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Surveillance of invasive meningococcal disease in Portugal, 2016-2018

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INTRODUCTION & OBJECTIVES

Since October 2002 the surveillance of Invasive Meningococcal Disease (IMD) in Portugal includes a mandatory laboratory notification in addition to the clinical notification, which had been mandatory since 1939. The Directorate-General of Health manages the epidemiological information and interventions.
The National Reference Laboratory (NRL) of *Neisseria meningitidis* at the National Institute of Health Dr. Ricardo Jorge, Lisbon (NIH) conduct a hospital laboratory network implemented throughout the country in 2002, the VigLab-DM, which supports the laboratory component of the surveillance. Meningococcal isolates and negative culture clinical samples are mandatory to been send do NRL, where lab confirmation and genotyping are proceed.

Surveillance data is, therefore, the basis for prevention and control policies. Vaccination against MenC was available since 2002 and, in 2006, the vaccine was introduced in the national immunization programme, aimed to children under one year of age. Since 2007 the number of invasive C strains became residual.
In April 2014, the multi-component vaccine 4CMenB was introduced in the market.
The aim of this study is to perform a descriptive analysis of laboratory-based surveillance of IMD from 2016 to 2018.

METHODS

The case definition of IMD is in accordance with ECDC guidelines. Suspected cases were confirmed by real time PCR targeting *ctrA* and *sodC* with Taqman probes (1). Groups were identified by PCR (1). DNA characterization present in clinical samples included *por*A, FetA and MLST, was performed through amplicon-based Sanger sequencing (2,3). Isolates genotyping was done by Whole Genome Sequencing.

RESULTS

The incidence rate of IMD has been decreasing since it has been monitored through the laboratory based surveillance system. In the 3-year period 2016-2018 the incidence rate ranged from 0.41 to 0.59 /100.000 inhabitants (Fig. 1).The vaccine MenC was introduced in the National Immunization Program in 2006. The vaccine MenB was introduced in the free market in 2014.

The proportion of lab confirmed cases is annually monitored and is one parameter of the surveillance evaluation (Fig. 2).

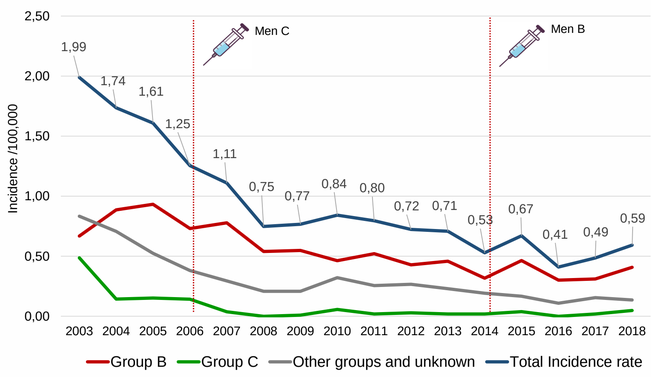


Figure 1 – Incidence rate/100,000 of IMD in Portugal, 2003-2018: global incidence, serogroups B, C and other or unknown serogroups.

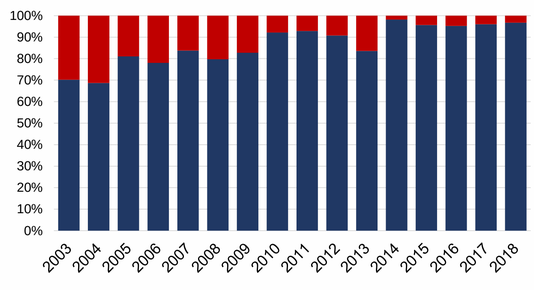
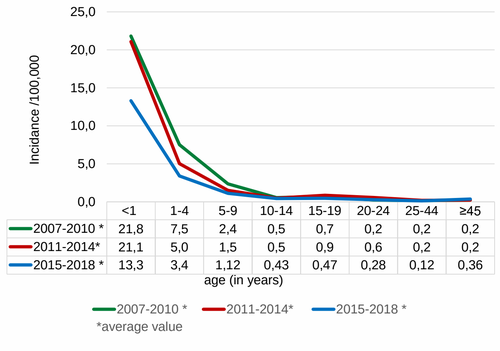


Figure 2 - Proportion of confirmed and probable/possible cases of IMD registered in Portugal, 2003-2018.

Since the annual number of cases is low, in order to get a more robust data, the incidence rate (IR) by age group was analyzed considering accumulated data in three successive 4-year period, starting in 2007.
The IR by age group showed the highest rate in children under one year of age, decreasing significantly in the group of 1 to 4 years of age and remaining very low after 10-14 years of age Although this pattern is the one observed in 2007-2010, there is a clear IR decreasing in the ages up to 1-4 years, in the period 2015-2018 (Figure 3).



	<1	1-4	5-9	10-14	15-19	20-24	25-44	≥45
2007-2010 *	21,8	7,5	2,4	0,5	0,7	0,2	0,2	0,2
2011-2014*	21,1	5,0	1,5	0,5	0,9	0,6	0,2	0,2
2015-2018 *	13,3	3,4	1,12	0,43	0,47	0,28	0,12	0,36

Figure 3 – Incidence rate by age group, Portugal 2007-2018

Cases due to serogroup B have been always the most frequent (70.7% of all confirmed cases). Cases due to serogroup C dramatically decreased since 2007 and are since there mostly reported in adults and/or non-residents, with the exception of one case occurred in an unvaccinated baby under one year of age, in 2014. It was observed an increasing number of cases due to W strains that has been maintained in 2019 (data not shown) (Table 1, Fig.4).

Table 1 – Number of invasive strains by serogroup and year of onset, Portugal 2003-2018

Year of onset	Group B	Group C	Group W	Group Y	NG	Other groups	UN	Total
2003	70	51	6	0	2	2	15	146
2004	93	15	4	4	0	2	7	125
2005	98	16	2	2	2	0	17	137
2006	77	15	1	5	1	0	4	103
2007	82	4	1	3	1	0	7	98
2008	57	0	0	3	1	1	1	63
2009	58	1	0	2	0	1	5	67
2010	49	6	0	0	3	2	22	82
2011	55	2	0	10	1	0	10	78
2012	45	3	1	4	2	0	14	69
2013	48	2	1	3	0	0	7	61
2014	33	2	0	5	4	0	10	54
2015	48	4	0	7	2	0	5	66
2016	32	0	1	6	0	0	2	41
2017	32	2	2	4	0	1	8	49
2018	41	5	5	6	0	0	2	59
Total	**918 (70.7%)**	**128 (9.9%)**	**24 (1.8%)**	**64 (4.9%)**	**19 (1.5%)**	**9 (0.7%)**	**136 (10.5%)**	**1298**

NG= Non-groupable
UN= Unknown

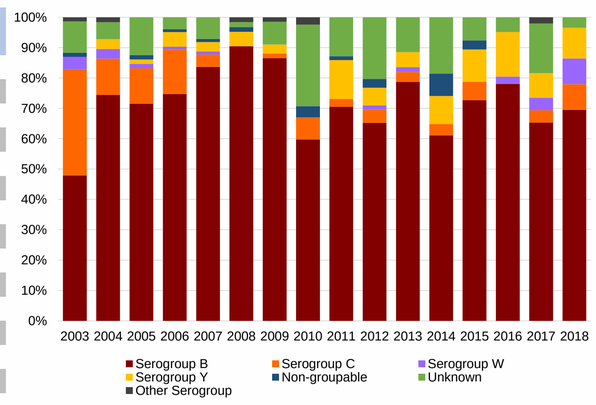


Figure 4 – Percentage of serogroups per year of onset, Portugal, 2003-2018.

Genotypes – data from a 3-year period 2016-2018

86 **group B** strains (MenB) (82% of all B stains) were characterized. They assigned to 13 different clonal complexes (cc) and 10.5% of them were unassigned (UA) to cc. B strains were mostly belonging to cc41/44 (29.1%) followed by cc213 (16.3%) (Fig 5 and 6).

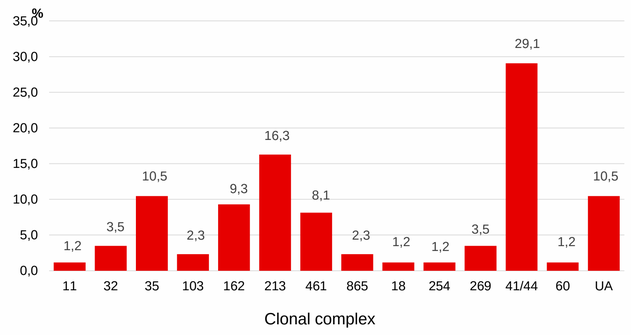


Figure 5 – Proportion of group B strains assigned to clonal complexes, 2016-2018

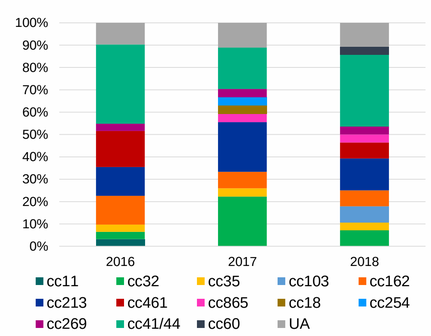


Figure 6 – Distribution of group B strains clonal complexes by year of onset

Group Y strains (MenY) were the second most frequent. The 15 characterized strains (93.8% of all Y stains) were mostly assigned to cc23. Clonal complex 103 represented 26.7% of the studied strains (Fig 7). Cases occurred in all age groups (Fig 8).

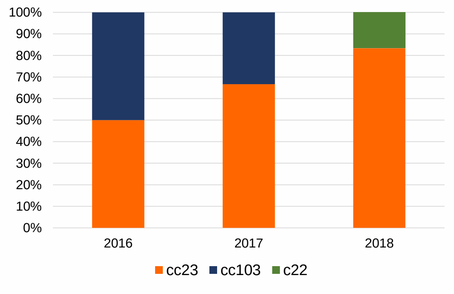
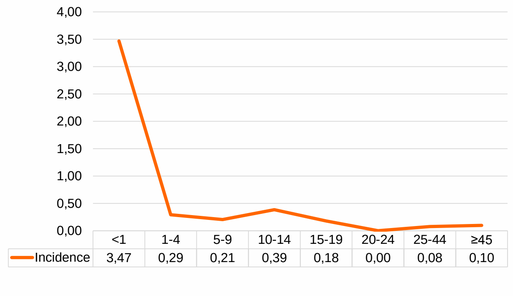


Figure 7 – Proportion of MenY strains by clonal complex.



	<1	1-4	5-9	10-14	15-19	20-24	25-44	≥45
Incidence	3,47	0,29	0,21	0,39	0,18	0,00	0,08	0,10

Figure 8 – Incidence rate of IMD due to MenY.

Seven **Group C** strains were characterized (85.7% from all MenC strains). All but one were assigned to cc11. Four strians had the same finetyping antigens P1.5,2:F3-6.

All **Group W** strains (MenW) were characterized. 6 strains were assigned cc11 (75%), mostly with finetyping antigens P1.5,2:F1-1, and 2 strains were cc22, both P1.18-1,3:F4-1 (Fig. 9 and 10). According to Antigen Sequence Types (BAST), MenW cc11 were classified into BAST 2, excepting one strain in which NadA peptide was absent.

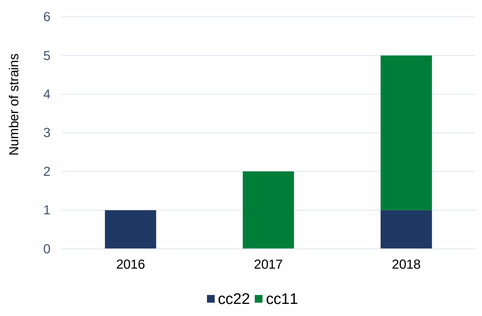


Figure 9 – Number of MenW strains by clonal complex.

Table 2– Age distribution of patients with IMD due to MenW, 2016-2019

Year of onset	Nº of cases MenW	Age of patient	Genotype
2016	1	6 years	W:P1.18-1,3:F4-1:St184 **cc22**
2017	2	88 years	W:P1.5,2:F1-1:ST11**cc11**
		62 years	W:P1.5,2:F1-1:ST11**cc11**
2018	4	47 years	W:P1.18-1,3:F4-1:St184 **cc22**
		70 years	W:P1.5,2:F1-1:ST11**cc11**
		97 years	W:P1.5,2:F1-1:ST11**cc11**
		52 years	W:P1.5,20:F1-1:ST11**cc11**
		7 months	W:P1.5,2:F1-1:ST11**cc11**
2019 (May)	5	15 months	W:P1.5,2:F1-1:ST11**cc11**
		12 months	W:P1.18-1,3:F4-1:ST8044 **cc22**
		53 years	W:P1.5,2:F1-1:ST11**cc11**
		7 months	W:P1.5,2:F1-1:ST11**cc11**
		5 months	W:P1.5,2:F1-1:ST11**cc11**
		83 years	WGS ongoing

CONCLUSIONS

- ❑ The incidence rate of IMD has been decreasing in Portugal since 2003. In the 3-year period from 2016 to 2018 the incidence rate was low (0.41-0.59 per 100,000 people) (Fig. 1) and under the average reported in the European countries (0.62-0.63 per 100,000 people);
- ❑ The data quality from the lab based surveillance system has been improving. ≥ 90% of cases were laboratory confirmed in the last 5 years (Fig. 2);
- ❑ Group B has been the most frequent, mostly belonging to cc41/44 and cc213;
- ❑ It has been observed an increasing number of cases due to MenW cc11;
- ❑ It is important to continue the IMD surveillance in order to evaluate the prevention and control policies implemented and improve them based on updated data.

References

(1) Laboratory methods for the diagnosis of meningitis caused by Neisseria meningitis, Streptococcus pneumonia and haemophilus influenza. CDC, WHO Manual, 2 nd Edition, 2011
(2) Paula Molling, et al. 2002.Direct and Rapid Identification and Genogrouping of Meningococci and porA Amplification by LightCycler PCR. J. Clin. Microb. 40.12 p 4531-4535.
(3) Maiden MC, et al. 1998. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. Proc Natl Acad Sci U S A 95: 3140–3145.