 [95% CI, 0.27–2.56], respectively), whilst MenY affected mainly 16–20-year-old adolescents and young adults (from 2010 to 2017, mean age-specific incidence rate was 0.88/100,000 [95% CI, 0.35–1.80], and overall mean crude incidence rate was 0.13/100,000 [95% CI, 0.003–0.70]). Phenotyping was only done on one MenW isolate which had the PorA subtypes P1.3,1.6 and on four MenY isolates, which had the PorA subtypes P1.5 and P1.5,1.2 (2 isolates each).

Discussion

The average annual incidence of confirmed IMD cases of 1.49/100,000 population (95% CI, 1.09–1.90) in Malta remains significantly higher than the mean incidence reported overall from 2000 to 2017 in Europe (0.97/100,000; 95% CI, 0.80–1.15; $p = 0.01$) [1, 26–32] and the USA (0.31/100,000; 95% CI, 0.22–0.41; $p = 0.0001$) [2], where a significant decrease in overall IMD has been observed over the last few years. The drop in MenB disease observed in Malta and similarly in the EU and the USA is very likely a result of natural variation in the epidemiological trends of MenB. However, the reduction in MenB disease has had no effect on the overall incidence of IMD in Malta since it was offset by the persistence of MenC disease and the appearance of MenW and Men Y disease since 2011. In contrast, the incidence rates of MenC IMD in the EU were significantly reduced (from 0.22/100,000, 95% CI, 0.14–0.31 in 2000–2008 down to 0.10/100,000, 95% CI, 0.09–0.11 in 2009–2017; $p = 0.003$) as a result of the introduction of MenC vaccination programmes in several European countries, many after catch-up campaigns targeting adolescents, and the introduction of routine adolescent vaccination [33, 34]. In the USA, the incidence of MenC and Y disease was reduced through the introduction of routine adolescent MenACWY vaccination since 2007 [35]. In

Salvador, Brazil, control of MenC disease was similarly rapidly achieved within 5 years following the introduction of a MenC vaccination programme targeting children < 5 years of age as well as 10–24-year-old adolescents and young adults [15]. Similarly, control of a MenA epidemic was achieved within 4 years in Mossala, Chad, following the introduction of a MenA conjugate vaccine targeting 1–29-year-olds in 2012 [36]. In contrast, a herd immune effect was not seen in the state of Bahia, Brazil (excluding Salvador), when a different MenC conjugate vaccination strategy that just targeted children from 2 months to 5 years of age was introduced [15]. Similarly, a strategy using a conjugate MenACWY vaccine targeting 9-month to 4-year-old children to control MenW disease in Chile provided direct protection to the vaccinated group but did not result in a herd immune effect [17]. These strategies emphasize that the success of meningococcal conjugate vaccines relies on their ability to interrupt meningococcal transmission through a decrease in meningococcal carriage, an effect that can only be achieved if adolescents are targeted in meningococcal vaccination programmes. Control of MenB disease is unlikely to be attained with a similar approach since MenB protein-based vaccines have no effect on carriage [18]; however, as observed in the UK, direct protection of infants and young children can still be achieved with a modest vaccine effectiveness of 59.1% 2 years after an infant priming and boost schedule [37]. Discrepancies between Malta and other countries could reflect geographical differences in the epidemiology of IMD; however, the lack of a national meningococcal vaccination programme in Malta is most likely contributing to the higher incidence rates of IMD.

The higher number of IMD cases from January to March is similar to the seasonality of IMD observed in Europe and the USA [31, 38]. In Malta, these 3 months of the year are the coldest months (mean 12–14 °C) with the highest values for relative humidity, which reaches around 80% [39], climatic factors that are known to be associated with a higher risk of IMD [40]. The peak in IMD seen in August in Malta is difficult to explain as this month is dry and is relatively less humid [39] but is characterized by the highest number of inbound tourists, the majority of whom come from Europe [41]. Inbound tourists reach a mean of 235,922 in August, reaching a proportion of 52% of the mean 456,526 individuals constituting the Maltese population [41]. Intriguingly, a similar peak in the number of IMD cases also occurs in August in tourists whose median age was 16.9 years compared with 13.3 years in Maltese individuals with IMD in the same month. Nineteen per cent of tourists visiting Malta in August are aged < 25 years [41] with adolescents and young adults, who have the highest rates of meningococcal carriage [42]; very likely to visit overcrowded places such as pubs, bars and discotheques; and human behaviour that is associated with a higher risk of meningococcal transmission [43–46]. Any causal association of climatic factors and IMD is challenging to reach in view of the

confounding effects of human behaviour and the seasonality of other infectious diseases caused by influenza and other respiratory viruses [40].

In Malta, infants suffer the highest overall rate of IMD, followed by children aged 1–5 years and teenagers, similar to the age distribution of IMD seen in Europe and the USA [1, 2]. The burden of capsular group B and C disease in Malta is similarly disproportionately highest in infants but also affects 1–5-year-old children, adolescents and young adults. In European countries, the highest MenB and C disease burden is similarly seen in infants (although the incidence rate reached 5.4/100,000 and 2.1/100,000 infants for MenB and C, respectively, much less when compared with the mean incidence rate of 9.66/100,000 and 6.72/100,000 infants for the corresponding capsular groups in Malta), with children less than 5 years old and adolescents and young adults being more affected than other age groups [1, 31]. Decay of transplacentally acquired maternal MenB and C antibody in infancy, subsequent lack of protective MenB and C bactericidal antibody in children in the absence of a MenB and C vaccination programme [47, 48] and nasopharyngeal mucosal damage from concurrent respiratory tract viruses, which are more common in children < 5 years old [49], possibly explain the higher risk of MenB and C disease in these age groups. The increased risk among adolescents and young adults is likely a result of increased exposure from changes in social behaviour leading to enhanced transmission of the meningococcus and lack of immunity [43]. The appearance of MenY disease in adolescents and MenW disease in infants reflects the recent rise of these capsular groups in Europe and poses a risk of disease in both age groups [1, 50].

Natural immunity from asymptomatic MenB and C carriage [48] or cross-reactive immunity to other microorganisms, such as *Escherichia coli* K92 which has a sialylated polysaccharide capsule that is structurally similar to that of MenC [51] and to *Neisseria lactamica* which shares antigens found on meningococcal outer membrane proteins [52], could contribute to the decreased incidence of MenB and C disease observed in the 25–45-year-olds; however, there are no robust data to support this hypothesis. The rise in non-MenB disease after 65 years of age could plausibly be due to a decline in immunity from immunosenescence [53], but further studies are needed to ascertain this.

The overall CFR of 12.6% for cases of IMD is similar to the 8–15% reported in Europe and the USA [1, 2]. CFR from MenB and C disease, which reached 11.5% and 17.4%, respectively, and which affected children predominantly, was also similar to the 7–15% MenB and C CFRs reported in the USA and Europe [1, 54]. Although MLST typing was not done, the MenB phenotype P1.15,P1.19 is known to belong to the sequence type 32 clonal complex which is hyperendemic in Europe [55], and the MenC phenotypes C2a:P1.5,P1.2, C2a:P1.5 and C:NT:P1.5,P1.2 have all been previously identified as belonging to the

hyperinvasive ST-11 meningococcal clone in other European countries [56–58].

Utility of meningococcal vaccination

MenB vaccination

Currently, two protein-based MenB vaccines are available: MenB-4C, (*Bexsero*, GlaxoSmithKline Biologicals, Belgium) licenced from 2 months of age, and a MenB-fHbp vaccine (*Trumenba*, Pfizer Ltd., New York) licenced from 10 years of age [59, 60]. Introduction of a MenB vaccine will address the most prevalent cause of IMD in Malta, although projections of vaccine effectiveness would require whole genome sequencing and vaccine antigen sequence typing of the MenB isolates. In the past, a serotype-specific MenB outer membrane vesicle vaccine, *MenZB*, that matched the MenB strain B:4:P1.7–2,4 causing a prolonged epidemic in New Zealand (which was used in a 3 dose schedule for mass vaccination of < 20 year olds from 2004 to 2006 and subsequently for routine infant vaccination up to 2008), had an estimated effectiveness of 80% in children < 5 years of age and an overall effectiveness of 68% [61, 62]. A reduced two-dose infant schedule of the currently available MenB-4C vaccine at 2 and 4 months followed by a boost at 12 months of age, as introduced in the UK, would be expected to result in a modest 59% vaccine effectiveness up to 2 years following the last vaccination assuming high vaccine coverage and favourable vaccine sequence matching with invasive MenB strains [37]. In contrast to meningococcal conjugate vaccines, indirect protection in unvaccinated population groups from herd immunity is very unlikely to be observed since MenB-4C has not been shown to reduce MenB carriage, or other pathogenic capsular types, in a large cohort of Australian adolescents [18] indicating that MenB transmission will still occur despite vaccination. Similarly, carriage data have also discouragingly not demonstrated a reduction in MenB carriage following vaccination with a Menb-fHbp vaccine during an outbreak [19]. The lack of an impact on MenB carriage makes the utility of catch-up vaccination campaigns against MenB questionable [18, 19]. Protection against MenB disease in infancy, early childhood and adolescence will have to rely on the direct protection offered by a MenB vaccine. Infant MenB vaccine priming and boost schedules will still need boosting in adolescence as, similar to the antibody decline seen with conjugate MenC vaccines, bactericidal antibody will not last into the teenage years [63, 64]. Introduction of MenB vaccination at 2 and 4 months with a boost at 12 months of age together with two-dose vaccination of adolescents starting from the age of 12 years would be expected to have an impact on MenB disease in Malta.

MenACWY vaccination

Monovalent MenC and quadrivalent MenACWY vaccine formulations became available on the private market in Malta in 2009 and 2011, respectively, but were never introduced on the national schedule. A mean of 1296 conjugate vaccines against MenC was given per year in children aged < 16 years, amounting to vaccination of around 2% of the paediatric population per year (National Immunization Service, personal communication; Pfizer Malta, Vivian Corporation, personal communication). Such practice of meningococcal conjugate vaccination on request results in individual protection, but considering the epidemiology of MenC, W and Y disease over the last 10 years is evidently not enough to induce herd protection. Control of infant MenC and W disease in Malta may be achieved with the introduction of a routine infant MenACWY vaccination programme consisting of a single MenACWY dose at 3 months of age, followed by a 12 month boost, a schedule which would induce protective MenC bactericidal antibodies in infants and toddlers [65] and with extrapolation also to MenW. This would have potentially prevented 30.4% (7/23) and 40% (2/5) of cases of invasive MenC and MenW disease, assuming 100% vaccine efficacy. An effective national MenACWY conjugate vaccine strategy would also need to target adolescents, not only to target MenY disease observed in 11–20 year olds in Malta but also to contribute towards a desired herd immune effect and reduce the corresponding IMD in non-vaccinated groups, especially in the elderly > 65 years of age in whom 83.3% (10/12) of IMD was caused by MenC, W and Y. Furthermore, adolescent vaccination would eventually serve the purpose of boosting those children who would have received the routine infant and toddler MenACWY schedule since adequate protection against all of these capsular groups will not persist until adolescence [66, 67].

Alternatively, a single conjugate MenACWY vaccine dose could be introduced at 12 months of age concurrently with immunization of adolescents. Such a schedule using a monovalent MenC conjugate vaccine was introduced in Ontario, Canada, in 2004/2005 [68]. Although a reduction in invasive capsular group C disease was seen in vaccinated and unvaccinated age groups, the reduction in the incidence of MenC disease in infants over the subsequent 8 years was not statistically significant [68]. In contrast, the introduction of routine MenCC vaccination in 2001 in 14-month-old children following a catch-up vaccine campaign in 14-month to 18-year-olds in The Netherlands resulted in control of invasive MenC disease, even in infants [69]. Similarly, the introduction of routine infant MenC conjugate vaccination in 1999 concurrently with a catch-up vaccine campaign in 1 to 25-year-olds in the UK was also successful [70], although a MenC boost was introduced at 12 months of age in 2006 due to low vaccine efficacy rates just within 4 years of infant

vaccination [12]. The importance of a catch-up campaign targeting adolescents and young adults to control MenC disease was also observed in Brazil where sole vaccination of children < 5 years of age in the state of Bahia did not result in a herd immune effect in contrast to Salvador where the concurrent introduction of a catch-up campaign targeting 10–24-year-olds resulted in control of MenC disease in all age groups [15]. Similarly, vaccination of 9-month to 4-year-old children with a conjugate MenACWY vaccine without adolescent catch-up vaccination did not control MenW disease on a population level in Chile [17].

Considering such data, the introduction of a routine infant and toddler MenACWY vaccination programme concurrently with the launch of a one-time MenACWY vaccine catch-up campaign targeting children aged from 1 to 5 years old and adolescents and young adults aged from 12 to 20 years old in Malta would not only induce direct protection of these high-risk age groups but also result in indirect protection of unvaccinated individuals from decreased MenC, W and Y transmission by adolescents. Such induction of herd protection would translate in a reduction in IMD in older unvaccinated individuals (as seen in countries introducing a MenC catch-up vaccination programme), the disease burden in whom was substantial over the last 18 years (47.4%, 18/38 cases) in Malta. Herd immunity against MenC, W and Y could then be sustained through a routine MenACWY vaccine dose at 12 years of age. Once the epidemiology of Men disease shows that control of invasive MenC and W disease in infants has been achieved (reflecting minimal MenC and W transmission), which, as seen in the UK for MenC, would be expected to be reached within 5 years [70], then the infant MenACWY dose may be dropped. This would leave a routine meningococcal conjugate vaccine schedule consisting of a single MenACWY dose at 12 months of age, which is important for priming, followed by a booster dose in adolescence. The induction of robust protection against invasive MenACWY disease in adolescence would protect teenagers and young adults from possible transmission of these capsular groups from the large number of foreigners that visit Malta and mix with the young population in summer.

Currently, the Maltese national immunization schedule in early childhood consists of the following: diphtheria, tetanus, acellular pertussis, inactivated polio and Hib (DTaP-IPV-Hib) vaccine at 6 weeks, 3, 4 and 18 months; hepatitis B vaccine at 12, 13 and 18 months; and the measles, mumps and rubella vaccine at 13 months and between 3 and 4 years of age. Adolescents receive a tetanus, diphtheria and inactivated polio (Td-IPV) vaccine at 14-16 years with girls being vaccinated with 2 doses of the human papilloma virus vaccine at 12–<13 years of age. Introduction of a conjugate MenACWY vaccine at 3 months and 12 months of age with another routine dose at 12 years would easily fit within this schedule even when

a pneumococcal conjugate vaccine is eventually introduced. Similarly, MenB vaccination in a 2, 4 infant priming and 12 month boost in addition to two-dose vaccination starting from 12 years of age can also be easily accommodated within the national vaccination programme.

Conclusions

Capsular groups B, C, W and Y meningococcal disease are endemic in Malta, a country with a relative high incidence of IMD. The introduction of MenACWY vaccination following a single dose in early infancy with a boost in the 2nd year of life and in adolescence would be expected to impact MenC, W and Y disease in Malta. The concurrent launch of a one-time MenACWY vaccine catch-up campaign in children aged between 1 and 5 years and adolescents and young adults aged 12–20 years would be expected to induce herd protection and help achieve a faster decline in MenC, W and Y disease. Furthermore, a MenB immunization programme consisting of a 2 dose prime and boost MenB infant vaccine schedule in addition to MenB adolescent vaccination at 12 years of age would also be projected to provide direct protection and reduce the incidence of MenB, which is responsible for the highest meningococcal disease burden in Malta.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by David Pace. The first draft of the manuscript was written by David Pace, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

The study was approved by the Faculty of Medicine and Surgery University of Malta Research Ethics Committee (Ref No: FRECMDS_ 1819_38).

Conflict of interest The authors declare that they have no conflict of interest.

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