



# 15<sup>th</sup> EMGM Congress

The European Meningococcal and Haemophilus Disease Society

**27-30 May 2019**

**PT Meeting Centre | Lisbon | Portugal**

**BOOK OF ABSTRACTS**

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## **BOOK OF ABSTRACTS**

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Epidemiology and Surveillance I

## OC - (EMGM2019-13263) - GLOBAL EPIDEMIOLOGY OF BACTERIAL MENINGITIS ACCORDING TO TWO MAJOR MODELLING EFFORTS: WHAT'S THE TRUE PICTURE?

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### Introduction & Aims

WHO recently launched the Defeating Meningitis by 2030 initiative<sup>1</sup>. The scope includes organisms considered to be responsible for the majority of acute bacterial meningitis, and for which vaccines are either available or likely to become available in the next few years.

As a result of deficiencies in country-specific health data in many low and middle income countries, there is a heavy reliance on global health estimates to track progress in global health initiatives.

We aimed to define the current global burden of meningitis caused by *Neisseria meningitidis* (*Nm*), *Streptococcus pneumoniae* (*Spn*), *Haemophilus influenzae type b* (*Hib*) using two major global modelling efforts so that progress can be monitored over time.

### Materials and Methods

Meningitis estimates from the following models were compared: 1) Institute for Health Metrics and Evaluation GBD2017<sup>2</sup>, 2) Maternal Child Epidemiology Estimation (MCEE)/ Johns Hopkins University (JHU) Child Mortality estimates: syndromic<sup>3</sup> and meningitis pathogen<sup>4</sup> model (published 2018).

### Results

Our comparison demonstrated that:

- GBD2017 estimated there to be over 144,000 deaths in 2015 from meningitis in 1-59 month old children compared to MCEE/JHU's estimate of around 105,000 deaths
- There was agreement between models that deaths due to meningitis are declining but at a slower rate than many other vaccine preventable diseases
- GBD2017 estimated higher global incidence of pathogen specific meningitis in 1-59 month olds in 2015 than MCEE/JHU. GBD2017 estimated an incidence of 34/100,000, 31/100,000 and 40/100,000 for meningococcal, Hib and pneumococcal meningitis respectively compared to MCEE/JHU's estimate of 5/100,000 and 12/100,000 for Hib meningitis and pneumococcal meningitis respectively.
- Global mortality and proportions of meningitis deaths attributable to *Spn* and *Hib* in children aged 1-59 months also differed substantially between GBD2017 and MCEE/JHU estimates
- A high proportion of global child deaths (over 90% in one model) are based on verbal autopsy data leading to considerable uncertainty in these estimates

### Conclusion

Differences in meningitis estimates across different initiatives make it difficult to define the current burden of disease. Further work to improve models is necessary to define the current burden of disease and measure progress towards defeating meningitis by 2030.

### References

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2. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2018. Available from <http://vizhub.healthdata.org/gbd-compare>. [Accessed 1 February 2019]
3. World Health Organisation and Maternal Child Epidemiology Estimation Group. 2018. WHO-MCEE estimates for child causes of death 2000-2017. [ONLINE] Available at: [https://www.who.int/healthinfo/global\\_burden\\_disease/estimates/en/index2.html](https://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html). [Accessed 1 February 2019].
4. Wahl, B., O'Brien, K.L., Greenbaum, A., Liu, L., Chu, Y. and Black, R., 2016, June. Global burden of *Streptococcus pneumoniae* in children younger than 5 years in the era of pneumococcal conjugate vaccines (PCV): 2000-2015. In International Symposium on Pneumococci and Pneumococcal Diseases (pp. 26-30).

## OC - (EMGM2019-13177) - CASE FATALITY RATES OF INVASIVE MENINGOCOCCAL DISEASE BY SEROGROUP AND AGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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### Introduction & Aims

Invasive meningococcal disease (IMD) is uncommon but still causes considerable public health burden due to its high mortality and morbidity. This review aims to quantitatively synthesise all published evidence pertinent to mortality caused by IMD and assess the effect of age and serogroup on case fatality rates (CFRs).

### Materials and Methods

The PubMed and Embase databases, and the Cochrane Library were searched. Articles reporting national CFRs and published in English between January 2000 and May 2018 were eligible. The studies reporting mortality resulting from a specific symptom of IMD (e.g. meningococcal meningitis) were excluded. Mixed-effects logistic regression with a restricted cubic spline was used to analyse CFRs as a function of age. Random-effects meta-analyses were performed to estimate an overall CFR and CFRs by serogroup.

### Results

Among 48 eligible studies reporting national CFRs, 40 studies were included in meta-analyses representing 163,758 IMD patients. CFRs ranged from 4.1% to 20.0% with the pooled overall CFR of 8.3% (95% confidence interval (CI): 7.5%-9.1%). Serogroup B was associated with a lower pooled CFR (6.9% (95%CI: 6.0%-7.8%)) than other serogroups (W: 12.8% (95%CI: 10.7%-15.0%); C: 12.0% (95%CI: 10.5%-13.5%); Y: 10.8% (95%CI: 8.2%-13.4%)). For laboratory confirmed IMD cases, the predicted CFR was 9.0% in infants, gradually decreased to 7.0% in 7-year olds, subsequently increased to 15.0% in young adults aged 28 years, stabilised between 15-20% in mid-aged adults and reached a high in elderly people.

### Conclusion

Our findings can provide useful information for better understanding the mortality risks, and quantifying the burden associated with IMD mortality.

### References

## OC - (EMGM2019-13293) - INVASIVE HAEMOPHILUS INFLUENZAE INFECTIONS IN GERMANY: COMBINED DATA FROM THE NOTIFICATION SYSTEM AND LABORATORY SURVEILLANCE 2001 – 2016

Thiên-Trí Lâm (Germany)<sup>1</sup>; Anja Takla (Germany)<sup>2</sup>; Heike Claus (Germany)<sup>1</sup>; Ole Wichmann (Germany)<sup>2</sup>

1 - University of Wuerzburg, Institute for Hygiene and Microbiology; 2 - Robert Koch Institute, Department for Infectious Disease Epidemiology

### Introduction & Aims

Hib vaccination was introduced in Germany in 1990 and resulted in drastic epidemiologic changes. *H. influenzae* (Hi) from blood and cerebrospinal fluid are notified according to the German Infection Protection Act. The German National Reference Laboratory for Meningococci and *H. influenzae* (NRZMHi) has taken up laboratory surveillance since 2009. Here, we present the national surveillance data in Germany from 2001 to 2016.

### Materials and Methods

Notification data for 2001-2016 were available through the SurvNet@RKI system. Information included month/year of birth, sex, notification week/year, county and state of residence, disease onset, clinical presentation, vaccination, and outcome (survival/death). Serotype and ampicillin susceptibility data from the NRZMHi were available since 2009. Data were linked using an automated algorithm followed by manual search.

Proportions and incidences were compared using Chi-squared test. For estimation of incidence rate ratios Poisson regression was used. Following multiple imputation for missing data, the secular trend was estimated by a Poisson model in each version of the completed data. The results were subsequently pooled using Rubin's rules.

### Results

4,044 Hi cases were notified 2001-2016. Matching was successful for 1,910 out of 3,253 cases (59%) 2009-2016. Incidences 2001-2016 were highest in patients aged <1 year (15.2/1 mio) and ≥80 years (15.5/ 1 mio). The latter age group also showed highest case-fatality (13.2%). Mean incidence was 3.0/1 mio inhabitants. Non-typeable Hi (NTHi) ranged 52.9%-56.0% in age groups <10 years, and 74.7%-91.4% in ≥10 years. 351 cases were capsulated, with 241 (69%) Hif, 58 (17%) Hib, 45 (13%) Hie, and 7 (2%) Hia. No Hic or Hid occurred.

Trend analysis showed a pronounced increase among patients aged ≥80 years. An increasing trend was also observed in patients aged <1 year. Hif cases displayed a yearly increase by 13% that was caused by a systematic increase in patients aged <5 years and ≥60 years, respectively. No trend was detected for Hib, and only five breakthrough infections were found.

For ampicillin resistance, trend analysis showed an odds ratio of 1.11 per year for ampicillin resistance.

### Conclusion

Incidence of invasive NTHi infections has been rising markedly among elderly patients and reflects trends observed in other countries. Increased infection rates in infants aged <1 year also confirm previous findings and need further attention. Ampicillin resistance was not critical, however rising. Therefore, further resistance surveillance is warranted. The results underline the value of laboratory surveillance as a complement to the statutory notification system.

### References

## OC - (EMGM2019-13241) - GENOTYPIC ENHANCED SURVEILLANCE AFTER THE INTRODUCTION OF 4CMENB IN ENGLAND, THE FIRST 29 MONTHS

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1 - Public Health England; 2 - University of Oxford

### Introduction & Aims

4CMenB (Bexsero) was developed to target serogroup B meningococci (MenB). It comprises four main antigens - factor H-binding protein (fHbp; variant 1, peptide 1), *Neisseria* adhesin A (NadA, variant NadA-2/3, peptide 8), Neisserial heparin-binding antigen (NHBA; peptide 2) and Porin A (PorA; P1.4). Broadly speaking, the fHbp component potentially protects against meningococci expressing fHbp variant 1, but not variant 2 or 3, peptides. The NadA component potentially protects against meningococci expressing NadA-1 and NadA-2/3, but not NadA-4/5 or NadA-6, peptides. The PorA component protects against meningococci expressing PorA P1.4. NHBA does not form discrete antigenic 'variant' groupings but does offer some cross-protection.

The UK introduced routine infant immunisation with 4CMenB in September 2015. Approximately half of UK cases yield a culture. We present genotypic characteristics of post-vaccine English MenB case isolates received by the Public Health England Meningococcal Reference Unit (MRU) including comparisons with pre-vaccine cases.

### Materials and Methods

Since June 2010, isolates received by the MRU undergo genome sequencing and submission to the Meningitis Research Foundation Meningococcus Genome Library. Antigen and MLST data were exported. Gaps were filled using BLAST searches and/or Sanger sequence analyses.

### Results

All but one of the MenB isolates received between 1<sup>st</sup> September 2015 and 31<sup>st</sup> January 2018 (total n=478) were potentially covered by NHBA. For the remaining antigens, 125 (26.2%), 241 (50.4%) and 112 (23.4%) isolates were potentially covered by 0, 1, and 2 antigens, respectively. Among the under-three year-olds (<3s; n=163) the corresponding figures were 62 (38%), 74 (45.4%) and 27 (16.6%). Overall, the <3s had lower proportions of several potentially well-covered ccs versus older age groups, including cc32 (6.7% vs 9.6%) and cc41/44 (30.7% vs 36%), and higher proportions of several relatively poorly covered ccs including cc213 (16.0% vs 13.0%) and cc461 (4.9% vs 3.6%). The respective ccs each had a higher proportion of NHBA-only covered isolates among the <3s. The proportion of cc41/44 and cc213 isolates decreased and increased, respectively, with increasing number of doses among vaccinees, and as compared with <3s in previous years.

### Conclusion

Case numbers remain low, especially among vaccine eligible individuals. There are early indications that the proportion of disease due to potentially well-covered ccs is decreasing among vaccinees in favour of that due to ccs predicted to be poorly covered. These data complement phenotypic analyses of strain coverage generated using the Meningococcal Antigen Typing System to evaluate the performance of the vaccine and may inform the formulation of next generation vaccines.

Session: Poster Session I

Room: Auditorium III

Epidemiology and surveillance of invasive meningococcal, pneumococcal and Haemophilus influenzae disease

**PO-001 - (EMGM2019-13232) - INVASIVE MENINGOCOCCAL DISEASE IN SWEDEN 2018**Sara Thulin Hedberg (Sweden)<sup>1</sup>; Tiia Lepp (Sweden)<sup>2</sup>; Bianca Stenmark (Sweden)<sup>1</sup>; Paula Mölling (Sweden)<sup>1</sup>; Martin Sundqvist (Sweden)<sup>1</sup>; Hans Fredlund (Sweden)<sup>1</sup>; Susanne Jacobsson (Sweden)<sup>1</sup>

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**Introduction & Aims**

Invasive meningococcal disease (IMD) is notifiable in Sweden. The reporting system comprises of mandatory notification of cases and mandatory laboratory notification of samples to the Public Health Agency of Sweden, Stockholm. All samples are sent to the National Reference Laboratory (NRL) for *Neisseria meningitidis* in Örebro for further typing and surveillance.

**Results**

Preliminary data shows that 56 cases of IMD (incidence 0.55/100 000 population) were reported in Sweden 2018. Among the patients 57% were females and 43% males, aged from 1 month to 92 years with mean age of 49 years. The incidence was highest among infants (<1 year), elderly (age group 70-79) and teenagers (age group 15-19). The case fatality rate decreased in 2018 to 9% compared to 20% in 2017 and 13% in 2016. Five people died from the disease during 2018 (MenW, n=2; MenY, n=2 and ng, n=1). None of the IMD cases in 2018 had any epidemiological linkage.

Laboratory confirmation was obtained in 55 of the 56 cases of IMD: 52 were culture-confirmed and three were PCR-confirmed, 51 of the isolates were sent to the NRL for *Neisseria meningitidis* for further typing. The serogroup distribution was 41% MenW (n=21), 29% MenY (n=15), 16% MenC (n=8), 10% MenB (n=5) and 4% non-groupable isolate (n=2). As in previous years the W:P1.5,2:F1-1:ST11 (cc11) (n=20) and Y:P1.5-2,10-1:F4-1:ST23 (cc23) (n=7) were predominant followed by C:P1.5,2:F3-3:ST11 (cc11) (n=7).

Antibiotic susceptibility testing was performed using gradient strip (Etest, BioMerieux). Decreased susceptibility to penicillin was seen in 21% of the isolates (MIC >0,064 mg/L) of which one was resistant (MIC=4 mg/L). All isolates were susceptible to cefotaxime, chloramphenicol, ciprofloxacin, rifampicin and meropenem. No  $\beta$ -lactamase producing isolates has so far been found in Sweden.

**Conclusion**

To conclude, the incidence of IMD continues to be relatively low in Sweden, however, the shift in serogroup distribution of *N. meningitidis* in Sweden has continued; the previously dominating disease-causing MenB and MenC have been replaced, firstly by MenY, which emerged in 2009 and now by MenW, which emerged in 2015. The MenW has increased from only causing invasive disease in 0-6 cases per year from 1990 to 2014, to become the dominating serogroup in Sweden from 2016 onwards.

**PO-002 - (EMGM2019-13237) - EPIDEMIOLOGY OF INVASIVE MENINGOCOCCAL DISEASE IN FINLAND, 2016-2018**

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<sup>1</sup> - National Institute for Health and Welfare

**Introduction & Aims**

Surveillance of invasive meningococcal disease (IMD) is needed for outbreak investigations and monitoring changes in disease epidemiology in relation to national vaccination policies. In Finland, meningococcal vaccines (MenACWY) are currently offered as a part of the national immunization program only to army conscripts upon entry into service. ACWY conjugate and MenB vaccines are available on the market and are mostly given to travelers. We report the epidemiology of IMD in Finland in 2016-2018.

**Materials and Methods**

Notification of laboratory confirmed IMD is mandatory in Finland and all blood and cerebrospinal fluid isolates are requested to be sent to the National Reference Laboratory (NRL) for species verification and further characterization. At the NRL, all isolates from 2016-2018 were serogrouped by slide-agglutination. Whole genome sequencing (Illumina) was used to characterize the isolates in more detail.

**Results**

During 2016-2018, altogether 51 laboratory-confirmed IMD cases were notified to the National Infectious Disease Register. The annual incidence varied from 0.29 per 100,000 population (16 cases) in 2017 and 2018 to 0.35 (19 cases) in 2016. Sixty-three percent (32/51) of the cases occurred among women. The median age of the patients was 48 years (range 3 months to 93 years). Five (9.8%) cases occurred in children aged 0–6 years, 14 (27.5%) cases in adolescents and young adults aged 15-20 years, and the rest of the cases (32; 62.7%) among adults aged  $\geq 25$  years. All but one case were culture-confirmed, mostly by blood culture (81%). The majority of cases (19; 37.3%) were caused by serogroup Y, followed by serogroup B (15; 29.4%), C (12; 23.5%), and W (4; 7.8%). Serogroup Y tended to cause disease among older people (median age 60 years) than the other serogroups. Of the five cases among children ( $\leq 6$  years), three were caused serogroup B and two by serogroup C. During 2016-2018, a prolonged MenC outbreak occurred in the Helsinki area, and in 2017, a small MenB outbreak among military conscripts. The genomic relationship among the isolates and their antigen profiles will be presented.

**Conclusion**

IMD is endemic in Finland but the incidence is low compared to previous decades. The majority of cases were sporadic. Serogroup W IMD was still rare in Finland. Serogroup B IMD has declined during the past years and accounts currently for around one third of all cases. The reduction in serogroup B IMD has shifted the disease burden to adults and older people.

## PO-003 - (EMGM2019-13343) - EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE IN GERMANY 2010 THROUGH 2018: DATA FROM THE LABORATORY SURVEILLANCE

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### Introduction & Aims

Introduction:

In Germany, invasive meningococcal disease (IMD) has to be notified statutory to the Robert Koch-Institute via local health agencies. Laboratories are requested to submit meningococcal isolates or culture-negative specimen to the German national reference laboratory for Meningococci and *Haemophilus influenzae* (NRZMHi) for laboratory surveillance on a voluntary basis. Both dataset are matched annually; 80-90% of the notified cases are submitted to the NRZMHi. IMD incidence derived from statutory data declined from 0.47 cases/100.000 inhabitants in 2010 (MenB: 0.29, MenC: 0.09) to 0.36 in 2018 (Men B: 0.19 and MenC: 0.04).

Aims:

To describe recent changes in IMD epidemiology in Germany.

### Materials and Methods

We analysed data of the German reference laboratory according to serogroup, finetype (Serogroup:PorAVR-1, PorAVR-2:FetAVR), multilocus sequence typing (MLST) clonal complex and demographics for 2010-2018.

### Results

Over time MenB and Men isolates decreased, whereas a moderate increase of MenW and MenY isolates was observed since 2016.

The most common MenB finetypes were B:P1.7-2,4:F1-5 (ST-41/44c) and B:P1.22,14:F5-5 (ST-213c). From 2010 to 2018 the number of B:P1.7-2,4:F1-5 isolates decreased from 43 to 9; all age groups were affected. The number of B:P1.22,14:F5-5 isolates remained quite stable (range 9-17, median 12). Finetype B:P1.22,14:F5-1 (ST-269c) emerged 2012 in Rhineland-Palatinate.

The most common MenC finetypes were C:P1.5,2:F3-3 (ST-11c) and C:P1.5-1,10-8:F3-6 (ST-11c). From 2010 to 2018 the number of C:P1.5,2:F3-3 isolates decreased from 33 to 4, predominantly in subjects aged less than 20 years. The number of C:P1.5-1,10-8:F3-6 isolates remained quite stable (range 7-18, median 11). Mostly affected were subjects aged more than 20 years. The highest number of cases in 2013 was associated with cases in men-who-have-sex-with-men.

The most common MenY finetype was Y:P1.5-2,10-1:F4-1 (ST-23c), which mostly affected adolescents and adults. After few cases in the years 2003-2015, isolates with finetype Y:P1.5-1,2-2:F5-8 (ST-23c) emerged 2016 in the same age group.

Before 2016, MenW:P1.18-1,3:F4-1 (ST-22c) was the most common serogroup W finetype with less than 10 cases in Germany. In 2015, cases with finetype W:P1.5,2:F1-1 (ST-11c) moderately increased in number.

In 2017 and 2018, 74.0% and 70.9% of the isolates were susceptible to penicillin. All were susceptible to cefotaxime, and all but one were susceptible to rifampicin and ciprofloxacin, respectively.

### Conclusion

IMD incidence in Germany remains low. MenB predominated in infants and children, whereas MenC, MenW and MenY isolates were mostly from subjects older than 20 years. In 2016 an increase of MenW and MenY cases was observed.

### References

**PO-004 - (EMGM2019-13211) - INVASIVE MENINGOCOCCAL DISEASE IN POLAND**

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 1 - National Reference Centre for Bacterial Meningitis, National Medicines Institute

**Introduction & Aims**

*Neisseria meningitidis* is a commensal of the human upper respiratory tract but may cause severe invasive disease, mostly presented as meningitis and septicaemia, with high case-fatality rate. The aim of the study was to characterise invasive meningococcal disease (IMD) in Poland between 2017 and 2018, based on laboratory confirmed cases.

**Materials and Methods**

The study encompassed all invasive meningococcal cases confirmed by the National Reference Centre for Bacterial Meningitis (NRCBM) between 2017 and 2018. The isolates were reidentified and characterised by susceptibility testing, MLST analysis, *porA* and *fetA* sequencing. A PCR technique was used for meningococcal identification directly from clinical materials in the case of a negative culture

**Results**

Between 2017 and 2018, the NRCBM identified 378 of laboratory confirmed IMD cases (290 by culture and 88 by PCR) with overall incidence 0.53 and 0.45/100.000, respectively. The incidence in patients under 1 year of age was 11.72 and 10.65, respectively. A serogroup was defined for 369 (97.6%) cases. Majority of IMD infections were caused by meningococci of serogroup B (MenB, n=247; 65.3%), followed by serogroup C (MenC, n=90; 23.8%), W (n=26, 6.9%), Y (n=5, 1.3%) and X (n=1, 0.3%). The percentage of MenW increased from 4.4% in 2017 to 9.8% in 2018. Decreased susceptibility to penicillin (MIC  $\geq$  0.12mg/L) characterised 32.3% of isolates. All meningococci were susceptible to cefotaxime, chloramphenicol, rifampicin and ciprofloxacin. Amongst 266 meningococci analyzed by MLST, 113 STs were found, although 84 of them were represented by one isolate only. More than 58.0% of isolates belonged to seven known clonal complexes (cc) with the most common 32/ET-5cc (18.8%), ST-41/44cc (16.2%), ST-103cc (6.4%), ST-213cc (5.6%) and ST-11cc (5.3%). Among MenB isolates 15 ccs were found; the most common were representatives of ST-32/ET-5cc (25.9%) and ST-41/44cc (16.1%). MenC group was less heterogeneous with six cc identified. The most frequent were isolates of ST-41/44cc (24.2%) and ST-103cc (22.6%). Among MenW the most common were isolates of ST-11cc (27.3%) and of ST-9316 (36.4%, no cc).

**Conclusion**

Poland, where population-based vaccination against meningococci was not introduced so far, belongs to European countries with a low IMD incidence rate. In 2018, the percentage of MenW increased twice among IMD cases in comparison with previous year. Clonal complexes of ST-32/ET-5cc and ST-41/44cc are well established in our country.

## PO-005 - (EMGM2019-13144) - THE EPIDEMIOLOGICAL SITUATION OF IMD IN SLOVAKIA IN YEARS 2015-2018.

Anna Kružlíková (Slovakia)<sup>1</sup>

1 - Anna kružlíková

### Introduction & Aims

Active surveillance of IMD and nasofaryngeal carrier in National reference centrum for meningococci (NRC) was introduced in the Slovak Republic in 1993. The 2008s brought about the use of molecular methods. The aim is to describe and inform about the epidemiological situation of IMD in Slovakia in years 2015-2018.

### Materials and Methods

In the NRC for meningococci, the isolates and clinical specimens (e.g. cerebrospinal fluid, blood or post-mortem specimens) from IMD cases are confirmed and characterized by classical and molecular laboratory methods. Active surveillance of IMD in Slovakia consists of infectious diseases data in EPIS database and data of NRC for Meningococci.

### Results

130 cases of invasive meningococcal disease (IMD) were reported in Slovakia in years 2015 - 2018. In National Reference centrum (NRC) for Meningococci we confirmed 110. IMD showed the highest incidence in infants 0-2 years of age. The serogroup B prevailed in 60%, serogroup C 27%, W135 and Y 1% and in 11% the group was not determined. The highest morbidity was recorded every year in Prešov region. Higher morbidity affected male than female sex (58% >42%). Clinically 40% - 57% it was meningitis, in other cases sepsis or meningitis with sepsis and Waterhouse-Friderichsen syndrome. 21 of the 130 diseases were fatal. 17 deaths were about 0-4 years old children. Next 4 deaths were about 17, 68 and 78 years old patients. All deaths were caused by serogroup B (11x), serogroup C (6x) with identified cc11, NG (3x). On one occasion death was not confirmed. In the group of invasive strains *N.meningitidis* we noticed 8% resistant strains to PNC, 22% strains of with threshold sensitivity against PNC. Resistant strains were betalactam-negative. Remains strains were sensitive to PNC and all tested strains were sensitive to CTX, CIP, RIF. We performed multilocus sequence typing (MLST) of some selected strains from IMD. By clonal analysis of 74 invasive strains we determined that the most common causative hypervirulent cc involved in IMD in 2008 - 2018 was cc11 - C and 32 - B, 41/44 - B,C,Y, 18 -B and 269 - B,C. The vaccination of the population by a combination of MenB vaccine and tetravalent A,C,Y,W conjugate vaccine is voluntary in Slovakia.

### Conclusion

Advanced molecular methods are essential for high quality surveillance of IMD in Slovakia. The most prevalent cc causing IMD in the Slovak Republic in 2008 - 2018 were cc11, cc32, cc41/44, cc269 and cc18. One third of all invasive strains disposed of reduced sensitivity against PNC.

### References

## PO-006 - (EMGM2019-13202) - MOLECULAR CHARACTERIZATION OF INVASIVE *N. MENINGITIDIS* IN SLOVENIA, 2010-2017

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<sup>1</sup> - National Laboratory for Public Health Microbiology

### Introduction & Aims

Invasive meningococcal disease represents an important public health issue despite its low incidence in Slovenia. In 1993 we started the national surveillance project. The objectives of our study were to characterise the Slovenian invasive meningococcal isolates using the WGS data.

### Materials and Methods

Isolates of invasive *N. meningitidis* were collected in order to investigate the molecular epidemiology of invasive meningococci. We sequenced 61 isolates from 2010 to 2017. The genome sequences of the isolates were determined on the PGM, Ion Torrent (Life Technologies). Whole genome sequence (WGS) data were collected, de novo assembled and submitted for the automated annotation and analysis to the PubMLST/Neisseria website, BIGSdb.

### Results

In the period 2010 to 2017 we received 66 invasive meningococcal isolates. The incidence rate varied from year to year and was the highest in children, in the age group less than two years in the year 2015 when it reached 14.2/100,000. Whereas the average annual incidence in the group of children (0-14 years) was 1.6/100,000 and in the group of adults ( $\geq 15$  years) it was 0.2/100,000. The average annual incidence in the most affected age group (children 0-2 years) was 7.5/100,000. The most prevalent was serogroup B (46 strains; 69.7%), followed by serogroup C (11 strains; 16.7%), serogroup Y (7 strains; 10.6%) and serogroup Z (1 strain; 1.5%). We observed four main clonal complexes; ST-41/44 complex (14 isolates; 23.0%), ST-11 complex (8 isolates; 13.1%), ST-32 complex (7 isolates; 11.5%) and ST-269 complex (7 isolates; 11.5%). The most homogenous was ST-11 complex, which consisted of only ST-11 and the predominant finetype was P1.5-1,10-8:F3-6. On the other hand we observed a high diversity in the serogroup B, Based on presence or absence of genes encoding Bexero vaccine antigenic variants, 55.7 % isolates showed none 16.4 % were cross-reactive and 27.9 % of isolates contained exact antigenic variant found in the vaccine. In the serogroup Y we observed two main complexes; ST-23 complex and ST-167 complex.

### Conclusion

The incidence rate is quite low and the epidemiologic situation is still endemic in Slovenia. The isolates are heterogeneous, but all the main hyper virulent clones are present, so surveillance is essential for prevention and recognition of disease clusters.

WGS has become accessible and economically feasible method for the analysis of national strain collections in and in the future it will certainly serve as an important means of surveillance method.

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## PO-007 - (EMGM2019-13173) - SURVEILLANCE OF INVASIVE MENINGOCOCCAL DISEASE IN THE CZECH REPUBLIC

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### Introduction & Aims

The invasive meningococcal disease (IMD) surveillance program was launched in the Czech Republic in 1993 when a new hypervirulent complex, cc11, of *Neisseria meningitidis* serogroup C emerged in the country.

### Materials and Methods

The database of active surveillance of IMD is a compilation of the routine notification data on infectious diseases in the Czech Republic and data of the National Reference Laboratory for Meningococcal Infections, after exclusion of duplicate cases.

### Results

IMD surveillance data from 2017 show that IMD incidence reached 0.6/100 000 and the case fatality 14.7 %. Serogroup C was on the rise (36.8 %) and serogroup B on the decline (48.5 %). Since 2006, serogroups Y and W have been on the rise (in 2017, serogroup Y accounted for 1.5 % of IMD cases and serogroup W for 4.4 %), causing high case fatality rates. The present increase in serogroup C in the Czech Republic can be interpreted as the return of hypervirulent clonal complex cc11. Serogroup B is represented by a mix of clonal complexes: cc41/44, cc32, cc18, and cc269. Meningococci of serogroup Y are most often classified into hypervirulent cc23. Meningococci of serogroup W belong to clonal complexes cc865, which is specific to the Czech Republic, and hypervirulent cc11, which is spread worldwide. The analysis of the age-specific incidence of IMD shows the highest long-term incidence in the smallest children under 1 year of age, followed alternatively by 1-4-year-olds or 15-19-year-olds in individual years. The age-specific distribution of serogroups has changed over the last two years. Serogroup B is no longer prevalent in small children and serogroup C is no longer prevalent in adolescents, but both serogroups are evenly distributed across these age groups. Given the low incidence of IMD in the Czech Republic, the immunisation against meningococcal disease is not included in the national immunisation program, but individual protection is recommended by the Czech Vaccination Society ([http://www.szu.cz/uploads/IMO/2018\\_Recommendation\\_for\\_vaccination\\_againts\\_IMD.pdf](http://www.szu.cz/uploads/IMO/2018_Recommendation_for_vaccination_againts_IMD.pdf)).

The aim is to provide as early, as complex, and as long protective immunity as possible to each vaccinated individual. The combination of the conjugate tetravaccine A, C, W, Y and vaccine MenB is recommended. Since January 2018, vaccination against IMD is also promoted by the new Czech legislation in individuals with a health indication.

### Conclusion

Precise surveillance data are necessary for providing adequate recommendation for vaccination in the country.

## PO-008 - (EMGM2019-13281) - EPIDEMIOLOGY AND SURVEILLANCE OF MENINGOCOCCAL DISEASE IN ENGLAND.

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1 - Public Health England Meningococcal Reference Unit, Manchester; 2 - Public Health England Immunisation and Counter Measures

### Introduction & Aims

Public Health England (PHE) performs surveillance of invasive meningococcal disease (IMD) to ascertain case numbers, characterise strains and inform vaccine policy: in August 2015, conjugate ACWY vaccine was introduced for teenagers and in September 2015 4CMenB (Bexsero®) was introduced into the national infant schedule.

To describe the epidemiology of IMD in England.

### Materials and Methods

Clinicians notify suspected cases of meningococcal meningitis/septicaemia to local Health Protection Teams. Hospital microbiology laboratories in England submit invasive meningococcal isolates to PHE for phenotypic characterization and MICs of penicillin, cefotaxime, rifampicin and ciprofloxacin are determined. Since July 2010 case isolates have undergone whole genome sequencing (WGS)\*. Clinical samples are submitted for non-culture detection and capsular group confirmation by PCR.

### Results

Laboratory confirmed cases rose from mid-1990s to peak at 2,595 (in 1999/00) then fell to 636 in 2013/14 increasing since to between 724 and 811 cases annually (755 in 2017/18). During 2017/2018, 295 cases (39%) were confirmed by PCR alone. Since November 1999 the major decrease in serogroup C was due to the MenC conjugate vaccine programme. From 2005/06 to 2014/15, there have only been 13-33 serogroup C cases annually but 42 were confirmed in 2015/16 and 64 in 2017/18.

There has been a decrease in serogroup B cases from 1,424 (2001/02) to 397 (2016/17). In 2017/18 serogroup B accounted for 54% (404 cases) of all confirmed cases; Where the UK national infant 4CMenB vaccination has resulted in reduced disease in targeted cohorts (1).

Serogroup Y accounted for 12% (88 cases) of IMD in 2017/18; Where, serogroup Y cases have remained stable since peaking at 103 cases in 2015/16. Having increased yearly since 2009, serogroup W represented 26% (193) of cases in 2017/18, reduced from 225 cases in 2016/17. The cases are predominantly phenotype W:2a:P1.5,2 and cc11 by WGS(2). The outbreak stimulated the the ACWY conjugate vaccine programme for UK teenagers which replaced the previous MenC dose in teenagers.

### Conclusion

Continued accurate surveillance and characterisation of meningococcal cases is essential to monitor recent UK vaccine interventions and schedule modifications.

\*Meningitis Research Foundation Meningococcus Genome Library (<http://www.meningitis.org/research/genome>).

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## PO-009 - (EMGM2019-13349) - SURVEILLANCE OF INVASIVE MENINGOCOCCAL DISEASE IN PORTUGAL, 2016-2018

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### Introduction & Aims

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 the interventions. Data from surveillance is therefore the basis for prevention and control policies. Vaccination against MenC started in 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 (data from 2018 are preliminary).

### Materials and Methods

The case definition of IMD is in accordance with ECDC guidelines. Hospital laboratories send meningococcal isolates to the reference laboratory for genotyping, as well as negative culture clinical samples from suspected cases for lab confirmation and genotyping. Probable and possible cases were confirmed by real time PCR targeting *ctrA* and *sodC*. Groups were identified by PCR; *porA*, *FetA* and MLST characterization was performed through amplicon-based Sanger sequencing (clinical samples) or WGS (isolates).

### Results

In the 3-year period, 154 cases of IMD were reported (150 confirmed and 4 possible/probable). The incidence rate ranged from 0.41 cases per 100,000 inhabitants in 2016 to 0.47 in 2017 and 0.58 in 2018.

Group B was the most frequent (76.2% in 2016, 62.5% in 2017 and 70.0% in 2018), presenting a large genetic diversity. The most common subtypes within B strains were P1.7-2,4, mostly belonging to cc162 and cc41/44, and P1.22,14 (13.3%), almost all belonging to cc213.

Serogroup Y was the second most frequent (14.3% in 2016, 8.3% in 2017 and 10.0% in 2018), mostly belonging to cc23.

Serogroups W and C represented 5.3% and 4.7%, respectively, of all invasive strains from the 3-year period. None of the patients with IMD due to MenC was vaccinated.

One serogroup Z strain was identified in 2017.

### Conclusion

The incidence rate of IMD in Portugal has been low in the 3-year period from 2016 to 2018, under the average of incidence rate in the European countries (0.63-0.62 per 100,000 people). Group B has been the most frequent, mostly belonging to cc41/44 and cc213.

It is important to continue the IMD surveillance in order to evaluate the need of policies regarding current vaccines.

**PO-010 - (EMGM2019-13159) - INVASIVE MENINGOCOCCAL SEROGROUP C DISEASE IN ITALY, 2012-2017**

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**Introduction & Aims**

During the last years, a decline of serogroup C *Neisseria meningitidis* (MenC) incidence following the meningococcal serogroup C conjugate vaccine introduction was observed worldwide. However, outbreaks continue to occur in different countries due to hypervirulent serogroup C strains. In Italy one outbreak in 2009 and an epidemic in Tuscany Region in 2015-2016 occurred, associated with severe Invasive Meningococcal Diseases (IMD) due to the hyperinvasive MenC strains. To describe the trend of MenC incidence in Italy from 2012 to 2017 by age group and clinical characteristics. Moreover, the molecular features, including genetic relationships among MenC isolates, have been analyzed.

**Materials and Methods**

Laboratory-confirmed cases due to *N. meningitidis* were based on the reporting to the Ministry of Health and to the ISS as National Reference Laboratory. Susceptibility to cefotaxime, ceftriaxone, ciprofloxacin, penicillin G and rifampicin was determined by MIC Test Strip Method (EUCAST breakpoints). Whole genome or single gene sequencing allowed to identify MLST, finetype, antibiotic resistance genes and cgMLST on a subsample of isolates (<http://pubmlst.org/neisseria/>).

**Results**

From 2012 to 2017, 302 laboratory confirmed cases due to MenC were reported within the National Surveillance System (<http://old.iss.it/mabi/>). During these years, the MenC incidence showed a slight increase from 0.05 cases to 0.09/100.000 inhabitants in the general population, involving in particular adults >24 years, with a peak of 0.1-0.13/100,000 in 2015-2016, respectively, determined by the outbreak occurred in Tuscany. The median age of patients was 31 years. The main clinical pictures were sepsis (40%), meningitis and meningitis/sepsis. The case fatality rate was 26%. Two meningococci were resistant to rifampicin (MIC 0.38 mg/L). Moreover, 119 isolates showed a decreased susceptibility to penicillin G. Ten different clonal complexes (cc11, cc18, cc22, cc23, cc32, cc175, cc198, cc231, cc334, cc865) and 32 genotypic formulas (the most frequent: C:P1.5-1,10-8:F3-6:ST-11(cc11), C:P1.7-4,14-6:F3-9:ST-1031(cc334), C:P1.5,2:F3-3:ST-11(cc11)) were identified. Whole genome sequencing was performed on 175 MenC isolates. cgMLST analysis clustered the genomes by clonal complex. In particular, MenC/cc334 grouped together; MenC/cc11 splitted into two subgroups, one comprising isolates C:P1.5-1,10-8:F3-6:ST-11(cc11) and one C:P1.5,2:F3-3:ST-11(cc11).

**Conclusion**

In Italy, despite its incidence decline since 2005, MenC continues to be responsible of severe IMD cases and outbreaks. From 2012 to 2017, the C:P1.5-1,10-8:F3-6:ST-11(cc11) is the main strain identified and responsible of an epidemic in 2015-2016 with high case fatality rate. In the post vaccination era, the monitoring and the genomic analysis of MenC meningococci should be maintained in order to evaluate the relationship among IMD cases and the occurrence of hyperinvasive strains.

**References**

## PO-011 - (EMGM2019-13324) - INVASIVE MENINGOCOCCAL DISEASE IN GREECE: 2 YEAR EPIDEMIOLOGICAL DATA (2017-2018)

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### Introduction & Aims

Surveillance of Invasive Meningococcal Disease (IMD) is mandatory in Greece and is performed through the mandatory notification system. Clinical records are reconciled with laboratory records on national scale.

### Aim

The study presents the epidemiological data for the time period 2017-2018.

### Materials and Methods

A total of 75 cases of IMD were notified in Greece for the 2 year studied period (42 and 33 cases for 2017 and 2018 respectively). Clinical samples (CSF, blood) and cultures were sent in laboratory for further identification by conventional and molecular methods.

### Results

The average annual incidence was 0.34/100 000 for both years; a decrease was observed compared to previous 2 years (0.5/100 000). In regards to the age, an incidence decline was observed in all age groups, with the exception of the infants <1 year of age (6,10 vs 4,67). Specifically, 1-4 years (2,19 vs 2,55), 5-9 years (0.46 vs 0.91), 10-14 (0.28 vs 0.85) and 15-19 years (0.37 vs 1.03) as well as in adults (>20 years) (0.20 vs 0.28). The case fatality rates (CFR) were 7.14 and 12.12 (2017 and 2018 respectively).

Among the 64 laboratory confirmed IMD cases, MenB was identified in 78.1% (50/64) followed by MenC 9.4% (6/64), while, MenY (7.8%; 5/64) and MenW (4.7%; 3/64) cases remained low.

The highest incidence rate for serogroup B was observed in age groups of <1, 1--4 and 5-9 years (average incidence 2.1 and 0.57/100 000 respectively). The 5 MenY cases were related to the age groups of 20-60 years (n=4), 0-4 years (n=1), all belonging to 23 cc.

The most predominant clonal complex was 41/44cc (2017) (related to MenB cases), whereas 7-2 and 4 were the predominant combinations for VR-1, VR-2 respectively.

Finally, the highest percentage of reduced susceptibility to penicillin was found in the strains isolated during 2018 (78.5%; 11/14) accounting for the highest percentage observed in the past 25 years.

### Conclusion

There is a continuous decrease in the IMD incidence, MenB is the predominant, while MenY and MenW cases remain low most probably due to the implementation of the MenACYW vaccination program in adolescents, since 2011.

## PO-012 - (EMGM2019-13219) - CURRENT EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE IN INFANTS – UNITED STATES

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1 - U.S. Centers for Disease Control and Prevention

### Introduction & Aims

Infants have historically had the highest incidence of meningococcal disease in the United States. Quadrivalent meningococcal conjugate (MenACWY) vaccines are currently licensed but not routinely recommended for infants, while serogroup B meningococcal (MenB) vaccines are not licensed for infants in the United States. Here, we evaluate the current epidemiology of meningococcal disease in infants to inform prevention strategies.

### Materials and Methods

Incidence of meningococcal disease among infants aged <1 year from 2013 through 2017 was calculated using data from the National Notifiable Diseases Surveillance System supplemented with information provided by state health departments. Available meningococcal isolates were characterized using slide agglutination, polymerase chain reaction, and whole genome sequencing.

### Results

From 2013 through 2017, 194 cases of meningococcal disease were reported among US infants. Average annual incidence was 0.98 cases/100,000, declining from 1.20 to 0.63 cases/100,000 during this period. Among patients with known information, 11.9% (21/176) died, 80% (136/170) were white, 17.9% (29/162) were Hispanic, and no cases were known to be outbreak-associated. Among cases with known serogroup, serogroup B accounted for 70.2% (120/171), with an average annual incidence of 0.61 cases/100,000. Incidence of serogroup B meningococcal disease was highest in those aged <2 months (1.24 cases/100,000) and generally decreased with age: 0.70 (2-3 months), 0.76 (4-5 months), 0.39 (6-7 months), and 0.24 (8-9 and 10-11 months) cases/100,000. Among 82 available serogroup B isolates, 10 clonal complexes (CCs) were identified, with CC41/44 being the most common (N=35). In contrast, average annual incidence for serogroups C, W, Y, and nongroupable disease was lower (0.07, 0.06, 0.09, and 0.05 cases/100,000 respectively). Combined incidence of serogroup C, W, and Y disease ranged from 0.06 cases/100,000 in infants aged 10-11 months to 0.30 cases/100,000 in those aged 4-5 months. Among available isolates, 7/9 serogroup C isolates were CC103, 7/8 serogroup W isolates were CC11, and 3/5 serogroup Y isolates were CC23.

### Conclusion

Meningococcal disease incidence among infants is declining in the United States. Serogroup B accounts for over two-thirds of infant cases, with the greatest burden of serogroup B disease now among infants aged <2 months followed by those aged 2-5 months. With the predominance of serogroup B in young infants and very low incidence of serogroups C, W, or Y disease in infants overall, the number of meningococcal disease cases potentially preventable through MenB or MenACWY infant vaccination in the United States is low.

## PO-013 - (EMGM2019-13227) - MOLECULAR EPIDEMIOLOGY FOR VACCINATION POLICY: ENHANCING SURVEILLANCE OF MENINGITIS IN THE AFRICAN MENINGITIS BELT

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### Introduction & Aims

Meningitis caused by encapsulated bacteria is a global health problem and Africa suffers the greatest burden of disease with meningitis predominantly caused by *Neisseria meningitidis* (*Nme*), *Streptococcus pneumoniae* (*Spn*), and serotype B *Haemophilus influenzae* type b (*Hinb*). While molecular typing approaches have significantly improved the ability to detect these pathogens, every year, a large proportion of cases remain uncharacterised. Here, we outline the key goals of MEVACP project and how they will be addressed.

### Materials and Methods

MEVACP aims to enhance the surveillance of meningitis in the African meningitis belt with specific tasks including:

- i) a systematic review and evaluation of molecular diagnostic assays targeting *Nme*, *Spn*, *Hinb* and *Streptococcus agalactiae*, the causative agent of group B strep. This will lead to the public dissemination of recommended standardised protocols. The last such review was undertaken in 2011 (1) and many innovative approaches have been published subsequently, including major advances in quantitative PCR (qPCR) methods;
- ii) a comprehensive characterisation of capsule biosynthesis genes from each of these pathogens, using available whole genome sequence (WGS) data. This will both enhance our understanding of genetic variation in capsule loci and aid the development and improvement of diagnostic assays with, for example, *in silico* testing of targets used in assays;
- iii) the design, construction, and implementation of a freely-accessible, publicly available online platform broadly targeting members of the community and allowing visualisation of meningitis outbreaks across the belt.

### Conclusion

Over 1.2 million cases of bacterial meningitis are estimated to occur worldwide every year, with incidence and case-fatality rates varying by region, country, pathogen and age group (2). Vaccines are available against the three most common bacterial causes of meningitis (*Nme*, *Spn* and *Hinb*); however, these vaccines do not protect against all types of each species. Effective surveillance of infections caused by these bacteria is therefore essential and MEVACP aims to advance progress in the surveillance of disease caused by these pathogens.

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## PO-014 - (EMGM2019-13306) - INVASIVE DISEASES DUE TO NEISSERIA MENINGITIDIS AND HAEMOPHILUS INFLUENZAE IN ITALY, 2017-2018

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### Introduction

The Italian Invasive Bacterial Disease (IBD) Surveillance System is based on mandatory reporting to the Ministry of Health and to the Italian Institute of Health (Istituto Superiore di Sanità (ISS)). ISS coordinates all the surveillance activities and hosts the National Reference Laboratories (NRL) for Invasive Meningococcal Disease (IMD) and Invasive *Haemophilus influenzae* Disease (IHD).

### Aims

To describe IMD and IHD from 2017 to 2018 in Italy.

### Materials and Method

Lab-confirmed IMD and IHD cases and collected samples were further analyzed.

### Results

The average annual incidence in 2017 and 2018 (preliminary data) of lab-confirmed IMD and IHD was 0.28/100.000 and 0.24/100.000, respectively. IMD showed the highest incidence in infants under 1 year of age (2.48/100.000) and in children 1-4-year-olds (0.77/100.000). The majority of IMD cases belonged to serogroup B (MenB, 43%), MenC (30%), MenY (18%) and MenW (8%). MenB is the main cause of IMD in children under 5 years of age (1.91/100.000 in infants <1 year and 0.45/100.000 in 1-4-year-olds) and adolescents/young adults aged 15-24 years (0.26/100.000). MenC incidence was 0.21 and 0.06/100.000 in 1-4 years children and 0.09 and 0.17/100.000 in 15-24 year old in 2017 and 2018, respectively. Intermediated resistance to penicillin G was found in 67% of MenC. One MenB was resistant to rifampicin and 1 MenC to ciprofloxacin. MenB clustered in 8 ccs (21% cc213, 19% cc41/44, 16% cc162) and 90% of MenC belonged to cc11. In 2018, an outbreak due to 5 Men B/cc11 occurred in Sardinia Region.

IHD showed the highest incidence in infants <1 year (1.84/100.000) and in patients ≥65 years (0.63/100.000). A slight increase in infants (1.71 in 2017 to 1.97 in 2018) and in the elderly were observed (0.61 to 0.65). The majority of cases were due to NTHi (76.1%), followed by capsulated isolates (Hib 11.5% and Hif 4.6%). NTHi and Hib were the main cause of IHD in infants. One case of Hia, Hic and Hie was reported. All isolates were susceptible to antimicrobials except for ampicillin (25.3% were resistant, with 15.6 % β-lactams producers and 9.8% BLNAR). A great genetic heterogeneity was found among NTHi isolates, conversely, capsulated strains were more clonal.

### Conclusion

IMD and IHD incidences remained quite stable. The cc11 was the prevalent among the meningococci and also associated to an outbreak of MenB. For IHD, most cases were sustained by NTHi, but Hib disease continues to occur.

## PO-015 - (EMGM2019-13321) - MENINGOCOCCUS AND HAEMOPHILUS INVASIVE ISOLATES IN SERBIA – A TEN-YEAR REPORT

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### Introduction & Aims

The aim of the study is to present data for meningococcus and Haemophilus invasive isolates collected in Serbia from 2009. to 2018.

### Materials and Methods

In Serbia, isolates and clinical material from suspected cases are requested to be sent to Meningococcus and Haemophilus reference laboratory (MHRL) for confirmation and further characterization as recommended by EUCAST. Collected meningococcus and Haemophilus isolates are identified with commercial systems, serogrouping is performed by slide agglutination, and minimal inhibitory concentrations (MICs) are assessed by Etests. Identification, genogrouping and finetype (PorA, FetA) determination for meningococcus isolates are performed with commercial PCR tests. In the near future, MHRL will start performing basic genotypic characterization on *H. influenzae* strains, also.

### Results

During the previous ten years, MHRL has collected 68 *N. meningitidis* and 24 *H. influenzae* isolates. Majority of IMD infections in Serbia, were caused by serogroup B (76%), followed by serogroup C (15%), Y (6%) and W135 (3%). Decreased susceptibility to penicillin was determined in certain number of meningococcus isolates. All isolates were susceptible to ceftriaxone, cefotaxime, ciprofloxacin and rifampicin. The incidence of *N. meningitidis* isolates was highest in the age group < 1 year, followed by the 1-4 years of age group.

Male-to female ratio in invasive *H. influenzae* disease was 2.14, with non b-to-Hib ratio of 2.43.

### Conclusion

According to the National Institute for Public Health – Belgrade, Serbia belongs to countries with a low IMD incidence rate. Obligatory vaccination against meningococcus is not introduced so far, and is only advised to persons traveling to “risk areas”. Vaccination against *H. influenzae* type b, is mandatory in Serbia since 2007. The number of *H. influenzae* (including Hib and NT) strains collected in MHRL so far, does not correspond to the expected number of cases, due to difficulties in mandatory clinical and laboratory reporting system.

Serbian MHRL is reporting its data to EMERT database, implements ECDC and EMGM recommendations regarding *N. meningitidis* and *H. influenzae* invasive disease including case definition guidelines, and has recently took part in external proficiency testing scheme for the first time.

### References

## PO-016 - (EMGM2019-13238) - EPIDEMIOLOGY OF INVASIVE HAEMOPHILUS INFLUENZAE DISEASE IN FINLAND, 2016-2018

Maija Toropainen (Finland)<sup>1</sup>

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### Introduction & Aims

Surveillance of invasive *Haemophilus influenzae* (Hi) disease (IHD) is needed for outbreak investigations and monitoring changes in disease epidemiology in relation to national vaccination policies. We report the epidemiology of IHD in Finland in 2016-2018.

### Materials and Methods

Notification of laboratory confirmed IHD is mandatory in Finland and all blood and cerebrospinal fluid isolates are requested to be sent to the National Reference Laboratory for species verification and further characterization. At the reference laboratory, all isolates from 2016-2018 were serotyped by latex-agglutination. Whole genome sequencing (Illumina) was used to study serotype f (Hif) isolates from year 2018 in more detail. Vaccination status of Hib cases were determined from the National Vaccination Register and/or hospital records.

### Results

During 2016-2018, altogether 231 laboratory-confirmed IHD cases were notified to the National Infectious Disease Register. The annual incidence varied from 1.3 per 100,000 population (69 cases) in 2016 to 1.6 (89 cases) in 2018. Fifty-eight percent (135/231) of the cases occurred among women. The median age of the patients was 68 years (range 0–97 years) and 65% were 60 years or older. Five (2%) cases occurred in children aged 0–4 years. All cases were culture-confirmed, mostly by blood culture (95%). The majority of cases (79.2%) were caused by non-typeable *H. influenzae* (NTHi) which caused IHD especially among elderly people (median age 71 years). Among the encapsulated isolates, Hif (12.6%) was the most common, followed by Hib (3.5%) and Hie (3.0%). All Hie and 86% of Hif and 63% of Hib cases occurred among adults, aged 27–79 years. Of the five cases among young children ( $\leq 5$  years), two were caused by NTHi, two by Hif, and one by Hib (unvaccinated 3-month-old child). Altogether 13 Hif cases (incidence 0.2 per 100,000 population) occurred in 2018, including a small family outbreak. The genomic relationship among the Hif isolates will be presented.

### Conclusion

During the past ten years, IHD caused by NTHi has increased in Finland from around 0.6 to 1.1 per 100 000 population. The majority of NTHi cases occurred among older people aged 60 years old and over. The incidence of Hif disease is slightly increasing. Due to high vaccination coverage rate, the incidence of invasive Hib disease has remained low since the early 1990's.

## PO-017 - (EMGM2019-13294) - INVASIVE HAEMOPHILUS INFLUENZAE ISOLATES IN GERMANY 2017 AND 2018: LABORATORY SURVEILLANCE REPORT

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### Introduction & Aims

The National Reference Laboratory for Meningococci and *H. influenzae* (NRZMHi) performs species confirmation, serotyping, and antibiotic resistance testing of invasive *H. influenzae* (Hi) isolates from Germany. The results complement the National notification data. Here, we present laboratory surveillance data from 2017 and 2018.

### Materials and Methods

Isolates from blood and cerebrospinal fluid (CSF) are defined as invasive and must be notified. Invasive isolates are submitted to the NRZMHi on a voluntary basis. Species confirmation is based on factor-dependent growth and analysis of the genes *fucK*, *ompP2*, and *ompP6*. Phenotypic serotyping is complemented by *bexA*-PCR. Susceptibility to ampicillin is analysed according to EUCAST by gradient agar diffusion. Nitrocefin tests are done on all isolates to detect  $\beta$ -lactamase-negative ampicillin resistance (BLNAR).

### Results

In the two years period 2017/2018, 1510 submissions were analysed; 1256 isolates derived from patients with invasive infections. Hi was confirmed in 1230 cases. 1165 isolates derived from blood, 52 from CSF only, and six from both blood and CSF.

The NRZMHi transmits its results to the local health authorities in charge. In the statutory notification system 805 and 843 invasive Hi infections were registered in 2017 and 2018, respectively. Thus, a coverage of 73% can be assumed for 2017 and 75% for 2018.

The majority of blood or CSF isolates were non-typeable *H. influenzae* (NTHi, 1039 isolates, 84.5 %), followed by Hif as the most frequent capsular serotype (120 cases; 9.8%). Hib and Hie showed the same frequency (29 cases each; 2.4 %). Six Hia (0.5%), and no Hic or Hid were submitted. Remarkably, five Hia were found in 2018, whereas in previous years the number of Hia isolates rarely exceeded two. Among the analyzed cases, patients most affected were aged > 40 years (1068 cases; 86.8 % of all cases). A significant percentage of cases (81 cases; 6.6 %) was found in children aged <5 years.

Ampicillin susceptibility revealed 225 (20.3 %) ampicillin resistant Hi (MIC > 1  $\mu$ g/ml), 78 (69.3 %) showed  $\beta$ -lactamase production.

### Conclusion

The data from the laboratory surveillance of *H. influenzae* in Germany 2017/2018 reflect the epidemiology as observed in previous years. NTHi was by far the predominant type affecting mostly elderly patients. The occurrence of 5 Hia isolates is unusual and may reflect a trend observed in other countries. However, this finding needs further observation. Antibiotic resistance levels were comparable to previous years.

### References

**PO-018 - (EMGM2019-13203) - INVASIVE HAEMOPHILUS INFLUENZAE DISEASES IN POLAND, 1997-2018**

Alicja Kuch (Poland)<sup>1</sup>; Izabela Waško (Poland)<sup>1</sup>; Marlena Kiedrowska (Poland)<sup>1</sup>; Patrycja Ronkiewicz (Poland)<sup>1</sup>; Agnieszka Gołębiowska (Poland)<sup>1</sup>; Izabela Wróbel (Poland)<sup>1</sup>; Waleria Hryniewicz (Poland)<sup>1</sup>; Anna Skoczyńska (Poland)<sup>1</sup>

1 - National Reference Centre for Bacterial Meningitis

**Introduction & Aims**

*Haemophilus influenzae* is responsible for respiratory tract infections as well as invasive infections as e.g. meningitis, sepsis and epiglottitis. The majority of isolates are noncapsulated (non-typeable, NTHI) but encapsulated are also present and belong to six capsular types from a to f. The mass vaccination against Hib has started in Poland in 2007.

The aim of the study was to characterize Polish population of invasive *H. influenzae* isolated between 1997 and 2018.

**Materials and Methods**

The study was performed on all *H. influenzae* isolates collected between January 1997 and December 2018 by the National Reference Centre for Bacterial Meningitis during the routine monitoring of bacterial invasive infections in Poland. All strains were identified according to standard procedures. PCR reactions were run to confirm species identification, serotype determination, and to detect capsule-specific genes and changes in *ftsI* gene. MICs of antimicrobials were evaluated by microdilution methods and E-test. Beta-lactamase production was detected by nitrocefin assay.

**Results**

During the study 742 invasive *H. influenzae* isolates were collected. Until 2007 most of them (73.5%) were recovered from children below 5 years and were characterized as Hib (92%). *H. influenzae* serotype f (Hif) and non-typeable isolates (NTHI) were responsible for 1.2% and 6.5% of cases, respectively. Ampicillin resistance was mostly associated with beta-lactamase production (13.0%) and BLNAR phenotype [beta-lactamase positive, ampicillin resistant] (1.2%).

Between 2008 and 2018, most of *H. influenzae* isolates were recovered from patients above 5 years (76.1%). NTHI were responsible for 79.4% of infections, followed by Hib (11.5%), Hif (6.2%) and *H. influenzae* serotype e (2.4%). Two isolates of serotype a were for the first time detected in 2017 (0.5%). Ampicillin resistance was correlated with BLNAR phenotype (12.1%) and beta-lactamase production (11.5%). There were only five isolates with BLPACR phenotype [beta-lactamase positive amoxicillin-clavulanic acid resistance] (1.3%) between 2010 and 2018.

**Conclusion**

After introduction of Hib vaccine into the Polish National Calendar a significant decrease of infections due to *H. influenzae* type b was observed. At the same time, a shift in patients age toward elderly and an increase of infections caused by non-Hib isolates were found. NTHI, Hif, Hie and Hia are becoming emerging serotypes therefore should be monitored.

## PO-019 - (EMGM2019-13268) - EPIDEMIOLOGY OF INVASIVE HAEMOPHILUS INFLUENZAE DISEASE IN ENGLAND: NATIONAL SURVEILLANCE, 2017-2018

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### Introduction & Aims

Historically, *Haemophilus influenzae* serotype b (Hib) was the most common cause of invasive *H. influenzae* (Hi) disease and a major cause of acute bacterial meningitis, particularly in children <5 years old. Following the introduction of the Hib conjugate vaccine to the national childhood immunisation programme in 1992, the number of Hib cases initially fell dramatically, but started increasing in 1998. This increase was reversed following the introduction of a booster dose from 2003 onwards and Hib cases have remained very low since then. Since 2002, invasive disease caused by non-capsulated strains (NTHi) has been increasing steadily, and NTHi have caused the greatest proportion of disease almost every year since 1994. Cases caused by Hif and Hie capsulated strains have also been increasing, although in smaller numbers.

Aims: To describe the current (2017-2018) epidemiology of invasive disease Hi in England.

### Materials and Methods

Public Health England (PHE) conducts national surveillance of invasive Hi disease in England, including the species confirmation and serotyping of cultures.

### Results

During January 2017 to December\* 2018, 1462 cases of invasive Hi disease were reported to PHE. To date 79.7% have been serotyped (n=1165), of which non-capsulated strains (NTHi) were predominant (83.5%; 973/1165). Serotype f (Hif) comprised 63.5% of the remaining encapsulated Hi (122/192); a further 20.8% (40/192) were Hie, 9% (18/192) were Hib, and 6.3% (12/192) were Hia. There were no cases of Hic or Hid during this period.

The median age of cases varied by serotype: from 44 years (IQR=0-55 years) for Hib, 56 years (IQR=1.5-69.5 years) for Hia, 66 years (IQR=55-79 years) for Hif, 68 years (IQR=34-82 years) for NTHi, and 76.5 years (IQR=68.5-85 years) for Hie.

Incidence varied by serotype and age-group; of note, the incidence of invasive Hib disease was 0.02 cases per 100,000 which was a recorded low, with only 5 cases among the vaccine-eligible population in the two-year period. NTHi incidence was 0.87 per 100,000 (95% CI=0.82-0.93), with the highest incidence in neonates (38.7 per 100,000 (95% CI=28.2-51.8)).

There has been a sustained year on year increase in invasive NTHi (glm=1.061, 95% CI=1.053-1.069), Hie (glm=1.066, 95% CI=1.049-1.083) and Hif (glm=1.064, 95% CI=1.052-1.075) disease between 1990 and 2017.

### Conclusion

NTHi strains continue to cause the majority of invasive Hi disease in England. Of the capsulated strains, Hif and Hie are still the most common, and Hib cases remain very rare.

### References

\* The abstract contains data up to November 2018 which will be updated for the presentation

## PO-020 - (EMGM2019-13257) - EPIDEMIOLOGY OF INVASIVE (BLOOD/CSF) HAEMOPHILUS INFLUENZAE IN SCOTLAND 2008-2018

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### Introduction & Aims

In Scotland, the Hib vaccine was introduced in 1992, with booster campaigns in 2003 and 2006. Enhanced surveillance is undertaken on all invasive *H. influenzae* cases. The Scottish Microbiology Reference Laboratory Glasgow (SMiRL - Glasgow) receives all isolates from invasive disease from routine diagnostic laboratories in Scotland. This study describes the epidemiology of invasive (blood/CSF) *H. influenzae* isolates referred to SMiRL over the period 2008-2018.

### Materials and Methods

Referred isolates are characterised on the basis of their capsular serotype and genotypically by Multilocus Sequence Typing (MLST; described as Sequence Types (ST)).

### Results

Over the ten year period we received 587 isolates for typing. This comprised mostly blood cultures (n=578) with majority from patients in the >40 year age group (n=422), with 66 isolates from <5 years of age. The most common serotype detected was type F (n=54) with the majority of isolates classed as non-typeable (NTHi) (n=445). There has been an increasing proportion of NTHi isolates since 2008 (74%) rising to 91% in 2018. In terms of ST's, the level of diversity is very high with multiple ST's reported. The most frequent ST reported in any one year was ST124 (mainly serotype F), albeit with relatively low levels (n range from 4-10 in any one year). The exception being 2017 which saw ST103 (n=9 and NTHi) relatively increase in numbers.

### Conclusion

The efficacy of the Hib vaccine continues to be demonstrated with relatively small numbers of cases each year due to this serotype. However, invasive *H. influenzae* disease is now characterised by an increasing proportion of NTHi isolates with a diverse genotypic background affecting patients over the age of 40 and relatively few CSF isolates.

## PO-021 - (EMGM2019-13280) - HAEMOPHILUS INFLUENZAE INVASIVE DISEASE IN PORTUGAL, 2017-2018 - WHAT HAVE BEEN CHANGING AFTER HIB VACCINE IMPLEMENTATION?

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1 - Haemophilus influenzae Reference Laboratory-National Institute of Health Dr. Ricardo Jorge

### Introduction & Aims

*Haemophilus influenzae* is a frequent colonizer of the upper airways that can easily spread through respiratory tract leading to invasive infections in both children and adults. *H. influenzae* serotype b (Hib) has been prevented by vaccination, in Portugal, since 2000, but the emergence of non-typeable isolates (NTHi), as well as non-b serotypes responsible for invasive disease have been documented.<sup>1,2</sup>

We aim to characterize *H. influenzae* invasive isolates recovered in Portugal, during the last two years and compare results from previous studies.<sup>1,2</sup>

### Materials and Methods

As part of a laboratory-based surveillance system, 108 invasive *H. influenzae* were received at the National Reference Laboratory for *Haemophilus influenzae* for characterization. Capsular status was identified by PCR with primers and conditions described in the literature.<sup>3</sup> Antibiotic susceptibility was determined by microdilution, according to EUCAST guidelines.<sup>4</sup>  $\beta$ -lactamase production was assessed with nitrocefin. Genetic relatedness among the isolates was examined by MLST as previously described.<sup>5</sup> Sequences were analysed and submitted to the MLST website (<https://pubmlst.org/hinfluenzae/>) for assignment of the sequence type (ST). goeBURST analysis was performed using the PHYLOViZ platform.<sup>6</sup>

### Results

Among 108 *H. influenzae* isolates, 90% were from blood, and 66% were from adults. Serotyping revealed that 74% were NTHi (80/108) and 26% (28/108) were capsulated isolates. Among capsulated isolates, 10.7% were Hia, 60.7% Hib, 10.7% Hie and 7.1% Hif. Most of the isolates were susceptible to the antibiotics studied, with the exception of 12.9% (14/108) ampicillin resistant by  $\beta$ -lactamase producing and 9.6% (9/94) that correlates with BLNAR phenotype (MIC $\geq$ 1 to ampicillin and co-amoxiclavate).

MLST profiles revealed, as expected, high genetic variability (74.1%), with 23 different STs among 31 NTHi isolates tested. In opposition, encapsulated isolates were clonal with all Hia assigned to CC23, Hib assigned to CC6, (ST6 and ST1231), Hie to CC18, and Hif to CC124.

### Conclusion

After vaccine implementation and the great decline observed in Hib invasive disease (from 81% in 1989-2001 to 13% in 2002-2010),<sup>1,2</sup> we are now concerned about Hib isolates (16%) that still in circulation in our country, affecting mostly children (88%), and accounting for 47% of vaccine failures. In addition, Hia increased, from 2% in the last period of five years (2012-2016) to 3% in this two years period (2017-2018), with all isolates from infants, up to two years old.

It is important to continue the surveillance of *H. influenzae* invasive disease to monitor the true magnitude of these problems and develop public health prevention strategies.

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## PO-022 - (EMGM2019-13325) - HAEMOPHILUS INFLUENZAE IN GREECE: 16 YEAR OF CONTINUOUS SURVEILLANCE (2003-2018).

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### Introduction & Aims

Due to mass vaccination programs implemented in all European countries, the incidence of meningitis due to *H.influenzae* type b remains low. However, concern exists for the long-term effectiveness and possible disease replacement by other *H. influenzae* serotypes. Therefore, continuous surveillance and monitoring is of high public health importance

### Aim

The study presents a 16 year continuous surveillance of meningitis cases due to *H. influenzae* in order to monitor possible serotype replacement.

### Materials and Methods

A total of 127 *H. influenzae* cases were recorded during the 16 year period (2003-2018) and confirmed either by culture or PCR. Strains were cultured in chocolate agar and DNA was extracted from clinical samples (CSF and whole blood) (MagCore HF16 Automated Nucleic Acid Extractor, RBC Bioscience). Two multiplex-PCR assays were employed for the identification of *H.influenzae* (*hel* gene) and Hib (*bexA* gene), and further identification of serotypes a, c, d, e, f by a multiplex-PCR assay.

### Results

Of 127 *H. influenzae* laboratory confirmed cases during the study period, the majority (95/127; 74.8%) were solely confirmed by PCR assays, while 25.2% (32/127) were culture-confirmed.

Forty-eight (48) cases were caused by Hib, while 77 cases were caused by non-b *H. influenzae* (average incidence 0.021 and 0.038 per 100.000 respectively). Among them, serotype f was identified in three cases and serotype a in only 2 cases, while the remaining were non-typeable (NTHi).

An increase in NTHi cases was observed the past 8 years (2011-2018) (61 cases) compared to the previous period 2003-2010 (15 cases), mainly affecting older ages (>50 years). Few Hib cases are identified annually, mainly observed among infants <1 year (18.1%; 23/127) and 1-4 years (7.9% ;10/127). Although the majority of NTHi cases were recorded in adults >30 years of age (31.5%; 40/127), 5 cases were recorded during 2018 for the first time at the age group 1-4 years.

### Conclusion

Despite reduction of Hib disease, the increase in NTHi cases since 2011, has led to an increased awareness and closer surveillance for *H.influenzae* infections. Molecular techniques play an important role in diagnosis and typing of culture negative cases, allowing better epidemiological monitoring.

**PO-023 - (EMGM2019-13213) - EMERGING MENINGOCOCCI REPRESENTING ST-9316 IN POLAND**

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**Introduction & Aims**

The purpose of the study was to characterize *Neisseria meningitidis* isolates, belonging to ST-9316, responsible for invasive meningococcal disease (IMD) in Poland since 2009.

**Materials and Methods**

The study encompassed invasive meningococcal isolates collected since 2009, when MLST, *porA* and *fetA* typing has become a part of routine activities of the NRCBM. Minimal inhibitory concentrations were assessed by Etests or M.I.C.Evaluators and interpreted according to the EUCAST recommendation. Calculations were estimated for ST-9316 isolates against all meningococci.

**Results**

Between 2009 and 2018 1590 isolates has been registered and typed, including 71 (4.5%) belonging to ST-9316. Until 2014, ST-9316 meningococci represented a small proportion of all isolates (n=14, 1.4%) but this has changed significantly over the following years and in the period 2015-2018 their percentage increased 7 times (n=57, 10.2%, p<0.0001).

Majority of cases (n=48, 67.6%) concerned children below 4 years old of which 27 were infants.

Isolates belonged mainly to serogroups B (n=41, 57.7%) and W (n=20, 28.2%), followed by C (n=6, 8.4%), and Y (n=4, 5.6%).

Case fatality ratio (CFR) accounted for 8.4% and was similar to overall CFR for IMD in period 2009-2018 (9.2%). All fatal cases were caused by serogroup W except one isolate of MenB.

All isolates were susceptible to 3rd generation cephalosporins, chloramphenicol, ciprofloxacin and rifampicin. Decreased susceptibility to penicillin characterized 75.7% of ST-9316 isolates in comparison to 28.3% for all tested meningococci 2009-2018.

Analysis of *porA* and *fetA* revealed very high homogeneity; 80.3% of isolates possessed combination of VR1/VR2 5-2/10-1 and 61.4% of F5-8 FetA variant.

Interestingly, since 2009 there were 24 isolates which differed by one or two alleles from ST-9316; about half of them appeared for the first time.

**Conclusion**

Isolates of ST-9316, especially of serogroups B and W, are becoming more and more common.

The case fatality ratio connected with this sequence type was similar to general ratio observed for IMD in Poland, however almost all fatal cases were due to serogroup W.

Molecular analysis of *porA* and *fetA* showed that they constituted a very homogenous group, however temporal changes, single and double locus variants, have been constantly observed.

Antimicrobial susceptibility tests indicated that ST-9316 isolates are susceptible to most antibiotics used in IMD therapy, however percentage of nonsusceptibility to penicillin was worrying high.

Considering the increasing prevalence of ST-9316, the situation should be carefully monitored.

**References**

## PO-024 - (EMGM2019-13196) - ENHANCED SURVEILLANCE OF 4CMENB BY THE MENINGOCOCCAL ANTIGEN TYPING SYSTEM IN ENGLAND, THE FIRST 29 MONTHS

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### Introduction & Aims

4CMenB vaccine (Bexsero®) was introduced into the UK national infant immunisation schedule in September 2015 in a reduced 2+1 schedule with a catch up campaign for those born in May 2015. 4CMenB contains four main antigens: fHbp (factor H-binding protein), NHBA (Neisserial heparin-binding antigen), NadA (*Neisseria* adhesin A), and an outer membrane vesicle with the immunodominant Porin A (PorA). Invasive MenB isolates are diverse and this is reflected in the genetic distribution and degree of expression of the 4CMenB antigens. Protection afforded by PorA is limited to meningococci expressing P1.4. The remaining 4CMenB antigens provide some cross-protection depending on both the antigenic similarity and level of expression of the respective antigens on the infecting meningococcus. The Meningococcal Antigen Typing System (MATS) combines these properties to provide a relative potency (RP), versus a reference strain, for each of the three antigens for a given MenB isolate. If the RP exceeds a threshold level, then the strain is considered covered (MATS-positive) for the corresponding antigen. To supplement studies of vaccine effectiveness, the current study presents the results of MATS analyses of isolates from vaccine-eligible infants/children between 1<sup>st</sup> September 2015 and 31<sup>st</sup> January 2018.

### Materials and Methods

Following the introduction of 4CMenB, all invasive isolates received by the Public Health England Meningococcal Reference Unit undergo whole genome sequencing (WGS), and all MenB invasive isolates undergo MATS analysis.

### Results

There were a total of 216 laboratory confirmed cases of IMD in infants eligible for the MenB vaccine during the first 29 months of surveillance. MenB accounted for 145 (67%) of cases. Cultures were received from 84 (58%) of the MenB cases and thus were available for MATS analysis. Among the culture-positive cases, 24, 32, 23 and 5 vaccinees had received zero, one, two or three doses of vaccine, respectively. Of the respective isolates, 15 (63%), 19 (59%), 13 (57%) and 2 (40%), respectively, were MATS-positive. For cases reported in children who had received 3 doses, one was MATS-positive for NHBA only and the other was MATS-positive for fHbp and NHBA.

### Conclusion

National surveillance has identified a small number of culture-confirmed MenB cases in infants immunised with 1, 2 or 3 doses of 4CMenB. Only around half the isolates were MATS positive and, therefore, potentially vaccine preventable. Two culture-confirmed cases occurred in three-dose vaccinees in whom the infecting meningococcus was considered covered. These cases, the meningococci responsible, and how these data will aid our understanding of vaccine coverage and correlates of protection will be discussed.

## **PO-025 - (EMGM2019-13197) - THE GLOBAL IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES ON INVASIVE PNEUMOCOCCAL DISEASE INCIDENCE IN CZECH REPUBLIC**

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### **Introduction & Aims**

A sensitivity of the surveillance in Czech Republic has improved continuously, as confirmed by capture-recapture analysis. Pneumococcal conjugate vaccine (PCV) is available in the Czech Republic since 2005 ((PCV7). PCV was implemented into the National Immunisation Program. The surveillance of invasive pneumococcal disease (IPD) was implemented in the Czech in 2010 (PCV10 and PCV13 equally).

### **Materials and Methods**

The surveillance of IPD started in the Czech Republic since 2008 and the EU case definition of IPD was adopted. The typing of *S. pneumoniae* was performed in the NRL by the classical Quellung reaction and from 2013 by the PCR method.

### **Results**

In 2017, altogether 444 cases of invasive pneumococcal disease (IPD) were entered in the surveillance database (integrating NRL and EPIDAT data). The overall incidence of IPD increased from 3.1/100 000 population in 2016 to 4.2/100 000 in 2017. This increase was mainly due to a higher incidence of IPD in children under 1 year of age, reaching 3.6/100 000, which represents nearly four cases per 100 000 children of this age group, i.e. four times the figure of 2016 (0.9/100 000, i.e. nearly 1 case per 100 000). The most afflicted age group was again 65 years and over, with 238 cases reported, corresponding to an incidence of 12/100 000.

Twenty-two cases of IPD occurred in persons previously vaccinated with pneumococcal vaccines, five of whom were children aged 0-4 years and three were five- to nine-year-olds. The number of vaccinated increased in the age group 65 years and over.

Three cases of IPD caused by a vaccine serotype were reported in previously vaccinated children under five years of age. The overall case fatality rate decreased from 20.4 % in 2016 to 17.8 % in 2017. Seventy-nine deaths due to IPD were reported in 2017, i.e. 13 deaths more than in 2016. The most afflicted age group was 65 years and over, with 45 deaths due to IPD and a case fatality rate of 18.9 %. No fatal case occurred in children under five years of age. Four hundred and twenty (95 %) isolates of *Streptococcus pneumoniae* recovered from 444 cases of IPD were referred to the NRL for typing. All cases of IPD were reported to the EPIDAT database.

Twenty cases of IPD were diagnosed from clinical specimens by the PCR method alone. Serotype was not identified in 31 cases; in seven cases because of failure to refer the isolates to the NRL.

### **References**

**Supported by Ministry of Health of the Czech Republic, grant nr.17-29256A. All rights reserved.**

Session: Oral Session II

Room: Auditorium I

Epidemiology and Surveillance II

**OC - (EMGM2019-13214) - CURRENT STATUS OF SEROGROUP W MENINGOCOCCAL DISEASE IN POLAND**

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**Introduction & Aims**

*Neisseria meningitidis* serogroup W (MenW) has for many decades been an infrequent cause of meningococcal disease; however, following a MenW outbreak after the Hajj in 2000, and recently, MenW disease started to be common in some regions, including Europe. The aim of the study was to describe MenW epidemiology in Poland between 2014–2018.

**Materials and Methods**

The study encompassed all invasive meningococcal cases confirmed by the National Reference Centre for Bacterial Meningitis (NRCBM) between 2014 and 2018. The isolates were reidentified and characterized by susceptibility testing, MLST analysis, *porA* and *fetA* sequencing. A PCR technique was used for meningococcal identification directly from clinical materials in the case of a negative culture.

**Results**

From 2014–2018, 917 IMD cases were reported to the NRCBM. Among them, 98.9% had a serogroup result, of which 44 (4.8%) were MenW. Between 2014 and 2017 MenW percentage was 3.5% (range from 2.2 to 4.4%), however in 2018 increased significantly to 9.8% ( $p < 0.001$ ). Half of the cases occurred in children under three years old and the median age was 11 years. General male to female ratio was 1.9 but in children, under three years old it was 10.0. Case fatality ratio (CFR) for MenW cases with known outcome was 35.7% (10/28), compared to CFR of app. 10-12% for serogroups B and C. The highest CFR, 100% (5/5) was among adults aged 65 and over. MLST results to the level of ST and clonal complex (cc) were available for 28 and 34 isolates, respectively. Among them, two groups of isolates were found. First one consists isolates of ST-9316 and its single or double locus variants (73.5%), including one isolate of ST-167cc. Almost all of these isolates had VR1/VR2 *porA* combination of 5-2/10-1 and *fetA* variant F5-8. The second group encompassed isolates of ST-11cc (26.5%) with *porA* 5/2 and *fetA* F1.1, except one isolate. In infants, all ten cases were caused by meningococci of ST-9316 and its variants. CFR for ST-9316 cases with known outcome was 45.5%, whereas for ST-11cc cases, 40.0%.

**Conclusion**

In 2018 the NRCBM notified a significant increase in MenW disease in Poland. Based on other countries experience this trend needs to be carefully monitored.

## OC - (EMGM2019-13264) - EPIDEMIC POTENTIAL OF THE EMERGING MENINGOCOCCAL SEROGROUP W SEQUENCE TYPE-11 CLONAL COMPLEX: A MATHEMATICAL MODELING STUDY

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### Introduction & Aims

The recent emergence of strains belonging to the meningococcal serogroup W (MenW) sequence type-11 clonal complex and descending from the South American sub-lineage (MenW:cc11) has caused increased disease in a number of European countries (1–5). However, the epidemiological characteristics of MenW:cc11 have not yet been quantified.

### Materials and Methods

We designed a mathematical model of MenW transmission, carriage, and infection (6) to analyze the recent epidemiology of invasive disease caused by MenW:cc11 strains and by other MenW strains in England (1,2) and in France (3). Using state-of-the-art statistical inference methods (7), we fitted that model to age-stratified incidence data to estimate the transmissibility and the invasiveness of MenW:cc11.

### Results

During the epidemiological years 2010/11–2014/15 in England, the transmissibility of MenW:cc11 relative to that of non-MenW:cc11 was estimated at 1.20 (95% confidence interval: 1.15 to 1.26). The invasiveness of MenW:cc11 relative to that of non-MenW:cc11 was also found to exceed unity and to increase with age, with point estimates ranging from 4 in children aged 0–4 years to 19 in adults aged  $\geq 25$  years. In the period 2015/16–2017/18 that followed the introduction of the MenACWY vaccine in adolescents aged *ca.* 14 years and of the 4CMenB vaccine in infants, the observed cases of MenW disease were lower than those predicted by counterfactual model simulations of no vaccination. Based on the observed cases of disease during 2012–2016, the spread of MenW:cc11 carriage was estimated to have started in late 2011 (95% confidence interval: early 2011 to mid-2012) in France.

### Conclusion

Our study provides the first estimates of MenW:cc11 invasiveness and transmissibility. Such estimates may be useful to anticipate changes in the epidemiology of MenW and to adapt vaccination strategies.

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## OC - (EMGM2019-13209) - EVALUATION OF THE DEMOGRAPHY RECONSTRUCTION AND EPIDEMIC BEHAVIOR OF C:P1.5-1,10-8:F3-6:ST-11(CC11) NEISSERIA MENINGITIDIS ISOLATES CIRCULATING IN ITALY

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### Introduction & Aims

*Neisseria meningitidis* causes severe invasive disease (IMD) and outbreaks worldwide. In Italy, an outbreak due to the hypervirulent C:P1.5-1,10-8:F3-6:ST-11(cc11) strain of the serogroup C has caused several IMD clusters and a major outbreak in Tuscany in 2015-2016 and smaller outbreaks. We evaluated the evolutionary demography and epidemic behavior of C:P1.5-1,10-8:F3-6:ST-11(cc11) strain between 2012 and 2017, using a Bayesian method.

### Materials and Methods

One hundred and one meningococci belonging to the C:P1.5-1,10-8:F3-6:ST-11(cc11) genotype and two C:P1.5-1,10-8:F3-6:ST-2780(cc11), collected within the National Surveillance System of IMD in Italy from 2012 to 2017 were analyzed. Among the 103 isolates, 39 belonged to the "Tuscany-outbreak strain". The population dynamics were analyzed by a relaxed molecular clock and Bayesian skyline plot (BSP) model, implemented in BEAST. The parameter  $R_0$ , indicating the mean number of secondary cases generated by a single primary case, was calculated through BEAST under the Birth Death Basic Reproductive number model.

### Results

The analysis of the population dynamics on the whole dataset showed a decrease in the effective number of infections between 2010 and the end of 2012, followed by a growth between 2013 and 2016. The basic reproductive number  $R_0$ , estimated on the whole dataset, reported a mean value of 1.27 – 1.31 (95% HPD: 1.01 – 1.6), consistently with the different priors distributions selected. The estimation of  $R_0$  obtained after excluding the "Tuscany outbreak strains", was 1.23 – 1.27 (95% HPD: 0.9 – 1.6). According to the tree topology, the Italian isolates belonging to the clade that did not include the "Tuscany outbreak strains" showed  $R_0 = 1.26 – 1.31$  (95% HPD: 0.83 – 1.8). The estimation performed on the clade consisting of 55 isolates (including also the "Tuscany outbreak strains"), gave a mean  $R_0$  of 1.33 – 1.39 (0.91 – 1.9).

### Conclusion

Phylogenetic methods can improve knowledge of the temporal dynamics of an outbreak and help in predicting the likely course of the epidemic. The population dynamics showed a growth in the effective number of infections between the 2013 and 2016, in agreement with epidemiological data. The  $R_0$  estimated for the Italian strains is low, and consistent with those estimated in the literature for serogroup C meningococcal infection, suggesting that reactive vaccination may be effective in outbreak control.

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## OC - (EMGM2019-13267) - CHARACTERIZATION OF U.S. UROGENITAL AND EXTRAGENITAL MENINGOCOCCAL ISOLATES COLLECTED THROUGH THE ENHANCED GONOCOCCAL ISOLATE SURVEILLANCE PROGRAM (EGISP)

Caelin Potts (United States of America)<sup>1</sup>; Fang Hu (United States of America)<sup>1</sup>; Susanna Schmink (United States of America)<sup>1</sup>; Melissa Whaley (United States of America)<sup>1</sup>; How-Yi Chang (United States of America)<sup>1</sup>; Adam Retchless (United States of America)<sup>1</sup>; Sara Oliver (United States of America)<sup>1</sup>; Sancta St Cyr (United States of America)<sup>1</sup>; Laura Quilter (United States of America)<sup>1</sup>; Susan Hariri (United States of America)<sup>1</sup>; eGISP Working Group . (United States of America)<sup>1</sup>; Xin Wang (United States of America)<sup>1</sup>

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### Introduction & Aims

In 2015, two U.S. cities noted an increase in the detection of *Neisseria meningitidis* urethritis cases. The majority of cases reported during 2015-16 were caused by non-groupable *N. meningitidis* that belonged to the “U.S. NmNG urethritis clade” within the hypervirulent sequence type 11 clonal complex (CC11). To monitor the urethritis meningococcal strains and assess potential modes of transmission, we characterized urogenital and extragenital meningococcal isolates collected in sexually transmitted disease (STD) clinics participating in an enhanced Gonococcal Isolate Surveillance Program (eGISP).

### Materials and Methods

eGISP collects suspected *N. meningitidis* isolates from 11 STD clinics nation-wide. Suspected *N. meningitidis* isolates are defined as isolates that have a colony morphology consistent with *Neisseria* species by culture but are negative for *Neisseria gonorrhoeae* by nucleic acid amplification testing. Isolates were cultured from urethral swabs (from symptomatic males) and cervical swabs (from symptomatic females or females exposed to *N. gonorrhoeae*), as well as pharyngeal and rectal swabs from asymptomatic and symptomatic persons reporting sexual exposure at those anatomic sites. Suspected *N. meningitidis* isolates collected from November 2017 to November 2018 were tested by real-time PCR, slide agglutination, and/or whole genome sequencing (WGS) to determine the species and serogroup. Genome diversity of meningococcal strains was assessed by WGS.

### Results

We obtained 962 suspected *N. meningitidis* isolates and 89.6% (862) were confirmed to be *N. meningitidis*. Of the 862 confirmed, 6.3% (54) were urethral, 1.6% (14) were rectal, and 92.1% (794) were pharyngeal isolates. Urethral isolates were detected from eGISP sites in eight states and were predominantly NmNG (92.6%, 50); 1 NmB, 2 NmC, and 1 NmZ were also detected. 76.0% (38) of the NmNG urethral isolates were CC11, with a molecular profile consistent with the NmNG urethritis clade; additional CCs were also detected (CC41/44, CC35, CC198, CC23, CC32 and CC53). The rectal isolates were predominantly NmNG (85.7%, 12) belonging to CC41/44, CC1157, CC198, CC32, CC35 and CC750; none were CC11. The majority of pharyngeal isolates were NmNG (61.3%, 487) or serogroup B (32.3%, 257) by rt-PCR, but other serogroups were also detected (16 NmC, 3 NmW, 6 NmX, and 25 NmY).

### Conclusion

Meningococcal urethritis cases caused by the NmNG urethritis clade continue to be detected after 2015, albeit with lower numbers of cases observed, suggesting ongoing transmission. Continued surveillance will improve our understanding of meningococcal urethritis in the United States.



Session: Oral Session III

Room: Auditorium I

Clinical aspects

### **OC - (EMGM2019-13258) - PERSISTENCE REPORTING OF ABDOMINAL PRESENTATIONS AND NON-MENINGEAL FORMS OF INVASIVE MENINGOCOCCAL DISEASE**

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#### **Introduction & Aims**

Early presentations of invasive meningococcal disease (IMD) may be atypical and abdominal early presentations have been recently reported in particular with the emerging serogroup W isolates of the clonal complex ST-11. These isolates are derived from the expanding South American UK strain. IMD then evolves most frequently to meningococemia and/or meningitis. However, non-meningeal forms of IMD are also reported with isolates of NmW/cc11. We aimed here to describe the recent trends of these early symptoms and forms in France between 2014 and 2018.

#### **Materials and Methods**

The database of the National Reference Centre for meningococci in France was screened for the period 2014 to 2018 for early abdominal presentations during the first 24 hours of the onset of IMD. We also screened the database for non-meningeal forms on the basis of the detection of *Neisseria meningitidis* in other body fluids than blood and CSF (articular fluids, pericardic fluid and pleural fluids).

#### **Results**

In France, from 2014 to 2018, 99 cases with early abdominal presentations were collected. Of which, 32 W serogroup, 31 C serogroup, 22 B serogroup, 12 Y serogroup and 2 X serogroup. These cases were associated with high fatality rate of 33% versus 10% in all cases of IMD. Abdominal pain was the most frequent symptom (67%), then gastro-enteritis (22%) and diarrhea only (11%).

We also identified 80 cases of non-meningeal forms (age median 31.4 and 1.2 male to female ratio). Serogroup C was the most frequent among non-meningeal form (41%) followed by serogroup B (24%) and serogroup W (21%) and serogroup Y (10%). Arthritis was the most encountered non-meningeal form (92%). Most of serogroup W isolates were linked to the South American UK strain as determined by whole genome sequencing.

#### **Conclusion**

These data suggest continuous increase of early atypical presentations and non-meningeal forms of IMD due to NmW/cc11 that requires improving awareness and highlights the need for preventive strategies by vaccination.

#### **References**

## OC - (EMGM2019-13242) - CLINICAL PICTURE AND SEVERITY OF SEROGROUP W MENINGOCOCCAL DISEASE DIFFER FROM THAT OF DISEASE CAUSED BY OTHER SEROGROUPS, THE NETHERLANDS

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### Introduction & Aims

A steep increase of invasive meningococcal serogroup W (IMD-W) cases caused by sequence type-11 clonal complex (cc11) has occurred in the Netherlands since October 2015. Our aim was to compare the clinical picture and disease outcome of IMD-W with other serogroups when adjusting for case characteristics.

### Materials and Methods

All microbiological laboratories in the Netherlands submit *Neisseria meningitidis* isolates from blood, cerebrospinal fluid or other normally sterile material to the Netherlands Reference Laboratory for Bacterial Meningitis for typing. Clinical data of IMD cases are reported through the mandatory notification system. We included IMD cases reported from January 2015 up to June 2018. We assessed clinical manifestation and symptoms at disease onset as indicators for the clinical picture and calculated case fatality rates (CFR). Logistic regression was performed to compare clinical manifestations and mortality of IMD-W to IMD caused by meningococci serogroup B, Y, or C, adjusting for age, gender and comorbidities.

### Results

A total of 565 IMD cases were reported, of which 204 were IMD-W, 270 IMD-B, 63 IMD-Y, and 26 IMD-C. Compared to other serogroups, IMD-W patients were diagnosed more often with septicemia (W: 46%, B: 25%, Y: 35%, C: 28%) or pneumonia (W: 12%, B: 2%, Y: 19%, C: 4%), and less often with meningitis (W: 17%, B: 57%, Y: 22%, C: 32%,  $p < 0.001$ ). IMD-W cases presented more often with respiratory symptoms (W: 45%, B: 15%, Y: 32%, C: 21%,  $p < 0.001$ ). There was no significant difference in having at least one gastrointestinal symptom between serogroups ( $p = 0.056$ ). 16% of IMD-W patients presented with diarrhea without IMD-specific symptoms, like petechiae and neck stiffness (B: 5%, Y: 11%, C: 8%,  $p = 0.061$ ). The CFR of IMD-W was 17% (32/194), significantly higher than for IMD-B with 3.8% (10/263,  $p = 0.004$ ). IMD-Y and IMD-C had a CFR of 6.9% (4/59,  $p = 0.100$ ), and 18% (2/11,  $p = 0.138$ ), respectively. Serogroup W was associated with a higher CFR compared to non-W cases after adjusting for age, gender, comorbidities and clinical manifestation (odds ratio: 4.0, 95%-confidence interval: 1.6-11.0).

### Conclusion

Our study showed that the current increase in IMD-W incidence in the Netherlands, caused by a cc11 strain, is associated with a different clinical picture and a higher severity compared to IMD due to other serogroups. This difference could not be explained by the underlying differences in case characteristics. More research is needed to identify the bacterial factors involved in the clinical presentation and severity of IMD-W cc11.

## OC - (EMGM2019-13244) - SEROGROUP W CAUSES ATYPICAL CLINICAL PRESENTATIONS OF INVASIVE MENINGOCOCCAL DISEASE; A NATION-WIDE STUDY OF MENW CASES IN SWEDEN 1995-2017.

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### Introduction & Aims

Serogroup W has accounted for a major proportion of IMD (invasive meningococcal disease) cases in Sweden since 2016, an increase that has also been described in other countries. In addition, atypical symptoms have been reported for IMD caused by serogroup W in several countries<sup>1,2</sup>. The aim of this nation-wide survey was to describe the clinical picture of patients with serogroup W infections in Sweden.

### Materials and Methods

In this retrospective study, medical records from all patients in Sweden with IMD caused by serogroup W 1995-2017 were systematically reviewed using a standardized questionnaire where patient characteristics, in-hospital findings and outcome were studied. Clinical presentations were studied for the whole cohort, with a focus on clonal complex (cc) ST-11, which stand for the majority of MenW cases. In addition, clinical features in relation to the genetic differences between the dominating strains and other serogroup W isolates<sup>3</sup> will be further analyzed.

### Results

The median age was 42.5 years for the whole cohort (n=74), 30.5 years for patients infected by ST-11 (n=52) and 63.5 years for other isolates (n=22). Of all patients, 11/74 (15%) were found to have meningitis, 3/74 (4%) arthritis and 20/74 (27%) pneumonia. Noteworthy, 13/74 (18%) had clinically evident upper respiratory tract infection combined with bacteremia, including 7/74 (9%) with epiglottitis. Among patients without upper respiratory tract infection, a syndrome of vomiting alone or in combination with diarrhea was found in 31/60 (52%) of the patients.

### Conclusion

Among patients with serogroup W infections, two distinct atypical clinical pictures of IMD were found in a high proportion, upper respiratory tract infections and gastrointestinal symptoms respectively. This calls for a wider approach in the clinical evaluation of suspected IMD cases not only in Sweden, as serogroup W has emerged in several countries in recent years.

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**OC - (EMGM2019-13149) - RECURRING INVASIVE MENINGOCOCCAL INFECTIONS – QUANTIFYING THE RISK**

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**Introduction & Aims**

Invasive meningococcal disease (IMD) is a rare condition with a high case fatality rate. While most affected patients appear to suffer from only a single episode in their life span, there is anecdotal evidence for recurrent infection [1]. The incidence of recurring IMD, however, has not been quantified. The National Reference Laboratory (NRL) for meningococci has analyzed 6,001 cases of IMD in the past 17 years, which offers the opportunity to retrospectively quantify the risk of recurrent infection.

The aim of the study is to assess the risk of recurring invasive meningococcal infections in Germany.

**Materials and Methods**

Patients living in Germany with invasive meningococcal disease (IMD) that were registered by the NRL between 2002 and 2018 as part of the laboratory surveillance program were analyzed. IMD was assumed for cases, where *Neisseria meningitidis* was detected by culture or PCR from blood or cerebrospinal fluid. Recurring IMD was defined as the detection of *N. meningitidis* in a following sample from the same patient after an interval of at least 30 days. Patient identity was assessed by comparison of month of birth, sex, and county of living. In some cases, identity was reported beforehand by senders.

**Results**

Out of the 5,854 patients with an average observation period of 9.75 years, 14 suffered a second episode and one a third IMD episode. Assuming an average lethality of 9.6 % [2] and official life tables, the risk of a recurring IMD was 30 per 100,000 person years of survivors of the first episode compared to an average general incidence of IMD of 0.9 per 100,000 in the observation period (Source: <https://survstat.rki.de/>). The median interval from the first to the second episode was 1.61 years. Rare serogroups (Y: 21 %, W: 14 %, non groupable: 7 %, E: 3 %, Z: 3 %) were more common in patients with recurring IMD. The same strain has not been observed more than once in a patient.

**Conclusion**

Surviving IMD patients are at a more than 30-fold risk of IMD compared to the general population. Increased risk might be caused by undiagnosed complement deficiencies. The study most likely underestimates the risk of recurrent infection. The high risk of re-infection argues for vaccination of IMD patients following survival of disease.

**References**

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Session: Poster Session II

Room: Auditorium III

Public Health Threats, Prevention and control strategies

**PO-026 - (EMGM2019-13201) - COST-EFFECTIVENESS OF MENINGOCOCCAL ACWY VACCINATION OF TEENAGERS IN NORWAY**

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**Introduction & Aims**

The incidence of invasive meningococcal disease (IMD) was high in Norway during the 1970s-1990s, especially in young children and teenagers. Over the last 20 years the incidence has been declining. However, there is still an accumulation among teenagers with an annual incidence of 1-7 cases per 100 000, mostly caused by serogroup Y. Since 2011, there has been a national recommendation for meningococcal ACWY vaccination for 16-19 year olds engaged in activities that increase the risk of IMD. Vaccination is mostly offered through the school health service, but vaccine uptake is likely to be dependent on socioeconomic status since vaccination is given at the student's own cost. Currently, about 40% of graduating students aged 18-19 years are vaccinated to prevent IMD, which has been associated with the Norwegian graduation celebration ("Russ"). The aim of this study was to estimate costs and health gains of introducing meningococcal ACWY vaccination to Norwegian teenagers as part of the national immunization program.

**Materials and Methods**

A Markov model was used to analyze the cost-effectiveness of meningococcal vaccination of teenagers in Norway. Monte Carlo simulations were performed on several input parameters to evaluate impact of variations in variables such as vaccine effectiveness, incidence of IMD and costs. We used Norwegian epidemiological data from the Norwegian surveillance system for communicable diseases MSIS and current vaccine uptake from the Norwegian immunization registry SYSVAK in addition to estimation of sequelae and vaccine efficacy as observed in other countries. We followed two fictive cohorts from 15 to 105 years of age, one where 40% were vaccinated at age 18 as is the current situation and one where 90% were vaccinated at age 15.

**Results**

Vaccination of teenagers with meningococcal ACWY vaccine at 15 years of age gave a reduction of 2.9 hospital admissions, 0.19 cases of sequelae and 0.39 deaths from IMD. Incremental cost-effectiveness ratio for this intervention was 1.9 million NOK/QALY (approximately 200,000 Euro/QALY) which is much higher than current thresholds for cost-effectiveness in Norway. A 76% rebate on vaccine price is needed in order for meningococcal ACWY vaccination of teenagers to be cost-effective.

**Conclusion**

Introduction of meningococcal ACWY vaccine to Norwegian teenagers in the national immunization program is not cost-effective given current epidemiology and vaccine price.

**PO-027 - (EMGM2019-13168) - OUTBREAK OF ACUTE PHARYNGOTONSILLITIS IN JIGAWA STATE, NORTHWESTERN NIGERIA, 2015.**

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**Introduction & Aims**

Acute respiratory infections (ARI) are the commonest cause of acute morbidity in children especially those under five in the developing countries. Viral and bacterial organisms, transmitted mainly via airborne are the commonest causative agents of ARI in children. Infections generally occur in crowded environments with seasonal variations. Acute pharyngotonsillitis (APT) is a form of ARI affecting the membranes covering the pharynx and uvulae. *Streptococcus pyogenes* is the most common cause of acute pharyngitis and accounts for 15-30% of cases in children and 5-10% in adults. Other bacterial causes of APT include *Haemophilus influenzae* and *Streptococcus pneumoniae*. Hib and PCV vaccines against *H influenzae* and *S. pneumoniae* are yet to be introduced into the routine immunization system in Nigeria. Routine public health surveillance detected an increase in APT in Jigawa State. Here we report the findings of an investigation to determine the magnitude and source of the outbreak with the aim of initiating control and preventive measures.

**Materials and Methods**

A descriptive cross sectional analysis including review of the medical records was carried out across Birniwa, Maigatari & Hadejia LGAs in Jigawa State from September 2014 to February 2015. Active house-to-house case search was also conducted to identify additional cases. All suspected cases were clinically assessed by a physician to confirm diagnosis of APT. Throat swabs and blood specimens were collected from all suspected cases and sent for microscopy culture and sensitivity (MCS) as well as serum IgM the state specialist hospital. A line list of all suspected cases was entered into a Microsoft Excel spread sheet.

**Results**

A total of 48 clinically confirmed cases and 2 deaths were reported with case fatality ratio of 4.1%. The commonest symptom was painful swallowing (49%) while the least was fever (7%). The disease occurred in all age groups with highest attack rate among persons 5 to 9 years of age (25%) followed by those within 2 to 4 years of age (17%). The lowest was among those between 26-30 years of age (6.2%). Females (60.5%) were more affected than males. Of the 48, 32% were indeterminate, 20% were positive for *S. pyogenes* while 32% were positive for *H. influenzae* and 16.7% for *S. aureus*. No organism was however isolated from the blood culture.

**Conclusion**

Haemophilus influenza followed by streptococcus pyogenes and staphylococcus aureus were the predominant cause of acute pharyngotonsillitis in a mixed outbreak. Strengthening immunization against H. influenzae in children will prevent future recurrence of the outbreak.

## PO-028 - (EMGM2019-13205) - UNIVERSITY-BASED SEROGROUP B MENINGOCOCCAL DISEASE OUTBREAKS IN THE UNITED STATES

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### Introduction & Aims

In the United States, university students are at increased risk of serogroup B meningococcal disease compared to other adolescents and young adults who do not attend university. Since 2013, serogroup B meningococcal (MenB) vaccine has been available for use in response to serogroup B meningococcal disease outbreaks. We summarized university-based serogroup B meningococcal disease outbreaks and vaccination responses in the United States in the years following MenB vaccine availability.

### Materials and Methods

An outbreak was defined as  $\geq 2$ –3 cases of the same serogroup (unless genetically distinct by whole genome sequencing) occurring at a university within a 3-month period. Data were assembled from a variety of sources, including universities, local or state health departments, the U.S. Centers for Disease Control and Prevention, and publications. Outbreak duration was defined as the time from first to last case. Vaccination coverage was calculated as the number of first-doses of MenB vaccine administered divided by the target population for vaccination.

### Results

From 2013–2018, 11 university-based serogroup B meningococcal disease outbreaks occurred in 7 states, with a total of 41 cases and 2 deaths (5%). No known university-based outbreaks due to other serogroups occurred during this period. Median patient age was 19 years; 61% were male. Thirty-eight cases (93%) were in undergraduate students from 4-year degree-granting universities; 3 cases occurred in unvaccinated close contacts of undergraduate students. Outbreaks occurred at universities with 3,600–35,000 undergraduates. Outbreak case counts ranged from 2 to 9 cases (median: 3); outbreak duration ranged from 0 to 376 days (median: 24). All 11 universities implemented MenB vaccination: 3 used primarily MenB-FHbp and 8 used MenB-4C. Estimated first-dose vaccination coverage ranged from 14% to 98%. In 5 outbreaks, additional cases occurred 6–259 days following initiation of MenB vaccination.

### Conclusion

Although incidence is low, university students are at increased risk for serogroup B meningococcal disease and outbreaks in the United States. Though it is difficult to predict outbreak trajectories and evaluate the impact of public health response measures, achieving high MenB vaccination coverage is crucial to help protect individuals during outbreaks. Additional efforts to evaluate MenB vaccine effectiveness and identify current risk factors for meningococcal disease among university students could help guide responses to future serogroup B meningococcal disease outbreaks.

## PO-029 - (EMGM2019-13229) - VALIDITY OF SELF-REPORTED VACCINATION STATUS AND KNOWLEDGE AND ATTITUDES TOWARD MENB VACCINE AFTER AN OUTBREAK

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### Introduction & Aims

Nine cases of serogroup B meningococcal (MenB) disease occurred in young adults linked to a university in New Jersey between March 2013-March 2014. In response to the outbreak, the 4CMenB vaccine was made available during university-led clinics; students were recommended to receive 2 doses, spaced 10 weeks apart. Following the vaccination campaign, a seroprevalence study was conducted; as part of the study, we surveyed students about their MenB vaccination history. The aims of this analysis are to assess concordance between self-reported MenB vaccine doses and documented vaccination history; identify reasons for incomplete vaccination ( $\leq 1$  dose); and assess confidence in knowledge of meningococcal disease and the MenB vaccine.

### Materials and Methods

Students self-reported their vaccination status, including the number of doses, at two separate time points (2 and 20 months after vaccination). True vaccination status was confirmed via vaccination records. Incompletely vaccinated participants self-reported multiple reasons for receiving  $\leq 1$  dose. Confidence in knowledge of meningococcal disease and vaccines was assessed using a Likert scale.

### Results

Of 588 respondents with both self-reported and documented vaccination status available two months post-vaccination, 99.2% (95% CI: 98.4-99.9%) correctly recalled the number of doses received. Among those who remained unvaccinated ( $n=20$ ), the most common reasons were concern about side effects ( $n=12$ ) and little concern about meningococcal disease ( $n=8$ ). Among those receiving 1 dose ( $n=19$ ), the second dose was most commonly declined due to a lack of time ( $n=9$ ) or side effects experienced after the first dose ( $n=7$ ). Among 197 participants who returned 20 months post-vaccination, 93.9% (95% CI: 90.6-97.3%) correctly recalled the number of doses received. After the outbreak ended, only 31.4% (95% CI: 25.1-38.5%) reported being very confident in their understanding of meningococcal disease, including how it is transmitted; 32.1% reported being very confident in their understanding of MenB vaccine, including how many doses are needed (95% CI: 25.7-39.2%). 94.9% reported they would recommend the vaccine to others

### Conclusion

Our results indicate that young adults can accurately report their own vaccination status following multiple doses of a vaccine in both the short and longer term (2 and 20 months post-vaccination). Despite extensive public health messaging and awareness campaigns during the course of the outbreak, few individuals felt very confident about their knowledge of meningococcal disease or the vaccine, though nearly all would recommend the vaccine to others. Our evidence suggests that future studies may rely on self-reported vaccination status in similar settings; and that during future outbreaks, efforts are needed to improve public health messaging to build confidence in understanding disease risk and vaccination benefits.

## PO-030 - (EMGM2019-13249) - CLINICAL PRESENTATION OF ACUTE PHASE AND COMPLICATIONS/ SEQUELAE OF IMD IN EUROPE: RESULTS FROM A SYSTEMATIC LITERATURE REVIEW

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### Introduction & Aims

Although rare, invasive meningococcal disease (IMD) continues to be a health concern due to its severe morbidity with substantial short- and long-term consequences, and relatively high case fatality rate. Six serogroups (A, B, C, W, X, Y) of *Neisseria meningitidis* are responsible for almost all IMD cases. Serogroup distribution may vary temporally, geographically and with age. The severity of IMD manifestations ranges from transient bacteremia, with mild and non-specific symptoms, to fulminant sepsis with multi-organ failure. The aim of this review was to determine IMD burden in EU-27.

### Materials and Methods

A systematic review of PubMed, EMBASE and Cochrane Library databases was conducted (publication date 2000 to January 2018). Here we reported the results on acute events and complications/sequelae for all countries, age groups and serogroups.

### Results

Out of 182 included papers on IMD in EU-27 countries, 74 papers presented data on acute events (data from 16 EU-27 countries) and 37 presented data on complications/sequelae (data from 11 EU-27 countries). Reported data covered the period from 1977 to 2017. IMD acute events reported were meningococcal meningitis (range: 6.0-89.2% of the cases, n=98 estimates); meningococcal septicemia (range: 1.0-100.0%, n=94 estimates); septic shock (range: 3.6-54.0%, n=15 estimates); fulminant meningococemia (range: 14.3-28.0%, n=3 estimates), and bacteremia (range: 10.7-37.0%, n=9 estimates). The most common neurological complications were hearing loss (range: 0.9%-40.0%, n=16 estimates); seizure (range: 2.0%-13.0%, n=7 estimates); motor deficit (range: 0.0-12.9%, n=2 estimates); and visual disturbance (9.42%, n=1 estimate). The physical complications were skin scarring (range: 0.0-87.3%, n=15 estimates); amputation (range: 0.0%-40.0%, n=13 estimates); renal dysfunction (range: 0.0%-22.2%, n=8 estimates). Moreover our results showed a variation of sequelae depending on serogroups. For instance, Y serogroup had the highest sequelae rate (range: 12.0-53.8%, n=2 estimates) versus serogroup A (range: 4.0%, n=1 estimate, rare in Europe); B (range: 2.9-37.6%, n=8 estimates); C (range: 12.5-34.0%, n=3 estimates) and W (range: 10.7-15.4%, n=2 estimates).

### Conclusion

This review highlights the high morbidity of IMD with variation according to serogroup. Up to 57% of IMD survivors are affected by a broad range of complications (neurological or not), sometimes permanently which can impact their quality of life and the family members responsible for their care. Recent studies showed an increased incidence and spread of W & Y hypervirulent serogroups in different parts of the world over approximately the last decade warrants accurate surveillance and prompt action from national health authorities. The unpredictability of infection, striking otherwise healthy people, coupled with the poor prognosis for some patients despite appropriate management suggests the best strategy to control the burden of IMD is through immunization for disease prevention.

**PO-031 - (EMGM2019-13354) - HAEMOPHILUS INFLUENZA SEROTYPE A MENINGITIS - CASE REPORT**

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**Introduction & Aims**

Haemophilus influenzae (Hi) is a gram-negative pleomorphic bacillus that may present a polysaccharide capsule. Encapsulated strains may be differentiated into 6 serotypes (a to f). In Portugal, before vaccination with Hib vaccine was available (since 1994 and in national immunization program since 2000), serotype b was predominant. Latest available epidemiologic data from National Institute (2011-2016)<sup>1</sup> showed non-capsulated Hi strains to be predominant and serotype a to represent 2-5%<sup>1,2</sup>.

**Results**

A seven month-old girl with unremarkable medical history presented to the pediatric emergency room with fever, vomiting and irritability. Physical examination at admission revealed prostration and bulging anterior fontanel. Blood tests and lumbar puncture were performed and prompt empirical treatment with ceftriaxone (100 mg/Kg), vancomycin (stopped after cultural identification) and dexamethasone for 2 days were initiated. Laboratory data revealed cloudy cerebrospinal fluid (CSF) with 8,750 leukocytes/mm, predominantly polymorphonuclear (90%), glucose 30 mg/dL, and total protein 0.64 g/L, the gram stain showed gram-negative cocci bacteria; blood tests revealed 29100/mm<sup>3</sup> white blood cells with 80,7% neutrophils, pCr was 146,8 mg/L. Chemoprophylaxis of close contacts with ciprofloxacin was performed. The patient presented a very favorable clinical evolution under ceftriaxone and he was discharged after 10 days of treatment without any sequels. Blood and CSF samples were sent to the national reference laboratory and the organism was later on identified in CSF sample as Hi serotype A. No late complications were identified in one year follow-up.

**Conclusion**

The authors describe the a rare case of Haemophilus Influenzae serotype A in Portugal and emphasize the need for more information about Hi serotypes. Clinical microbiology laboratories should identify Hi serotype profiles to clarify their clinical importance and adequate surveillance should be warranted to evaluate the importance of serotype replacement.

**References**

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## PO-032 - (EMGM2019-13252) - BETA-LACTAM RESISTANCE OF INVASIVE HAEMOPHILUS INFLUENZAE ISOLATES IN BELGIUM, 2015-2018

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### Introduction & Aims

*Haemophilus influenzae* (*Hi*) is an important cause of acute otitis media, meningitis and sepsis. *Hi* has become increasingly resistant to beta-lactam antibiotics recommended for treating *Hi*-associated diseases such as ampicillin. The main resistance mechanism against ampicillins is conferred by  $\beta$ -lactamase production (BLPAR), which can be inhibited by clavulanic acid. Apart from that,  $\beta$ -lactamase negative ampicillin resistance (BLNAR) has been reported due to mutations in the penicillin-binding protein (PBP3) encoding gene, *ftsI*. Finally, strains named  $\beta$ -lactamase producing amoxicillin-clavulanate resistant (BLPACR), can combine these two mechanisms. Recently, an increase of "PBP3-mediated" resistance has been observed in several parts of the world. Representative data from Belgium have not yet been reported.

### Materials and Methods

Clinical isolates. A total of 109 invasive strains sent by clinical laboratories to the NRC have been analyzed (2015 to 2018) (data from 2018 are still under analysis): 26 strains were isolated from cerebrospinal fluids and 83 from blood cultures.

$\beta$ -lactam resistance analysis. The mechanisms of  $\beta$ -lactam resistance were tested by both phenotypic methods (determination of MIC to ampicillin and amoxicillin-clavulanic acid by E-test and beta-lactamase chromogenic test), and genotypic methods (sequencing of the *ftsI* gene).

### Results

Eighteen isolates (16.5%) were phenotypically resistant to ampicillin. Among these 18 isolates, 14 (77.8%) showed  $\beta$ -lactamase production, 1 of them being also resistant to clavulanic acid (BLPACR), and 4 isolates (16.7%) were phenotypic BLNAR *Hi* and resistant to amoxicillin-clavulanic acid. Analysis of the PBP3 sequences of all 109 isolates was done. Thirteen (11.9 %) of strains showed mutations leading to amino-acid substitutions in the transpeptidase domain of PBP3 known to be linked with a decreased susceptibility to beta-lactams: the 1 BLPACR and the 4 BLNAR and 8 strains remaining phenotypically susceptible to both ampicillin and amoxicillin-clavulanic acid. However, 7 strains were at the limit of the sensitivity for ampicillin (MIC: 1  $\mu$ g/ml) and 5 were at the limit of the sensitivity for amoxicillin-clavulanic (MIC: 2  $\mu$ g/ml). All the 13 strains belong to group II from Ubukata et al,2001 [1].

### Conclusion

Twelve percent of invasive strains show mutations compatible with a decreased susceptibility to  $\beta$ -lactam, of which 38% are phenotypically resistant.

These results highlight the importance of *Hi* antimicrobial resistance monitoring by both pheno- and genotypic techniques.

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## PO-033 - (EMGM2019-11122) - CEFOTAXIME-SUSCEPTIBILITY IN NEISSERIA MENINGITIDIS – A RELIABLE PREDICTOR FOR CEFTRIAXONE-SUSCEPTIBILITY?

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### Introduction & Aims

Cefotaxime and ceftriaxone are both parenterally applied generation 3a cephalosporin antibiotics. While biliary pseudolithiasis or nephrolithiasis are side effects more common after ceftriaxone treatment compared to cefotaxime treatment (Hum Exp Toxicol. 2017 Jun;36(6):547-553), ceftriaxone has the advantage of a longer half-life compared to cefotaxime (J Infect Dis. 1989 Sep;160(3):442-7). Both are used for the treatment of invasive meningococcal disease (IMD) but ceftriaxone is the recommended antibiotic as post-exposure prophylaxis (PEP) to pregnant close contacts of IMD cases to avoid secondary cases by eradicating supposed meningococcal colonization.

Differences in susceptibility between cefotaxime and ceftriaxone have been described for *Streptococcus pneumoniae* (Ann Pharmacother. 2008 Jan;42(1):71-9) but no data was published for *N. meningitidis* yet.

The aim of this study is to compare MIC-values of *Neisseria meningitidis* against cefotaxime and ceftriaxone prospectively and retrospectively to evaluate if testing for cefotaxime-susceptibility is a reliable predictor for ceftriaxone-susceptibility.

### Materials and Methods

At the German National Reference Laboratory for Meningococci and *Haemophilus influenzae*, all cultured *Neisseria meningitidis*-strains have been tested for cefotaxime-susceptibility since 2010 by gradient agar diffusion tests (bioMérieux ETEST® until 2016, Liofilchem® MIC Test Strip since 2017).

Minimal inhibitory concentrations (MIC) of 60 invasive meningococcal strains isolated in Germany were determined using gradient agar diffusion tests (Liofilchem® MIC Test Strip) starting in September 2018. The EUCAST clinical breakpoint of 0.125 mg/l was applied for the interpretation as susceptible against both, cefotaxime and ceftriaxone.

Two retrospective invasive isolates (NRZ number 13567 and 13814, both isolated 2016) with high known MIC values against Cefotaxime were tested using both, bioMérieux ETEST® and Liofilchem® MIC Test Strip, 10 times each.

### Results

The cefotaxime MICs of the 60 prospective isolates ranged between <0.002 and 0.016 mg/l, the ceftriaxone MICs between <0.002 and 0.002 (Fig 1). MIC values against ceftriaxone were for all isolates smaller or equal compared to MIC values against cefotaxime.

Also both retrospective isolates showed reproducible smaller MIC values against ceftriaxone compared to cefotaxime (Tab 1).

### Conclusion

The MICs against ceftriaxone were lower or equal in all tested *N. meningitidis* isolates compared to the MICs against cefotaxime. The MIC of *N. meningitidis* against cefotaxime can be used as a reliable predictor for ceftriaxone-susceptibility.

### References

## PO-034 - (EMGM2019-13217) - CIPROFLOXACIN-RESISTANT INVASIVE MENINGOCOCCAL SEROGROUP B STRAIN IN ITALY: AN IMPORTED CASE, JULY 2018

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### Introduction & Aims

Sporadic cases of infection due to *Neisseria meningitidis* with reduced susceptibility to ciprofloxacin have been reported in Europe, North and South America, and Australia since 2000. In Italy, within the Surveillance System of Invasive Meningococcal Disease (IMD) antimicrobial susceptibility is routinely performed.

The aim was to report an imported ciprofloxacin-resistant strain of *N. meningitidis* causing invasive disease.

### Materials and Methods

*N. meningitidis* identification was performed by Real Time PCR on cerebral spinal fluid (CSF) and on cultivated strain from blood. Antimicrobial susceptibility test was assessed by Etest and interpreted according to the EUCAST breakpoints. Whole genome sequencing (WGS) was obtained by Illumina technology and analysed referring to the <http://pubmlst.org/neisseria/> platform to define MLST, finetype, quinolone-resistance-determining region (QRDR). Core genome MLST (cgMLST) was also included.

### Results

On 1<sup>st</sup> of July 2018, a 41 year-old Russian citizen traveling in Italy was hospitalized with sepsis and meningitis caused by a serogroup B *N. meningitidis* strain. The patient was successfully treated with ceftriaxone (2 gr 2x/day) and discharged after 12 days without sequelae. Close contacts received ciprofloxacin at the first round of prophylaxis. Antimicrobial susceptibility testing revealed the resistance to ciprofloxacin (MIC, 0.25 mg/L) and an intermediate susceptibility to penicillin G (Pen<sup>I</sup>) (MIC, 0.125 mg/L). After these results, close contacts repeated the antibiotic treatment with rifampin. The strain resulted B:P1.17,16-4:F3-9:ST-7926 (UNK), a genotype never reported in Italy. Based on cgMLST no similarity was observed with invasive meningococcal B strains of recent isolation in our country. A new *gyrA* allele, the *gyrA*-212, showing the T91I amino acid substitution associated with fluoroquinolone resistance, and a new *penA* allele, the *penA* 787, with the amino acid substitutions F504L and the A510V, were identified. No mutations in the *parC*, *parE* and *mtrR* genes were detected.

### Conclusion

Ciprofloxacin is widely used for postexposure prophylaxis of close contacts of infected persons because it is simple to use (single oral dose) and lacks toxicity. Genomic analysis and antimicrobial susceptibility test are essential to monitor the circulation and the spread of resistant strains to better address the antimicrobial treatment and chemoprophylaxis of close contacts.

## PO-035 - (EMGM2019-13344) - FIRST INVASIVE MENINGOCOCCAL ISOLATE EXPRESSING A BETA-LACTAMASE IN GERMANY

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<sup>1</sup> - Institute for Hygiene and Microbiology, Wuerzburg

### Introduction & Aims

#### Introduction

Reduced susceptibility of meningococci towards penicillin, which is based on mutations in the chromosomally encoded penicillin-binding protein 2 (PBP2), increased in the last decade (1,2). Nevertheless, antimicrobial resistance in invasive meningococci is rare when compared to other microorganisms. For example, in contrast to gonococci only few meningococcal strains harbour plasmid-encoded beta-lactamases (3). Mostly, these plasmids were identical to gonococcal plasmids. Newer reports demonstrate chromosomal integration of a ROB-1 beta-lactamase gene in serogroup Y meningococci of sequence type (ST) 3587 (4,5).

#### Aim

Description of the first German invasive meningococcal isolate with a beta-lactamase

### Materials and Methods

Antimicrobial susceptibility testing by gradient agar diffusion was conducted as part of the national laboratory surveillance. Beta-lactamase production was detected with nitrocefin disks. Standard sequence typing procedures were applied.

### Results

In March 2017, the German national reference laboratory for meningococci and *Haemophilus influenzae* (NRZMHi) received an invasive meningococcal isolate from a 10-year-old girl suffering from Waterhouse-Friderichsen syndrome that subsequently was finetyped as Y:P1.5-2,10-2:F4-1:ST-3587 (serogroup:PorA-VR1,VR2:FetA-VR:ST). Susceptibility testing revealed a penicillin MIC of 12 µg/ml. Beta-lactamase production was tested positive. A ROB-1 beta-lactamase gene was identified. The isolate was susceptible to cefotaxime.

This is the first report of an invasive meningococcal isolate harbouring a beta-lactamase submitted to the NRZMHi. Its MIC was dramatically higher than those based on mutations in the PBP2 (max. 1 µg/ml). Similar isolates of ST-3587 (ST-23 complex) were recently identified in France and Canada, respectively (4,5). Whole genome sequencing applied on the French and Canadian isolates revealed a chromosomal location of the ROB-1 beta-lactamase gene which showed a high homology to that on the *Haemophilus influenzae* plasmid pB1000. A genome sequence of the German isolate will be obtained to analyse clonal identity to the French and Canadian isolates.

### Conclusion

Although disease caused by this beta-lactamase positive strain is obviously rare, careful surveillance of a spread of ROB1-positive strains is needed. Due to the yet sporadic nature of the observation and the widely used empiric cephalosporin therapy of invasive meningococcal disease, safety concerns regarding current therapeutic regimens do not exist.

### References

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Session: Oral Session IV

Room: Auditorium I

Neonatal infections

### OC - (EMGM2019-13236) - GENOMIC AND FUNCTIONAL ANALYSIS OF NEISSERIA MENINGITIDIS ISOLATES FROM INVASIVE MENINGOCOCCAL DISEASE IN NEONATES

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#### Introduction & Aims

The incidence of invasive meningococcal disease (IMD) varies with age. In children and adolescents, *N. meningitidis* is one of the leading causes of invasive bacterial infections, including meningitis, with the highest attack rates in children under one year of age.

However, the prevalence and the characteristics of IMD in neonates (under 28 days of age) is not well described. We recently reported 831 cases of meningitis among neonates in France between 2001 and 2013. *N. meningitidis* was the third-frequent germ after the two major bacterial species in the newborn: *Streptococcus agalactiae* and *Escherichia coli*.

We aimed in this work to explore the isolates of IMD from neonates by whole genome sequencing (WGS) and to explore their virulence during experimental infection in transgenic mice expressing the human transferrin.

#### Materials and Methods

The database of the national reference Centre for meningococci in France was screened (period 1999-2018) for cases of IMD among neonates (0-28 days old).

Phenotypic characteristics (serogroups, antibiotic susceptibility and antigen expression) as well as the analysis of WGS data were performed. Transgenic mice expressing the human transferrin were used for infection with all cultured isolates by intraperitoneal route. Invasiveness was scored by determining the colony forming units (CFU) in the blood of infected mice at T0, T3h and T24h. Cytokine production and apoptosis induction were also tested in the infected mice.

#### Results

A total of 53 cases of IMD among newborns were identified (of which 50 cultured isolates and three cases that were PCR-confirmed). 55 % of cases were detected in CSF. Serogroup B dominated (75%) followed by group C (19%) while groups W and Y accounted for 2% and 4%. The isolates were diverse with more than 12 different clonal complexes although hyperinvasive isolates represented 68% of the cases. Moreover, 20 different alleles of fHbp were detected with variant 1 alleles that accounted for 35% among all isolates and 38% among group B isolates of this set among the newborns. Cases were of early onset (<7 days) for 21% of cases.

Infection in transgenic mice showed that these isolates can be divided into three groups according to the CFU in the blood at 24h of infection compared to CFU after 3 hours of infection.

#### Conclusion

Although IMD among newborns represents a small proportion of all IMD cases, these cases deserve attention, as they may be difficult to detect. Moreover, particular aspects of these cases may influence the prevention strategies.

#### References

**OC - (EMGM2019-13192) - NONTYPEABLE INVASIVE H. INFLUENZAE DISEASE— UNITED STATES, 2008–2017**

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**Introduction & Aims**

Invasive *Haemophilus influenzae* (Hi) disease is an important cause of morbidity and mortality in young children and older adults. Since the introduction of effective Hi type b vaccines, nontypeable Hi (NTHi) is the most common cause of invasive Hi disease in all age groups in the United States. Other countries have identified increases in NTHi among pregnant women and neonates, but disease pathology among these at-risk populations remains poorly defined. We evaluated the epidemiology of invasive NTHi disease in the United States.

**Materials and Methods**

Cases of invasive NTHi disease from 2008-2017 were identified through Active Bacterial Core surveillance, an active, population- and laboratory-based surveillance system in 10 U.S. sites. Hi isolates from sterile sites were serotyped by real-time PCR and slide agglutination; maternal/neonatal paired isolates underwent whole genome sequencing. We estimated average annual incidence per 100,000, and examined select disease characteristics in infants <1 month of age (neonates), including preterm neonates (born <37 weeks gestational age), and women of childbearing age (15-44 years).

**Results**

During 2008-2017, 4,683 invasive Hi cases were reported to ABCs sites. Average annual incidence was 1.29/100,000 overall, 5.94/100,000 among children aged <1 year and 10.08/100,000 in adults aged ≥80 years. Case fatality ratio (CFR) was 15.6% overall, 8.3% among children aged <1 year, and 25.2% among adults aged ≥80 years. Of 188 neonates with invasive NTHi disease, 81% (152/188) were diagnosed on the day of birth; 71% (134/188) were preterm, of whom 15% (20/134) died. Average annual incidence was 43/100,000 among all neonates, and 320/100,000 among preterm neonates. From 309 women of childbearing age with invasive NTHi disease, 86 (27.8%) were pregnant or post-partum. No pregnant/post-partum women died. Compared to other women of childbearing age with NTHi disease, pregnant/post-partum women were more likely to have bacteremia (91.9% vs 56.1%,  $p<0.0001$ ) and less likely to have ≥1 underlying condition (31.4% vs 67.7%,  $p<0.0001$ ). There were three mother/neonate pairs with invasive NTHi disease at delivery. Each neonatal isolate had the same sequence type as the corresponding maternal isolate; however, the 3 pairs had 3 different sequence types.

**Conclusion**

NTHi causes substantial invasive disease, especially among pregnant/post-partum women, neonates, and older adults. Positive cultures on the day of birth and mother/neonate matched sequence types may indicate intra-uterine transmission. Effective public health measures to prevent perinatal NTHi infections have not been established, but enhanced surveillance and targeted interventions may be warranted, given the burden of disease in this population.

Session: Oral session V

Room: Auditorium I

Antibiotic Resistance

**OC - (EMGM2019-11133) - MENINGOCOCCAL QUINOLONE-RESISTANCE ORIGINATED FROM SEVERAL COMMENSAL NEISSERIA SPECIES**Mingliang Chen (China)<sup>1</sup>; Chi Zhang (China)<sup>1</sup>; Xi Zhang (China)<sup>1</sup>; Min Chen (China)<sup>1</sup><sup>1</sup> - Shanghai Municipal Center for Disease Control and Prevention**Introduction & Aims**

A high frequency of quinolone-resistance (72%) was found in *Neisseria meningitidis* in China during 2005 and 2012 [1]. GyrA mutations of T91I and D95N were responsible for the resistance, but little is known about the origin of these mutations.

**Materials and Methods**

During 2005-2018, 192 *N. meningitidis* isolates and 290 commensal *Neisseria* strains were collected, including *N. lactamica* (n=249), *N. polysaccharea* (n=15), *N. subflava* (n=11), *N. cinerea* (n=8), *N. mucosa* (n=6) and *N. oralis* (n=1). The minimum inhibitory concentrations (MICs) of ciprofloxacin to *N. meningitidis* were determined by the agar dilution method, and quinolone-resistance was defined as MIC  $\geq$  0.06  $\mu$ g/ml [2]. Genes of *gyrA* and *parC* were sequenced to investigate the quinolone-resistance associated mutations.

**Results**

During 2005 and 2018, the quinolone-resistance was found in 68.2% (131/192) of *N. meningitidis* isolates, and their MICs were 0.06  $\mu$ g/ml (n = 14), 0.125  $\mu$ g/ml (n = 73), and 0.25  $\mu$ g/ml (n = 44). All the quinolone-resistant isolates harboured mutations in T91 (n=121) and/or D95 (n=11) in GyrA, without mutations in ParC. Among the resistant *N. meningitidis* isolates, 51 *gyrA* alleles (included in *Neisseria* PubMLST database) were identified, while in the commensal *Neisseria* isolates, 99.3% (288/290) harboured mutations in GyrA (T91 and/or D95) and represented 74 *gyrA* alleles. To investigate the origin of the quinolone-resistance in *N. meningitidis*, nucleotide sequences of the 128 *gyrA* alleles identified in Shanghai *Neisseria* isolates (192 *N. meningitidis* and 290 commensal *Neisseria* species isolates) and the 153 *gyrA* alleles represented by 17,100 *Neisseria* isolates included in *Neisseria* PubMLST database were employed to perform a phylogenetic analysis. Five clusters corresponding to *N. meningitidis*, *N. lactamica*, *N. cinerea*, *N. polysaccharea*, and *N. subflava* were identified. Eight alleles represented by 53/131 (40.5%) of *N. meningitidis* isolates were grouped into the *N. meningitidis* cluster, which meant their quinolone-resistance came from point mutation by themselves. Other 35 alleles represented by 78/131 (59.5%) *N. meningitidis* were outside the *N. meningitidis* cluster, which suggested the quinolone-resistance was acquired by horizontal gene transfer, including from *N. cinerea* (n=18), *N. lactamica* (n=12), *N. subflava* (n=4), and *N. polysaccharea* (n=1). In the *N. lactamica* cluster, *gyrA*-97, *gyrA*-98, *gyrA*-114, *gyrA*-116, and *gyrA*-230 were shared by *N. meningitidis* (n=21) and *N. lactamica* (n=64) isolates.

**Conclusion**

During 2005-2018, the frequency of quinolone-resistant *N. meningitidis* was 68.2% in Shanghai, all of which harboured mutations in GyrA. Over half of the resistant isolates acquired the resistance by horizontal gene transfer from commensal *Neisseria* species.

**References**

[1] Zhu B, Fan Y, Xu Z, et al., *Genetic diversity and clonal characteristics of ciprofloxacin-resistant meningococcal strains in China*. *J Med Microbiol*, 63, 1411-1418, 2014.

[2] Hong E, Hedberg ST, Abad R, et al. Target gene sequencing to define the susceptibility of *Neisseria meningitidis* to ciprofloxacin. *Antimicrob Agents Chemother*, 57, 1961-1964, 2013.

## OC - (EMGM2019-13259) - EMERGENCE OF RESISTANCE TO THIRD GENERATION CEPHALOSPORINS IN HAEMOPHILUS INFLUENZAE BY ALTERATION OF FTSI GENE.

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### Introduction & Aims

Antibiotic susceptibility testing of *Haemophilus influenzae* lacks molecular tools due to allow deciphering non-plasmidic mechanisms of resistance. We aimed to use whole genome sequencing to explore the antibiotic susceptibility to beta lactams antibiotics in *H. influenzae*.

### Materials and Methods

All culture-confirmed cases due to *H. influenzae* isolated from a sterile site, that were received at the French national reference centre for *H. influenzae* during the period 2017-2018 (n=317) were characterized by whole genome sequencing (WGS), antibiotic susceptibility testing and characterising of *ftsI* gene. We also tested 121 isolates that were received from non-invasive infections.

### Results

Antibiotic susceptibility testing indicated that 24% of the invasive isolates were resistant to ampicillin but this percentage was significantly higher (53%,  $p < 0.001$ ) among the non-invasive isolates. Moreover, the proportion of beta-lactamase negative ampicillin resistant isolates (BLNAR) was significantly higher among non-invasive isolates compared to that of invasive isolates (24% versus 8%,  $p < 0.001$ ). BLNAR isolates were linked to modification in the *ftsI* gene encoding the penicillin binding protein 3 (PBP3). In particular, alleles of *ftsI* that harbored the mutations D350N, S357N, M377I and S385T were resistant to ampicillin and third generation cephalosporins. These isolates were more frequent among non-invasive isolates.

### Conclusion

The high proportion of ampicillin resistant isolates by mutation in *ftsI* among non-invasive isolates may suggest a biological cost of these mutations on the function of PBP3 that can lead to lower bacterial invasiveness. WGS should be used routinely for the characterization of *H. influenzae* isolates in order to reliably follow the emergence, spread and mechanism of antibiotic resistance.

### References

## OC - (EMGM2019-13283) - ANALYSIS AND SURVEILLANCE OF CEFTRIAXONE RESISTANT HAEMOPHILUS INFLUENZAE IN SCOTLAND, UK.

Rosin Ure (United Kingdom)<sup>1</sup>; Kevin Scott (United Kingdom)<sup>1</sup>; Diane Lindsay (United Kingdom)<sup>1</sup>; Pamela Lindsay (United Kingdom)<sup>1</sup>; Andrew Smith (United Kingdom)<sup>2</sup>; Sharif Shaaban (United Kingdom)<sup>3</sup>; Adriana Zalewska (United Kingdom)<sup>3</sup>; Julie Wilson (United Kingdom)<sup>3</sup>; Michael Lockhart (United Kingdom)<sup>3</sup>

1 - SMiRL, NHS Greater Glasgow & Clyde; 2 - Glasgow University & NHS Greater Glasgow & Clyde; 3 - Health Protection Scotland

### Introduction & Aims

Resistance to fluoroquinolones, third generation cephalosporins (CRO) and carbapenems is considered to be exceptional in *H. influenzae*. Clonally related virulent *H. influenzae* strains are Globally disseminated and CRO resistant isolates continue to emerge, threatening current empiric antibiotic treatment. The current Scottish monitoring of antimicrobial resistance early warning system (AMR-EWS) was established in August 2017. The system generates alerts associated with unusual antibiotic resistance reported in the Electronic Communication of Surveillance in Scotland (ECOSS) system. Notifications to diagnostic laboratories following identification through the AMR-EWS act as a prompt to ensure resistance is confirmed prior to reporting. The aim of this presentation is to provide background epidemiology on the incidence of CRO resistant *H. influenzae* and preliminary characterisation using whole genome sequencing in Scotland.

### Materials and Methods

Isolates referred to the Scottish Microbiology Reference Laboratory (SMiRL), Glasgow (respiratory bacteria section) were re-tested for antimicrobial susceptibility using E-test methodology and if confirmed were whole genome sequenced (Illumina platform). Reads were assembled de novo and put through ParSNP, as well as mapped to a reference sequence and put through SnapperDB in order to generate single nucleotide polymorphism (SNP) phylogenies.

### Results

For the period 2016 to-date (2019), SMiRL received 13 isolates of CRO resistant *H. influenzae* (12 sputum and 1 eye swab), sensitive to meropenem and phenotypically and genotypically non-typeable. Sequence types (STs) comprised 107 (n=5), 143 (n=2) and n=1 of 142, 388, 422, 1002, 1218, 2016. The two ST143 isolates demonstrated a 5 SNP difference between isolates, whilst the remainder of strains exhibited a large number of SNPs between each other. The two ST143 isolates demonstrated a 5 SNP difference between isolates, whilst the remainder of strains exhibited a large number of SNPs between each other. Analysis of the *ftsI* gene [1] revealed a new allelic type (107) for ST143. The remaining *ftsI* alleles comprised 16, 26, 40 and 107. A number of Penicillin Binding Protein 3 (PBP3) profiles such as Group III+: S385T, L389F and N526K were detected in a number of isolates [1,2]. Other workers [2] investigating spread and clinical impact of the virulent clone ST14CC were not detected in our cohort.

### Conclusion

Surveillance of isolates referred to SMiRL indicates that those strains belonging to ST14CC appear sporadically and at very low levels in the Scottish population. The presence of various substitutions in the PBP3 proteins (1) in isolates from Scotland merits careful surveillance to ascertain clinical impact and emergence of these strains.

### References

- [1] D. Skaare et al. Emergence of clonally related multidrug resistant *Haemophilus influenzae* with penicillin-binding protein 3-mediated resistance to extended-spectrum cephalosporins, Norway, 2006 to 2013. *Euro Surveill* 11, 19(49), 2014.
- [2] V. Månsson et al. The spread and clinical impact of ST14CC-PBP3 type IIb/A, a clonal group of non-typeable *Haemophilus influenzae* with chromosomally mediated b-lactam resistance - a prospective observational study. *Clinical Microbiology and Infection* 23, 209.e1e209.e7 2017.

Session: Oral Session VI  
Room: Auditorium I

WGS and metagenomics

## OC - (EMGM2019-13327) - MOLECULAR EPIDEMIOLOGY OF INVASIVE MENINGOCOCCAL DISEASE IN THE NETHERLANDS ASSESSED BY WHOLE GENOME SEQUENCING, 2017-2018

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1 - The Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam Medical Center; 2 - National Institute of Public Health and the Environment, Bilthoven

### Introduction & Aims

The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) receives nationwide over 90% of all cases of invasive meningococcal disease. A conjugate serogroup C vaccine was implemented into the national immunization program in 2002 as a single vaccination for children aged 14 months, which was replaced by a tetravalent MenACWY conjugate vaccine in 2018. The aim of this study was to evaluate the molecular epidemiology of invasive meningococcal disease by whole genome sequencing (WGS).

### Materials and Methods

Invasive meningococcal isolates received in 2017-2018 were characterised by serogrouping and WGS. Clonal complexes, finetypes and vaccine antigen types were assessed in the Bacterial Isolate Genome Sequence Database (BIGSdb) at PubMLST.org/neisseria. Potential vaccine coverage was assessed by the Bexsero phenotyping tool in BIGSdb.

### Results

In 2017-2018, the NRLBM received 418 cases of invasive disease (39% serogroup B, 44% W and 13% Y), with an overall incidence of 1.22 cases/10<sup>5</sup> inhabitants. The incidence was highest among 0-4 years of age: 4.64/10<sup>5</sup> (75% serogroup B; 21% W). Among 15-24 years of age the incidence was 2.05/10<sup>5</sup> (47% serogroup B; 37% W; 10% Y). The incidence among 50-64 year and ≥65 year olds was 1.14/10<sup>5</sup> (17% serogroup B; 62% W; 15% Y) and 1.68/10<sup>5</sup> (19% serogroup B; 48% W; 27% Y), respectively. Of 418 cases, 379 (91%) isolates were received. Of these, 351 were assessed by WGS. The majority (95%) of serogroup W isolates belonged to clonal complex 11 (cc11). Among serogroup Y, cc23 was the dominant clonal complex (75%). Serogroup B isolates comprised 11 different clonal complexes, with 79% of assigned isolates belonging to cc32 (33%), cc41/44 (21%), cc269 (13%) or cc213 (13%). Serogroup B isolates showed exact vaccine antigen matches in 42 out of 108 analysed isolates (39%). In addition, 31 isolates (29%) contained potentially cross-reactive antigens, resulting in a total of 73/108 (68%) isolates potentially covered by 4CMenB. Potential coverage was highest among 5-24 year olds (88%), while that among 0-4 year olds was 59%.

### Conclusion

Whole genome sequencing reveals the diversity of meningococcal isolates causing the disease in the Netherlands. Potentially, 59% of serogroup B cases among 0-4 years old are covered by 4CMenB. Vaccine coverage estimated using WGS data may provide valuable input for vaccination policy. However, expression of antigens is not measured. In addition, the Bexsero phenotyping tool in BIGSdb is based on the association between antigen peptide types and MATS. The latter may underestimate 4CMenB coverage.

## OC - (EMGM2019-13266) - THE EMERGENCE OF A NEW GENETIC LINEAGE (ST-9316) OF NEISSERIA MENINGITIDIS SGROUP W IN NORTH FRANCE

Ala-Eddine Deghmane (France)<sup>1</sup>; Eva Hong (France)<sup>1</sup>; Muhamed-Kheir Taha (France)<sup>1</sup>

<sup>1</sup> - Institut Pasteur, Invasive bacterial infections unite and National Reference Centre for Meningococci and Haemophilus influenzae, Paris, France

### Introduction & Aims

The epidemiology of invasive meningococcal disease (IMD) is changing frequently in time and space with changing of the incidence and/or the emergence and the expansion of new strains of *Neisseria meningitidis*. Here we describe the genomic characteristics using whole genome sequencing of an emerging NmW isolates in north France belonging to a new genetic lineage distinct from the clonal complex CC11.

### Materials and Methods

All invasive isolates that are received at the National Reference Centre are analyzed by whole genome sequencing (WGS, NextSeq 500, Illumina). The isolates are uploaded regularly to the PUBMLST and periodically analyzed using genome comparator tools. The SplitsTree4 (version 4.13.1) is used to visualise the resulting distance matrices as Neighbor-net networks.

### Results

Serogroup W isolates are increasing in France since 2013 and most of the isolates belonged to the clonal complex ST-11 and were derivatives of the South American UK strain. However, between 2013 and 2018, 24 cases of IMD due to isolates belonging to an unusual sequence type, the ST-9316, were identified in France mainly in the north part of the country. The majority of cases belonged to group W but few were of groups B and C. These isolates do not belong to any already defined clonal complex (CC). The cases were distributed as follows: 1 case in 2013, 2 cases in 2015, 6 cases in 2016, 9 cases in 2017 and 6 in 2018. The index case of this ST-9316 cluster was identified in December 2013 in the Hauts-de-France from a 29 years old woman. Cases were distributed in all groups of age.

Coregenome MLST clustered all the isolates belonging to the ST-9316 together and were distantly separated from the other isolates that differed by more than 1300 alleles. However, those isolates were closer to the isolates of the CC865. The W/ST-9316 isolates shared several identical allelic profiles that were different from those of lineages of CC11 isolates. Most of the corresponding genes encode metabolic enzymes. However, few other genes involved in interactions with host cells such as genes encoding FetA, PorA, factor H binding protein (Fhbp). Interestingly, all the W/ST-9316, unlike the W/CC11 isolates, lacked the *hmbR* gene encoding the haemoglobin receptor that is involved in the acquisition of iron from haemoglobin.

### Conclusion

Changing meningococcal epidemiology may occur rapidly and locally. Surveillance requires extensive and powerful approaches such as WGS to rapidly adapt preventive strategies.

### References

## OC - (EMGM2019-13335) - CGMLST CHARACTERISATION OF NEISSERIA MENINGITIDIS SEROGROUP C AND W STRAINS ASSOCIATED WITH INCREASING DISEASE INCIDENCE IN THE REPUBLIC OF IRELAND.

Robert Mulhall (Ireland)<sup>1</sup>; Desiree Bennett (Ireland)<sup>1</sup>; Holly Bratcher (United Kingdom)<sup>2</sup>; Keith Jolly (United Kingdom)<sup>2</sup>; James Bray (United Kingdom)<sup>2</sup>; Suzanne Cotter (Ireland)<sup>3</sup>; Piaras O'Lorcain (Ireland)<sup>3</sup>; Martin Maiden (United Kingdom)<sup>2</sup>; Robert Cunney (Ireland)<sup>1</sup>

1 - The Irish Meningitis & Sepsis Reference Laboratory; 2 - Department of Zoology, University of Oxford, Oxford, United Kingdom.; 3 - The Health Protection Surveillance Centre, Dublin, Ireland

### Introduction & Aims

At the start of this century in the Republic of Ireland (RoI), invasive meningococcal disease (IMD) was primarily caused by serogroups B (MenB) and C (MenC). MenC incidence decreased following the introduction of the meningococcal conjugate C programme in 2000. MenB incidence has declined continuously without intervention since 2000.

Since 2013 MenC and MenW disease incidence and associated mortality rates have increased. Over the 2002/2003 to 2012/2013 period, the average annual MenC incidence was 0.08/100,000. This increased to 0.34/100,000 during the 2013/2014 to 2017/18 period. Incidence peaked in 2016/17 reaching 0.72/100,000 with an associated case fatality rate of 14.7%. MenW disease incidence was 0.02/100,000 in 2013/2014, and has increased each year since then to 0.29/100,000 in 2017/18, with an associated case fatality rate of 28.6% (1).

We aimed to determine if:

(A) MenC increases were due to the emergence of a novel clone, or the re-emergence of cc11:MenC clones which were previously prevalent .

(B) MenW increases were due to novel 'Hajj' genotypes.

### Materials and Methods

We characterised 74 invasive and 16 carried MenC meningococcal isolates collected during the 1997/98 to 2016/17 epidemiological years by WGS. MenW isolates collected between 2010/11 and 2016/17 (n=22 invasive, n=16 carried) were compared to international examples of the Hajj clones (PubMLST.org/neisseria).

Genomes were assembled using VelvetOptimiser (2) and stored on the Bacterial Isolate Genome Sequence data base (BIGSdb) and compared using cgMLST (3,4). Isolate relationships were resolved into a NeighbourNet distance matrix and visualised using SplitsTree (5,6).

### Results

The majority of MenC and MenW study isolates were cc11. A single temporally structured cc11:MenC sub-lineage identified contained the majority (21/25) of isolates collected since 2013, and included all cc11:MenC carried isolates. Invasive and carried isolates were interspersed and distinct from cc11:MenC epidemic clones, which still circulate and cause sporadic IMD. Irish cc11:MenW disease and carriage isolates clustered among international examples of both the original UK 2009 clones, and novel 2013 clones, but not with the original Hajj clones.

### Conclusion

We have shown that the majority of MenC disease incidence in recent epidemiological years was caused by strain types distinct from the epidemic associated (ET-15) cc11:MenC strain of the late 1990s and early 2000s. We have identified the same aggressive MenW clone established in several other European countries, is now endemic here, and is responsible for the recent MenW incidence increases. This data has informed the National Irish Advisory Committee who are currently deliberating a change in vaccine policy to protect teenagers.

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## OC - (EMGM2019-13152) - SELECTIVE WHOLE GENOME AMPLIFICATION OF NEISSERIA MENINGITIDIS FOR CULTURE-FREE SEQUENCING OF CLINICAL SPECIMENS

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### Introduction & Aims

*Neisseria meningitidis* (Nm) is a leading cause of bacterial meningitis and sepsis worldwide, and clusters of Nm urethritis cases were recently reported in the US. Whole genome sequencing allows full characterization of Nm isolates. When viable Nm isolates are not available, shotgun sequencing can be used to characterize bacterial DNA from specimens such as cerebrospinal fluid (CSF), blood, or urine. However, bacterial DNA is overwhelmingly masked by the human DNA in specimens. We developed a DNA enrichment procedure to efficiently sequence Nm DNA from clinical specimens.

### Materials and Methods

Selective whole genome amplification (SWGA) [1] was optimized for Nm DNA enrichment using phi29 multiple-displacement polymerase and a set of 25 heptamer primers that preferentially bind Nm DNA rather than the human DNA. The procedure was applied to 12 CSF and 13 urine specimens that had tested positive for the Nm *sodC* gene using real-time PCR. The enriched and unenriched specimens were sequenced using MiSeq. Sequencing reads were identified as either human or bacterial by comparison to reference genomes. Nm reads were assembled for molecular typing.

### Results

SWGA increased the median percentage of Nm reads from 0.48% to 21.1% in CSF and from 0.086% to 57.2% in urine; the median enrichment was greater than 100-fold in both specimen types. Enrichment enabled identification of all seven MLST loci in 10 of 25 specimens, plus 90% of the 1605 Nm core genome loci in 8 of these 10 specimens, while none of the unenriched counterparts had similar assembly quality. Independent replicates of SWGA demonstrate a low error rate with allele discrepancies ranging from 0.12-0.73% per core genome locus.

### Conclusion

Overall, SWGA is a promising method of culture-free whole genome sequencing in terms of reliability, reproducibility, and affordability for. SWGA reduces the cost per specimen by multiplexing, produces sufficient reads for phylogenetic and allelic analysis, and assembles a full genome for some specimens. Importantly, the procedure may be extended to other bacteria using the same principles.

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## OC - (EMGM2019-13224) - HIGH DIVERSITY OF INVASIVE HAEMOPHILUS INFLUENZAE ISOLATES IN FRANCE REVEALED BY WHOLE GENOME SEQUENCING

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### Introduction & Aims

Invasive infections due to *Haemophilus influenzae* became less frequent since the implementation of vaccination against *H. influenzae* of serotype b. However, their changing epidemiology may not be clear due to lack of genotyping. We aimed to describe the 2017-2018 epidemiological trends of invasive *H. Influenzae* infections in France and to explore the microbiological characteristics of invasive versus non-invasive isolates.

### Materials and Methods

All culture- and PCR-confirmed cases due to *H. influenzae* isolated from a sterile site, that were received at the French national reference centre for *H. influenzae* during the period 2017-2018 (n=300) were characterized by whole genome sequencing (WGS) and serotyping

### Results

Most of the invasive isolates were non-typeable (75%) which was significantly less than the non-invasive isolates (99%,  $p < 0.0001$ ). Serotype b and f were the most frequently observed but serotype a was also present among invasive isolates. WGS analysis suggested a serotype (b) to (a) capsule switching. Non-typeable isolates showed extensive heterogeneity.

### Conclusion

Our data suggest that invasive *H. influenzae* isolates differed phenotypically and genotypically from non-invasive isolates. WGS should be used routinely for the characterization of *H. influenzae* isolates in order to reliably follow the epidemiology of *H. influenzae*.

### References

## OC - (EMGM2019-13216) - WHOLE GENOME MOLECULAR ANALYSIS OF MENINGOCOCCAL CARRIAGE ISOLATES FROM BURKINA FASO, 2016-2017

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### Introduction & Aims

*Neisseria meningitidis* serogroup A (NmA) has historically been responsible for most epidemics in the African meningitis belt<sup>1</sup>. In 2010, Burkina Faso completed the first nationwide mass vaccination campaign of the meningococcal A conjugate vaccine (MACV; MenAfriVac®)<sup>2</sup>. While carriage and disease due to NmA in Burkina Faso was substantially reduced following vaccination, other meningococcal strains continued to cause invasive disease.<sup>3</sup> A carriage study was conducted in Burkina Faso with the goal of assessing the continued impact of MACV on NmA carriage and analyzing the diversity of meningococcal strains carried in the region.

### Materials and Methods

Four cross-sectional carriage evaluation rounds were conducted among persons aged 9 months to 36 years in villages in two districts of Burkina Faso, Kaya and Ouahigouya, between 2016 and 2017. Oropharyngeal swabs were collected and *Neisseria meningitidis* was identified using classic microbiological methods. Suspected Nm isolates were serogrouped using slide agglutination and were sent to either the Norwegian Institute of Public Health, Oslo, Norway or the Centers for Disease Control and Prevention, Atlanta, Georgia for confirmation, whole-genome sequencing, molecular analysis and phylogenetic comparisons against invasive isolates.

### Results

Among 13,763 specimens, 1029 Nm isolates were confirmed. Most of the isolates obtained (932/1029; 90.6%) were nongroupable, and many (828/1029; 80.5%) had the capsule null genotype. These nongroupable isolates primarily belonged to clonal complex (CC) 192 (816/932; 87.5%). Groupable isolates (97/1029; 9.4%) belonged to CC11 (n=81, NmW), CC10217 (n=7, NmC), CC41/44 (n=4, NmC), CC178 (n=3, NmE) and ST-9945 (n=2, NmE). No NmA carriage isolates or isolates belonging to a sequence type associated with NmA were identified. Several CC11 carriage isolates clustered with CC11 invasive isolates. Two CC10217 carriage isolates belonged to ST-13402, a previously undescribed sequence type, and the remaining CC10217 isolates belonged to either ST-10217 or ST-12446. None of the CC10217 carriage isolates clustered with invasive isolates from bordering countries.

### Conclusion

The molecular epidemiological landscape of meningococcal carriage in Burkina Faso in the seven years following MACV introduction demonstrated a continued absence of NmA and a high proportion of nongroupable carriage isolates. Serogroupable isolates primarily belonged to CCs that have caused major outbreaks in recent years, such as CC11 NmW and CC10217 NmC. Additional carriage evaluations and molecular surveillance of *N. meningitidis* will be important to evaluate the long-term impact of MACV, monitor the emergence of outbreak-associated strains, and inform future vaccine development.

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Session: Poster Session III

Room: Auditorium III

Topic: Genomics and molecular strain characterization of *Neisseria meningitidis* and *Haemophilus influenzae*  
(PO 036 - PO 044)

### PO-036 - (EMGM2019-13239) - CLINICAL AND LABORATORY CHARACTERISTICS OF INVASIVE MENINGOCOCCAL DISEASE - CROATIA 2017-2018 TIME FOR CHANGES IN THE VACCINATION POLICY?

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#### Introduction & Aims

Incidence of invasive meningococcal disease (IMD) in Croatia did not change significantly for the last two decades (below 1/100 000). During these decades the prevalent serogroup was *Neisseria meningitidis* group B. Despite hospitalization fatal cases are still recorded every year. Today meningococcal vaccines for all groups are available (A, B, C, W, Y). Yet Croatian mandatory vaccination programme does not include meningococcal vaccines.

#### Materials and Methods

Data were obtained from the meningococcal database of the University Hospital for Infectious Diseases (UHID) for 2017 and 2018. Age, serogroup, seasonality, detection methods, antibiotic susceptibility, clinical presentation and outcome were analysed. The Croatian Institute of Public Health (CIPH) data on mandatory reported cases for the same period were included.

#### Results

During 2017 and 2018, 35 patients with IMD were hospitalized at UHID - 19 in 2017 and 16 in 2018. A total of 42.9% of cases (15/35) were recorded in group of children up to 2 years of age, and 25.7% (9/35) in group of 15 to 25 years of age. Almost half of cases (16/35 or 45.7%), occurred during January and February. Most of IMD cases presented as sepsis 57.1% (20/35), some of them as sepsis and meningitis 8.6% (3/35), and 34.3% (12/35) cases as meningitis alone. The sample sent to the laboratory was blood for all 35 patients. Cerebrospinal fluid was sent for 18/35 (51.4%) patients. By PCR 42.9% (15/35) of isolates were detected as well as by culture and PCR both, while 14.2% (5/35) isolates were detected by culture only. Serogroup B represented 57.1% (20/35) of isolates. However, in 2017 serogroup C constituted 42.1% (8/19) of isolates. Most patients were treated in the intensive care unit 62.9% (22/35). All isolates from UHID in 2017 were susceptible to penicillin, ceftriaxone, ciprofloxacin and rifampicin. In 2018 even 5/16 isolates had intermediate susceptibility to penicillin but were susceptible to all other tested antibiotics. At the relevant period to the CIPH 38 IMD cases in 2017 and 31 IMD cases in 2018 and six deaths (3 each year) were reported.

#### Conclusion

The Croatian vaccination programme is mandatory and free of charge. Primo-vaccination begins at two months of age. In 2018 to the hexavalent vaccine (DTP-Polio-Hib-HBV) pneumococcal vaccine is added. Characteristics of IMD and meningococcal isolates through 2017-2018 and children fatal cases are signal to re-evaluate the need for introduction of meningococcal vaccine as a part of the mandatory vaccination programme, considering the increased rate of group C in 2017.

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## PO-037 - (EMGM2019-13243) - INCREASE OF A SPECIFIC STRAIN OF INVASIVE SEROGROUP B MENINGOCOCCAL DISEASE IN 2016-2018 IN THE NETHERLANDS

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### Introduction & Aims

From November 2016 to May 2017, a local Public Health Service in the Netherlands reported in a small region (population: ~180,000) six cases of serogroup B invasive meningococcal disease (IMD-B), all with finetype P1.22,14:F5-1, of which four cases were directly or indirectly linked to a high school. We aimed to determine the spread of IMD-B:P1.22,14:F5-1 in the Netherlands before and after the local cluster, and to describe these cases in time, place, person and strain to inform public health action.

### Materials and Methods

The Dutch national surveillance system for IMD includes clinical, epidemiological and microbiological data. We included all IMD-B cases reported from 2005 to 2018. Isolates from 2016-2018 were assessed by whole genome sequencing. Cluster analysis using *N. meningitidis* core genome v1.0 application was performed and Bexsero coverage was assessed at <https://pubmlst.org/neisserial/>. We compared IMD-B:P1.22,14:F5-1 cases with IMD-B cases with other finetypes.

### Results

Of 1403 IMD-B cases reported from 2005 to 2018, 25 (1.8%) had finetype P1.22,14:F5-1. The first case of IMD-B:P1.22,14:F5-1 occurred in 2009 (0.81% of MenB cases), followed by two cases in 2014 (3.8%), three in 2016 (4.5%), 12 in 2017 (16%), and seven in 2018 (9.5%). Of 22 cases reported in 2016-2018, 11 cases were 10-19 years old (50%), 14 had meningitis (64%), and one case died (5%). There were no significant differences between IMD-B:P1.22,14:F5-1 cases and other IMD-B cases in terms of age, sex, clinical presentation and severity.

Of 22 B:P1.22,14:F5-1 isolates, 20 were assessed by whole genome sequencing. Of these, 19 were of clonal complex 32 (cc32) and one of cc269. Cluster analyses of the 19 B:P1.22,14:F5-1:cc32 isolates and 27 other B:cc32 isolates (from 2017-2018) showed that the B:P1.22,14:F5-1:cc32 isolates grouped together into two subgroups. One subgroup comprised 12 isolates; 10 of these were from patients in a large region in the South-West of the Netherlands including the four cases linked to the high school. The other subgroup comprised five isolates of which three were from patients in another region in the South-West. All B:P1.22,14:cc32 isolates were potentially covered by Bexsero because of an exact match with one of the antigens in the vaccine.

### Conclusion

There was ongoing transmission of the B:P1.22,14:F5-1:cc32 strain in multiple regions in the Netherlands. However, B:P1.22,14:F5-1:cc32 causes only a small fraction of IMD-B cases, which is not increasing further. Although B:P1.22,14:F5-1:cc32 isolates were covered by Bexsero, group vaccination was not initiated around the local cluster, as the target population could not be defined.

## PO-038 - (EMGM2019-13207) - MOLECULAR CHARACTERIZATION OF INVASIVE NEISSERIA MENINGITIDIS OF SEROGROUP B IN ITALY

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### Introduction & Aims

The recent development of two meningococcal B (MenB) vaccines, that afford protection against multiple strains, provides new opportunities for preventing invasive meningococcal disease. In Italy, in 2017, the incidence of MenB IMD cases was higher among infants less than 12 months of age (2.8x100,000); other small peaks were recognized among children (1-4 years, 0.44x100,000) and among adolescents and young adults (15-24 years, 0.3x100,000).

To obtain molecular characterization on MenB collected from IMD in Italy from 2014 to 2017, with particular regard to the finetype and fHBP subfamily A and B and their variants.

### Materials and Methods

One-hundred and fifty-five MenB positive samples were analyzed by Whole Genome (for those culture positive, n=109) or Sanger Sequencing (culture negative, n=46) for typing. The <https://pubmlst.org/neisseria/> website was used to determine the *fhp* allele types.

### Results

cc-162 (25%), cc-41/44 (19.5%) and cc-213 (16%) were the three main cc<sub>s</sub>. Overall, 71 MenB belonged to subfamily A fHBP, 83 to subfamily B fHBP and one was an A/B hybrid fHBP. Twenty-two variants of subfamily A fHBP were found and A05 was the most frequent (n=14; 19.7%), followed by A06 (n=10; 14.1%) and A22 (n=10; 14.1%). Twenty variants of subfamily B fHBP with B231 variant (n=27; 32.5%) as the most frequent, followed by B03 (n=11; 13.2%) and B24 (n=9; 10.8%) were found.

The majority of the subfamily A variants, including the main variants A05, A06 and A22, were detected among MenB isolated in young adults or adults (age range 25-64 years; n=29; 40.8%). The majority of the subfamily B variants were detected in MenB causing disease in adolescents or young adults (age range 15-24 years; n=23; 27.7%).

The main correlations were between A05 and cc-213 (n=14, 100%) characterized by the predominant ST-213 (n=11; 78.6%); A06 and cc-461 (n=9; 90%) with ST-1946 (n=7; 70%) and A22 and cc-41/44 (n=6; 60%) with ST-414 as the main ST (n=4; 40%). The variant A05 was also correlated with P1.22,14 PorA subtype. B03 was mainly associated with cc-41/44 (n=8; 72.7%); B24 with cc-32 (n=5; 55.5%) and B231 was exclusively found among MenB belonging to cc-162 (n=25; 100%), with ST-162 as the predominant (n=22; 88%) and with F3-6 FetA subtype.

### Conclusion

A high heterogeneity was observed among MenB circulating in Italy in the period. A05 and B231 fHBP variants were the most frequent. Given marked variation among B meningococci molecular based scrutiny is crucial to evaluate strain variability during the time.

## PO-039 - (EMGM2019-13171) - GENOMIC EPIDEMIOLOGY OF NEISSERIA MENINGITIDIS SEROGROUP W ISOLATES COLLECTED IN SWITZERLAND BETWEEN 2010 AND 2016

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### Introduction & Aims

*Neisseria meningitidis*, also known as meningococcus (Men) can cause bacterial meningitis and septicaemia. Virulent isolates are classified in serogroups according to capsule components. In Switzerland the incidence of serogroup W (MenW) has steadily increased from 5% in 2005 to 35% in 2015. Sequence Type (ST)-11 was the prevalent genetic lineage and the only ST identified in 2016. MenW ST-11 strains are hypervirulent and often cause outbreaks world-wide mainly due to two circulating lineages: one originating from a South-American and the other from Saudi Arabian (Hajj clone) outbreaks. Here, we investigated potential clonal relationships among Swiss MenW by whole-genome sequencing (WGS).

### Materials and Methods

Illumina MiSeq 2x300 sequencing was performed on 40 Swiss MenW isolates collected between 2010 and 2016. Multi-Locus Sequencing Typing (MLST) was inferred on *de novo* assembled genomes and phylogenetic analyses were performed with a core genome MLST (cgMLST) gene approach. ST-11 samples were further analysed by considering cgMLST Single Nucleotide Polymorphisms (SNPs). Potential outbreaks were evaluated by considering the relative amount of SNPs between samples, the canton and date of sample isolation. Swiss isolates were also connected to reference European strains of South-American and Hajj-clone-related lineages.

### Results

Of the 40 MenW samples analysed, 34 belonged to ST-11. SNPs analyses revealed that ST-11 isolates were clustered in three main blocks. Block I contained 14 samples, 7 of which were isolated between February and July 2015 in the canton of Basel (5) and in its neighbouring regions: Bern (1) and Aargau (1). Given the narrow time window and the low number of SNPs (range = 1-4), our results argue in favor of a monoclonal outbreak. The block II contained 3 samples isolated between January and February 2014 in the canton of Ticino. No SNPs were found among these 3 samples, thereby they represented the same circulating strain. The block III contained 2 and 7 isolates from 2015 and 2016, respectively, with 1-37 SNPs identified in pairwise comparisons. These isolates likely resulted from the expansion of a strain circulating in 2015 in the German and French speaking Swiss cantons. Comparisons with other European strains showed that samples of Block-I derive from the Hajj clone lineage whereas Block-II and Block-III isolates are related to the South-American lineage.

### Conclusion

We identified potential monoclonal outbreaks by WGS and we also established connections between Swiss MenWs and other European strains.

### References

## PO-040 - (EMGM2019-13172) - WHOLE GENOME SEQUENCING OF NEISSERIA MENINGITIDIS W ISOLATES FROM THE CZECH REPUBLIC

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### Introduction & Aims

This study presents the results of the whole genome sequencing (WGS) analysis of *Neisseria meningitidis* serogroup W isolates from the Czech Republic recovered in 1984–2017. Altogether, 31 isolates, 22 from invasive meningococcal disease (IMD) and nine from healthy carriers were analysed.

### Materials and Methods

WGS was conducted by the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, using the Illumina MiSeq platform. WGS data were in our laboratory subsequently processed and optimised, using the Velvet *de novo* Assembler. The genome contigs were submitted to the *Neisseria* PubMLST database. Genomes were then analysed and compared using the BIGSdb Genome Comparator tool (scheme *N. meningitidis* cgMLST v1.0 – 1605 loci). The distance matrices were generated automatically and phylogenetic networks were constructed and edited using the SplitsTree4 and the Inkscape tool.

### Results

The study set included isolates that belonged to the following clonal complexes: cc22 (n = 10), cc174 (n = 3), three complexes, each represented by one isolate (cc41/44, cc53, cc1136), and three isolates unassigned to clonal complex. Only four study Czech isolates belonged to the hypervirulent clonal complex cc11, which is not consistent with the recent global upward trend in *N. meningitidis* W cc11 cases. Three of these four cc11 isolates were recovered between 1994 and 1996 and thus do not belong to the new lineages of *N. meningitidis* W cc11, which are spreading worldwide. Isolate 63/16 from 2016 originates from a Canadian traveller from Hungary to the Czech Republic. The most interesting finding of this study is that eight of 31 Czech isolates of *N. meningitidis* W belong to clonal complex cc865, sequence type ST-3342. Based on the data available in the PubMLST database, cc865 is uncommon in serogroup W and was only detected in seven countries (one isolate from each). So far, sequence type ST-3342 has only been identified in the Czech Republic. All cc865 isolates from other countries were assigned to different sequence types. It is interesting to note that each of these cc865 isolates has a unique sequence type. This body of evidence could support the assumption that isolates cc865, ST-3342 originate from a common ancestor that evolved in the Czech Republic.

### Conclusion

WGS analysis contributed considerably to a more detailed molecular characterization of *N. meningitidis* W isolates recovered in the Czech Republic over a 33-year period and precised the base for the update of the recommendation for vaccination in the Czech Republic.

## PO-041 - (EMGM2019-13228) - LINKING CLINICAL, EPIDEMIOLOGICAL AND GENOMIC DATA FOR MENINGOCOCCAL DISEASE IN SCOTLAND

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### Introduction & Aims

Scottish invasive meningococcal disease (IMD) data (2009 to 2016) comprising individual clinical and epidemiological data were linked to whole genome sequence data. Here, clinical-WGS linkage and case control data are presented.

### Materials and Methods

For all IMD cases (n=780) combined clinical information included: hospitalisation (pre- and post- IMD episode); prescribing; microbiological; and mortality data. The hospital-based case-control study used up to six controls per case, matching on age, gender, hospital, and date of admission (within 2 days). Conditional logistic regression was used to derive the odds ratio to allow comparison among cases and controls, accounting for the matched design. Cases and controls were stratified by age group (0, 1-4, 5-15, 16-25, 26-64, 65+ years), an interaction test used to determine if the comparison between cases and controls differed significantly among age groups.

### Results

From 337 meningococcal isolates sequenced, serogroup B were the most predominant (233, 69%), followed by serogroups W and Y (both 44, 13%), and serogroup C (14, 4%). Most isolates belonged to: cc269 (63, 19%); cc41/44 (59, 18%); cc11 (48, 14%); and cc23 (35, 10%). Relative to all other age groups, cases aged 65 years and over had an increased risk of clinical complications and death within one year. They also showed specific increased risks of: sepsis; pneumonia; bone complications; and renal failure. Serogroups, C, W, and Y were associated with an increased risk of clinical complications and death within one year compared to B. There was no impact of clonal complex (cc) on death, although cc11 and cc23 were linked with an increased risk of any clinical complications, and cc22 and cc23 were associated with pneumonia, relative to other clonal complexes. Risk of meningococcal disease sequelae differed by age, with those aged over 65 years suffering from an increased risk of amputation/bone, renal failure and skin sequelae compared to other age groups. Sequelae affecting the skin were also increased in those aged 1-4yrs, relative to other ages.

### Conclusion

Our understanding of IMD has been enhanced through linkage of genomic data with clinical and epidemiological data. Such analyses provide an important background for detecting changing patterns of clinical presentations and sequelae. Correlation with meningococcal WGS attributes allows greater scope for understanding and prevention, creating an ongoing resource for analysis and comparison. Combined with these more in-depth insights, the generation WGS data in real-time will provide, information for health protection purposes, including indications for vaccine use.

### References

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## PO-042 - (EMGM2019-13355) - FIRST CASE OF A NONINVASIVE INFECTION CAUSED BY NEISSERIA MENINGITIDIS SEROGROUP X IN PORTUGAL

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### Introduction & Aims

Neisseria meningitidis serogroup X (NmX) recently emerged as a cause of meningitis outbreaks in African meningitis belt in sub-Saharan Africa, but sporadic cases have been reported in developed countries. We present the first noninvasive infection caused by Neisseria meningitidis serogroup X in Portugal.

Case report: a 49 years old male was admitted in the hospital emergency department in April 2018, presenting a right upper lobe cavity lung lesion, a significant weight loss and some immunosuppressive disorders. He had no evidence of invasive disease.

The bronchoalveolar lavage culture, was processed in the hospital laboratory, the result was found to be positive to Neisseria meningitidis. The strain was sent to the National Reference Laboratory for group characterization and genotyping

The purpose of this study was to understand the genomic evolution of this noninvasive strain.

### Materials and Methods

After whole genome sequencing and de novo assembly, the Portuguese strain was genetically characterized. A comparative gene-by-gene analysis was also performed based on 1,605 N. meningitidis core loci, which constitute the MLST core-genome scheme (cgMLST) V1.0, to evaluate the genetic relationship between this PT strain and other serogroup strains with available genomes on Neisseria PubMLST database (until January 2019).

### Results

The finetype of the Portuguese strain was X:P1.19,15-1:F5-2. A new sequence type (ST) has been identified. Phylogenetic analysis showed that the Portuguese NmX isolate is highly divergent (in ~970 loci) from other NmX isolates reported worldwide, including the NmX ST-181 that were responsible for most meningitis outbreaks in the African meningitis belt. Interestingly, it exhibits phylogenetic proximity with serogroup B iso-lates, suggesting a possible capsular switching phenomenon.

### Conclusion

So far, NmX capsular switching has been mostly associated with NmA. Here, we describe a new NmX strain that, although in a speculative basis, seems to emerge from NmB strains. Ongoing targeted genomic studies will test this hypothesis. From our knowledge, this is the first case of inferior respiratory infection caused by NmX worldwide.

**PO-043 - (EMGM2019-13356) - NEISSERIA MENINGITIDIS SEROGROUP W IN PORTUGAL: A 16-YEAR STORY**

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**Introduction & Aims**

Since the implementation of the laboratory based surveillance system of invasive meningococcal disease (IMD) in Portugal, in October 2002, there is evidence of a very low incidence rate of IMD due to *N. meningitidis* serogroup W (MenW). Considering the worldwide emergence of new sublineages of MenW, belonging to the clonal complex 11 (cc11), with an increasing mortality and unusual clinical presentation, and the slight increase of invasive MenW strains in Portugal since 2016 we aimed to understand the genetic evolution of these Portuguese strains. The goal of this study was to know the phylogeny characteristics of the MenW strains isolated in Portugal and to understand their evolutionary relationship with strains of the same serogroup and clonal complex, with a diverse geographical and temporal distribution.

**Materials and Methods**

MenW strains, isolated in Portugal from 2003 to 2018, were subjected to whole-genome sequencing (WGS). For genomic comparison, 1,560 genomes MenW cc11 available on *Neisseria* PubMLST database (<http://PubMLST.org/neisseria>) (until November 15<sup>th</sup> 2018) were selected. For the bioinformatics analysis, the chewBBACA free software was used for a comparative "gene-to-gene" based approach of 1,605 *N. meningitidis* core loci, which constitute the MLST core-genome scheme (cgMLST) V1.0. To evaluate the possible evolutionary relationship between isolates MenWcc11, the goeBURST algorithm from the PHYLOVIZ online platform was used.

**Results**

During the 16-year study period, 24 cases of IMD due to MenW were registered in Portugal. From 2003 to 2007 it was observed a decreasing trend in the number of cases, mostly affecting children, followed by a eight years period with just two cases (2012 and 2013).

From 2016 it was observed an increasing trend in the number of cases, affecting mainly adults. Only one case was due to MenW genotyped as W:P1.18-1,3:F4-1:cc22. From all the remaining cases, MenW cc11 strains identified were genotyped as W:P1.5,2:F1-1:cc11, clustering to the lineages Original UK and Novel UK, which emerged from the South-American strain.

**Conclusion**

Although the number of invasive MenW strains isolated in Portugal is low, data indicates a scenario quite similar to the one observed in other European countries, where it has been reported an increasing number of IMD cases due to MenW cc11 lineages emerging from the South American strain. As they are associated with atypical clinical picture and high fatality rate, it would be prudent to maintain a high level of surveillance to monitor the cases by MenW cc11.

## PO-044 - (EMGM2019-13233) - THE MENINGOCOCCAL CAPSULE LOCUS CONTAINS SEQUENCES ACQUIRED BY HORIZONTAL GENETIC TRANSFER FROM NEISSERIA SUBFLAVA, AND OTHER NEISSERIA SPECIES

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### Introduction & Aims

Possession of a meningococcal capsule from one of serogroups A, B, C, W, X or Y is virtually essential for *Neisseria meningitidis* to cause invasive meningococcal disease. It has been proposed that the capsule locus may have been acquired in a formerly capsule null isolate by horizontal genetic transfer (HGT) from another species, conferring pathogenic potential upon the bacterium [1,2,3]. The aim of this study was to further characterise the evolutionary history of the meningococcal capsule, and determine whether phylogenetic analyses of sequences within the capsule locus are consistent with an HGT acquisition model.

### Materials and Methods

Whole genome sequencing data were obtained from pubmlst.org/neisseria, hosted on BIGSdb, and GenBank, making use of isolates from the 107 global dataset, UKMenCar4, the MRF genome library and others. Isolates included meningococci from a broad range of serogroups and clonal complexes, as well as other *Neisseria*, and species from other genera. Isolates were investigated using phylogenetic analyses including the Neighbor-Net algorithm, BOOTSCANning within Recombination Detection Programme 4, and maximum likelihood.

### Results

In splits graphs generated using the Neighbor-Net algorithm, meningococcal Region B sequences grouped with the most weight with putative homologues in *N. subflava*, whilst Region C grouped with isolate 10022 (CP023429.1) belonging to the novel species "*N. weixi*". However, splits graphs were highly reticulate, and BOOTSCANning of the sequences of interest was consistent with Region B from some meningococci, and Region C from all meningococci, being mosaic.

Sequences for which BOOTSCANning best supported *N. subflava* as the nearest neighbour grouping were further analysed using maximum likelihood phylogenies; meningococcal sequences were found to be nested within homologous *N. subflava* sequences, consistent with horizontal genetic transfer of sequences from *N. subflava* to *N. meningitidis*.

Region D, and its duplicate Region D' in the meningococcal capsule locus, were also investigated using the Neighbor-Net algorithm and BOOTSCANning. In many cases, analyses were consistent with acquisition of *rfbBAC' + galE1* by HGT from other *Neisseria* species, as opposed to duplication of *rfbBAC + galE* native to capsule null meningococci, although analyses were impeded by re-orientation events that take place within the capsule locus.

### Conclusion

The evolutionary history of the meningococcal capsule is complex, with evidence of HGT events involving *N. subflava*, as well as other *Neisseria* species. This has resulted in highly mosaic sequences within the capsule locus. Analyses were consistent with, but not proof of, *en bloc* acquisition of capsule in meningococci, for which *N. subflava* could be a plausible donor.

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**PO-045 - (EMGM2019-13198) - MENINGOCOCCAL CARRIAGE IN TEENAGERS IN NORWAY**

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**Introduction & Aims**

In Norway, the incidence of invasive meningococcal disease (IMD) was high during the 1970s-1990s, especially in young children and teenagers. Over the last 20 years the incidence has been declining. However, there is still an accumulation among teenagers with a yearly incidence rate of 1-7 cases per 100 000, mostly caused by serogroup Y. Since 2011, there has been a national recommendation for meningococcal ACWY vaccination of 16-19 year olds engaged in activities that increase the risk of IMD. Vaccination is usually performed by school health services at the student's own cost, with an uptake of around 40% in graduating students aged 18-19 years. The aim of the study was to analyze the risk of IMD in Norwegian teenagers by analyzing carriage of *Neisseria meningitidis* in oropharyngeal swabs. Data on risk factors for meningococcal carriage were assessed using a questionnaire.

**Materials and Methods**

Students aged 13-16 (lower secondary school) and 16-19 (upper secondary school) in eastern Norway were invited to participate in the study. Oropharyngeal swabs were collected in Oct-Nov 2018 and plated on site. Standard culturing techniques were used and species identification was confirmed with MALDI-TOF. Isolates were further characterized by whole genome sequencing.

**Results**

Oropharyngeal swabs were obtained from 1361 of the 1365 included students. Mean age was 16 years and 61% were females. Overall carriage rate of *N. meningitidis* was 7.7%, with lowest carriage in the lower secondary schools (2.5%) compared to upper secondary schools (10.1%). Carriage rate was highest in students graduating from upper secondary schools (16.2%). Non-groupable (NG) isolates dominated (58.1%), followed by isolates carrying serogroup Y (21.9%) and B (11.4%) capsular genes. Serogroup C, W and X capsular genes occurred each in 2.9% of the strains. There were 28 sequence types (STs) among the 105 isolates. Most NG isolates belonged to ST-823 (29.5%), while all isolates with serogroup Y capsular genes belonged to the ST-23 clonal complex. The dominant STs were observed in many of the schools.

**Conclusion**

Carriage rate of *N. meningitidis* in Norwegian teenagers increased with age. In 2018, 50% of the IMD cases in Norway were caused by the ST-23 clonal complex, the second most common clonal complex found in the carriage isolates. Carriage studies are important to provide knowledge of the current epidemiology in order to guide vaccination policies for groups at risk of IMD.

**References**

## PO-046 - (EMGM2019-13215) - MOLECULAR CHARACTERISTICS OF NEISSERIA MENINGITIDIS CARRIAGE ISOLATES RECOVERED DURING THE SEROGROUP C OUTBREAK IN TUSCANY, ITALY.

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### Introduction & Aims

Between 2015-2016, Tuscany Region was affected by an outbreak of invasive meningococcal disease (IMD) due to *Neisseria meningitidis* serogroup C clonal complex 11 (MenC:cc11). To gain insight into the origin and spread of the outbreak strain, several initiatives and studies were implemented by public health authorities, including a cross-sectional carriage survey.

The aim of this study was to assess the main genomic traits of meningococcal carriage isolates collected during the survey.

### Materials and Methods

Eighty-five meningococcal isolates, derived from asymptomatic carriers, aged 11-45 years, were received at the National Institute of Health (Istituto Superiore di Sanità, ISS), as National Reference Laboratory (NRL) for IMD, which carried out the whole-genome sequencing analysis. *De novo* assembled genomes were scanned by the BIGSdb platform to assign the genotypic profiles, *i.e.* capsular genogroup, PorA (P1). VR1,VR2, FetA (FVR, ST (cc). The 4CMenB vaccine antigen variants and the allele types of genes involved in antimicrobial resistance and denitrification pathway were also included in the analysis.

### Results

The majority of carriage isolates had the capsule null locus (*cnI* 52.9%); among those groupable (36.5%), serogroup B was the most prevalent (71.0%), followed by Y (22.6%). Serogroup C was culture negative and identified by PCR. Overall, cc1136 (22.3%), cc198 (15.3%) and cc53 (14.1%), exclusively associated with *cnI*, were found. MenB was associated to cc865 (22.7%) and cc41/44 (18.2%); MenY to cc23 (85.7%). Sixty-four genotypic profiles were identified, of which 83% represented by single isolates; the most common profile was *cnI*:P1.18-4,25:F4-49:ST-1136 (cc1136) (8.2%). Eight isolates (9.4%) showed a genotypic match to at least one of the 4CMenB vaccine antigens. Mutated *penA* alleles were found in 82.3% of isolates; *penA9* was the most frequent (24.7%) and found mainly among cc198 (38.1%). Finally, complete *aniA* and *norB* coding sequences were detected in 71.8% of carriage isolates, including 100% of *cnI* isolates and 45.4% of MenB.

### Conclusion

Overall, this study provided evidence of an extensive diversity among meningococcal carriage isolates collected during a MenC:cc11 outbreak in Italy. Even though an outbreak is a multifactorial event resulting from changes in host-pathogen interactions, the lack of outbreak-related carriage isolates suggests a quite low recovery of MenC:cc11 in the pharynx and is consistent with a high transmissibility of this hyper-invasive strain.

**PO-047 - (EMGM2019-13234) - MENINGOCOCCAL CARRIAGE AMONG UNIVERSITY STUDENTS IN SWEDEN**

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**Introduction & Aims**

Two serogroups of meningococci, Y (clonal complex [CC]23) and W (CC11), previously relatively harmless, have emerged and account for the majority of the disease in Sweden [1-3]. Because meningococci have been shown to be carried by about 10% of the population in other countries in endemic situations, invasive disease only represents a small portion of the meningococci circulating. The aim of this study was to investigate the meningococci carried asymptotically in order to understand changes in epidemiology.

**Materials and Methods**

Students at Örebro University were recruited to the study during September 2018 (sampling will continue in January, May and September 2019). The students filled out an anonymous questionnaire and swab samples were taken using E-swab (Copan). The E-swab samples were DNA extracted and screened for meningococci by PCR using the *ctrA* and *crgA* genes. The positive samples were cultured using selective and non-selective agar plates over-night. Identification was made using oxidase test and MALDI-TOF. All meningococcal isolates were whole-genome sequenced using MiSeq (Illumina). The 1605 loci included in the *Neisseria meningitidis* cgMLST v1.0 [4] defined in pubMLST.org was used to compare the carriers (n=105) to all invasive meningococcal isolates during 2018 in Sweden (n=51). PCR positive and culture negative samples will be genogrouped and characterized by MLST, PorA and FetA-typing.

**Results**

The preliminary results from the recruitment in September showed that 105 out of the 1,362 students (8%) were culture and PCR positive. Another 131 samples were PCR positive and culture negative, but have not yet been confirmed. The invasive isolates in Sweden belonged to CC11 (55%), CC23 (31%), CC32 (8%), CC41/44 (4%) and CC269 (2%). Preliminary data on 105 of the culture and PCR positive carrier isolates showed that the four most prevalent CCs were CC198 (16%), CC23 (13%), CC1157 (12%) and CC32 (11%). Only one isolate was CC11, and belonged to the UK 2013 strain.

**Conclusion**

The preliminary results indicate that there is a high prevalence of serogroup Y CC23 in carriage isolates as well as in invasive isolates. Although the increase of serogroup Y isolates started around 10 years ago, the results may suggest that the increased incidence was a reflection of a high carriage rate of serogroup Y meningococci in Sweden. Inversely, because only one carriage isolate belonged to CC11, which is the most prevalent CC among invasive isolates at the moment, this indicates that these isolates have a low carriage rate but higher attack rate.

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## PO-048 - (EMGM2019-13194) - EPIDEMIOLOGY AND MOLECULAR CHARACTERIZATION OF NEISSERIA LACTAMICA CARRIED IN CHILDREN YOUNGER THAN 15 YEARS IN SHANGHAI, CHINA

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### Introduction & Aims

*Neisseria lactamica* can induce natural immune against *N. meningitidis* and transfer antimicrobial resistance to *N. meningitidis* [1, 2]. *N. lactamica* was reported to be frequently found in the upper respiratory tract in young children in several countries [3-5], but little is known about the carriage and characterization of *N. lactamica* in children of China.

### Materials and Methods

During 2014-2016, oropharyngeal swabs were collected from 2,239 children younger than 15 years in Shanghai, China. *N. lactamica* isolates were isolated and tested the minimum inhibitory concentrations (MICs) of ciprofloxacin and penicillin. All the isolates were performed multi-locus sequence typing (MLST) and phylogenetic analyses based on the concatenated sequences of the seven loci used for MLST.

### Results

During 2014 and 2016, the overall carriage rate of *N. lactamica* was 8.9% (200/2,239), with no significant difference by gender (male 9.0% vs female 8.8%,  $P=0.88$ ). The *N. lactamica* carriage rate was 15.5% in children aged one year, and peaked at two years (37.1%), then decreased with age, with exception at ten years (11.4%). The MICs of ciprofloxacin to the 200 *N. lactamica* isolates ranged from 0.06 µg/ml to 1 µg/ml, with the MIC<sub>50</sub> and MIC<sub>90</sub> as 0.25 µg/ml and 0.5 µg/ml, respectively. The MICs of penicillin to the *N. lactamica* isolates ranged from 0.125 µg/ml to 4 µg/ml, with the MIC<sub>50</sub> and MIC<sub>90</sub> as 1 µg/ml and 2 µg/ml, respectively. According to the breakpoints for *N. meningitidis* recommended by EUCAST, all the *N. lactamica* isolates were resistant to both fluoroquinolones and penicillin. A total of 65 STs were identified, of which 58 were first discovered. Four clonal complexes (ccs) were represented by 74% (148/200) of isolates, with cc640 (45.5%) dominating, followed by cc613 (13.5%). Phylogenetic analysis showed that in *N. lactamica* STs, except the clusters corresponding to the four ccs, there were three clusters composed of STs not assigned to any known cc, including one close to cc613, one close to cc595, and one distant from any other cluster. Comparing with the same ccs from UK, Burkina Faso, and Brazil by sequences of the seven loci, cc640 from Shanghai constituted distinct STs, while cc595, cc613, and cc624 were much similar to those from other countries.

### Conclusion

The overall carriage rate of *N. lactamica* was 8.9% in children younger than 15 years in Shanghai, China, peaking at age group of two years (37.1%). All the *N. lactamica* isolates showed resistance to fluoroquinolones and penicillin. The clonal complex cc640 was predominate.

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## PO-049 - (EMGM2019-13340) - IMPACT OF PCV13 PRIVATE USE ON CARRIAGE OF PNEUMOCOCCAL SEROTYPES AMONG CHILDREN IN AN URBAN AND RURAL REGION OF PORTUGAL

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### Introduction & Aims

#### Background

*Streptococcus pneumoniae* (pneumococcus) colonizes asymptotically the human nasopharynx, particularly of young children. The pneumococcus causes infectious diseases worldwide such as otitis media, pneumonia, bacteremia and meningitis. The major virulence factor is the polysaccharide capsule, and at least 95 capsular types (serotypes) are currently known. In Portugal, a seven-valent pneumococcal conjugate vaccine (PCV7, targeting serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) became commercially available in 2001. In January 2010, PCV7 was replaced by a 13-valent vaccine (PCV13, targeting PCV7-types plus serotypes 1, 3, 5, 6A, 7F and 19A). In Portugal, PCV13 was introduced in the national immunization plan in July 2015.

We evaluated the impact of PCV13 private use on serotypes carried by children attending day-care centers in an urban and a rural region of Portugal.

#### Materials and Methods

Three periods were studied: pre-PCV13 (2009-2010), early-PCV13 (2011-2012) and late-PCV13 (2015-2016). Pneumococci were isolated from nasopharyngeal samples of 4,232 children up to 6 years old. All isolates were serotyped by multiplex PCR and/or the Quellung reaction.

#### Results

Pneumococcal carriage remained stable in both regions (range: 59.5-62.8%). Vaccination with PCVs was high in both regions (range: 76.8-89.3%). Carriage of PCV13 serotypes decreased significantly from the pre- to the late-PCV13 period (21.6% to 5.9% in the urban region; 15.9% to 6.8% in the rural region,  $p < 0.001$ ) mostly due to a decrease in the prevalence of serotype 19A (the most abundant serotype in the pre-PCV13 period). Serotype 19F was the most prevalent PCV13-type in the late-PCV13 period in both regions, albeit reflecting different scenarios: it decreased in the urban region over time from 4.4% to 1.7% ( $p = 0.009$ ), while it increased in the rural region from 1.6% to 4.5% ( $p = 0.017$ ). The most prevalent non-PCV13-types in the late-PCV13 period were 15B/C (5.9%), 23B (5.7%) and 11D (5.6%) in the urban region, and 15A (6.4%), 23A (5.0%), and 35F (4.8%) in the rural region.

#### Conclusion

We conclude that, after six years of PCV13 use in the private market, carriage of pneumococci remained stable among children attending day-care centers in Portugal due to serotype replacement. As children are major reservoirs of pneumococci these results should trigger a herd effect in other age groups.

## PO-050 - (EMGM2019-13353) - PCV13 IMPACT ON THE EVOLUTION AND ADAPTATION OF THE PNEUMOCOCCAL POPULATION CARRIED BY PORTUGUESE CHILDREN

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### Introduction & Aims

*Streptococcus pneumoniae* (pneumococcus) colonizes asymptotically the human nasopharynx. Children attending day-care centers are major reservoirs of pneumococci contributing significantly to their transmission in the community. Pneumococcus is also a major worldwide cause of infectious diseases worldwide such as otitis media, pneumonia, bacteremia and meningitis. The major virulence factor of pneumococci is its polysaccharide capsule, and at least 95 different capsular types (serotypes) are currently known. In Portugal, a seven-valent pneumococcal conjugate vaccine (PCV7, targeting serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) became commercially available in 2001. In January 2010, PCV7 was replaced by a 13-valent PCV (PCV13, targeting PCV7-types plus serotypes 1, 3, 5, 6A, 7F and 19A). PCV13 was introduced in the national immunization plan in July 2015.

### Materials and Methods

We evaluated the impact of PCV13 private use on clonal distribution of pneumococci carried by children attending day-care centers in an urban and a rural region of Portugal. Three periods were studied: pre-PCV13 (2009-2010), early-PCV13 (2011-2012) and late-PCV13 (2015-2016). We selected a sample of 657 isolates from this collection to be typed by Multilocus Sequence Typing (MLST), the state of the art technique for molecular typing of *S. pneumoniae*.

### Results

We identified 171 sequence types (STs), of which 39 were new allelic combinations, and 5 were new alleles. The most prevalent STs were ST439 (n=32, 4.9%), ST30 (n=29, 4.4%) and ST180 (n=28, 4.3%), associated with serotypes 23A/B, 16F and 3, respectively. For most serotypes covered by the vaccine, antibiotic resistant STs were selected overtime. The multiresistant ST179 was associated with vaccine type 19F in the late-PCV13 period. Serotype 19A was the most diverse serotype in the pre-PCV13 period with 13 STs; however, it was associated with only 3 STs in the late-PCV13 period. Regarding the serotypes not covered by the vaccine, in the late-PCV13 period, novel, fully susceptible STs were detected. These were of ST4083, ST5139, ST473, ST39, ST9976 and ST445 associated with serotypes 34, 15A (both ST5139 and ST473), non-typeable, 16F and 22F, respectively.

### Conclusion

In conclusion, following private use of PCV13, we observed a decrease in the number of clonal lineages associated with vaccine types and the emergence of clones, not detected in the early periods, associated with non-vaccine types.

Session: Oral Session VII  
Room: Auditorium I

H. influenzae – old vs new foes

### OC - (EMGM2019-13190) - RECENT EVOLUTION OF THE EPIDEMIOLOGY OF HAEMOPHILUS INFLUENZAE TYPE B AND SEROPREVALENCE IN FRANCE

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#### Introduction & Aims

The Hib vaccine was introduced in France in 1992. The schedule was 3+1 (2, 3, 4 months and a booster between 16-18 months) until 2012. A drastic decline in invasive Hib disease was observed thereafter. In 2013, the schedule changed to 2+1 (2, 4 months and a booster at 11 months). In 2018, an increase in the number of Hib invasive diseases was observed at the National Reference Centre that was associated with several cases of vaccine failures in children under the age of 5 years. We describe here these trends and results from a serosurvey before and after the schedule change.

#### Materials and Methods

Hib invasive disease was confirmed by the detection of *H. influenzae* in a sterile site. Isolates were typed by PCR. Hib isolates were also checked for the production of the capsule. A serosurvey was also performed to determine the prevalence of anti-polyribosylphosphate (anti-PRP) IgG antibodies in about 500 residual samples (from 2010 to 2018) from subjects of different ages (0-96 years).

#### Results

The number of invasive Hib isolates remained low in France (<10 cases per year) until 2018 where the number of cases was doubled with most of the cases among children <5 years old and more than 10 vaccine failures.

Mean anti-PRP IgG concentrations were highest among 2 year olds under the original schedule (3+1 for the period 2010-2013) at 4.5 µg/mL and then declined close to 1.0 µg/mL until the age of 20 years corresponding to the age groups vaccinated since 1992. However, the seroprevalence curve changed significantly in the period 2016-2018 (under the new schedule 2+1). The highest Mean anti-PRP IgG concentrations was observed among the 6-11 months of age but with lower mean of 2.9 µg/mL. The concentrations declined to <1 µg/mL at the age of 4-5 years.

We also explored the cases of vaccine failure that were among children vaccinated according to the 2+1 schedule and that corresponded to a decline of the IgG concentrations to <1 µg/mL.

#### Conclusion

The boost at the second year of life may be important to secure persistent high levels of anti-PRP IgG. These data should be important to adapt vaccination strategies against Hib in France as well as other countries using the schedule of 2, 4 and 11 months.

#### References

## OC - (EMGM2019-13331) - HAEMOPHILUS INFLUENZAE SEROTYPE B VACCINE FAILURE IN PORTUGAL: A NEW THREAT?

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1 - Haemophilus influenzae Reference Laboratory-National Institute of Health Dr. Ricardo Jorge; 2 - Departamento Pediatria-Hospital Vila Franca de Xira; 3 - Infectious Diseases Unit, Department of Paediatrics- Centro Hospitalar Universitário de Lisboa Norte

### Introduction & Aims

Invasive disease due to *Haemophilus influenzae* type-b (Hib) suffered a dramatic reduction in countries that introduced routine immunization of infants with the conjugate vaccine. However, along with the relative increase of *H. influenzae* non-typeable invasive strains (NTHI), the emergence of non-b serotypes as well as Hib disease due to vaccine failure (VF) have been described.<sup>1-4</sup>

The aim of our study is to identify and characterize Hib VF in children living in Portugal.

### Materials and Methods

From January 2010 to December 2018, 94 invasive *H. influenzae* strains isolated from paediatric patients in 25 Hospitals were characterized. Serotype was identified by PCR with primers and conditions described in the literature.<sup>5</sup> Antibiotic susceptibility was determined by microdilution. Genetic relatedness was examined by MLST as previously described.<sup>6</sup> Sequences were analysed and submitted to the MLST website (<https://pubmlst.org/hinfluenzae/>) for assignment of the sequence type (ST). A case of VF was considered if invasive Hib disease occurred  $\geq 2$  weeks after one Hib vaccine dose, given after the first birthday, or  $\geq 1$  week after  $\geq 2$  doses, given at  $< 1$  year of age.<sup>1</sup>

### Results

Among 94 invasive *H. influenzae* isolates, 29 (30.8%) were Hib, with half of the cases occurring in the last two years and 72% among pre-school children. Eighteen (62%) cases were considered VF: three infants, seven between 13 and 47 months old and eight  $\geq 4$  years old. A risk factor for VF was identified only in one case. The main diagnosis were pneumonia (6), meningitis (5), epiglottitis (3) bacteremia (2), sepsis (1), and arthritis (1). One patient died. All isolates from VF cases were characterized in CC6 (ST6, ST190, ST1231) according to the expected results for Hib. In addition, WGS published data from our laboratory showed that five Hib isolates from VF, segregated together with Hib isolates (37) from both pre- and pos-vaccination periods. All VF isolates were susceptible to ampicillin.

### Conclusion

Although the numbers are small, an alert is made by this study, as Hib VF seems to be increasing in previously healthy children with a clinical course that may be as severe as the observed in unvaccinated children. Also 44% of the VF occurred at an age ( $\geq 4$  years-old) where invasive Hib disease was unusual before Hib-conjugate vaccination. Further analysis should be made considering vaccine formulations used, as no difference in vaccine schedule was made in the NIP, possible decline of protective antibody titers and a correlation with Hib carriage in our population.

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## OC - (EMGM2019-13311) - THE RISE (AND FALL) OF INVASIVE HAEMOPHILUS INFLUENZAE SEROTYPE A (HIA) DISEASE IN ENGLAND

Sarah Collins (United Kingdom)<sup>1</sup>; Natalie Groves (United Kingdom)<sup>1</sup>; Norman K Fry (United Kingdom)<sup>1</sup>; Shamez N Ladhani (United Kingdom)<sup>1</sup>; [David Litt](#) (United Kingdom)<sup>1</sup>

1 - Immunisation and Countermeasures Division, Public Health England

### Introduction & Aims

Due to the successful national childhood immunisation programme, invasive *Haemophilus influenzae* serotype b (Hib) disease is now rare in England.<sup>1</sup> Consequently, NTHi are now responsible for the majority of invasive *H. influenzae* disease; Hif and Hie account for nearly all encapsulated serotypes.<sup>2</sup> Invasive Hia infections are historically very rare (average <1 case/year). However, an increase in cases of invasive Hia disease in England was noted since December 2016.

**Aims:** To describe the epidemiology, clinical characteristics and genomics of the post-2015 cases of invasive Hia disease and to compare these with previously reported cases.

### Materials and Methods

Public Health England (PHE) conducts enhanced national surveillance of invasive *H. influenzae* disease in England. Following the recent increase Hia cases, detailed clinical information was requested for Hia cases since 2008 from general practitioners and clinicians. Bacterial isolates were characterised by serotyping, multilocus sequence typing (MLST) and whole genome sequencing (WGS).

### Results

Between January 2008 and December 2015, only five invasive Hia cases were reported in England. However, from December 2016 to December 2017 10 cases were reported. There were three additional cases in 2018.

The post-2015 cases were predominately diagnosed in older adults (median 56 years; IQR=2-73 years); seven were male, six female. Eight cases were known to have comorbid conditions. The cases were geographically diverse, with no known epidemiological links. In comparison, the five pre-2016 cases' median age was 1 year old (IQR=0.5-37 years p=0.2); four were male, 1 female, and three had comorbid conditions.

MLST analysis revealed that isolates from 2014 onwards were closely related and clustered around ST23, whereas older isolates were genetically dispersed. WGS analysis confirmed this distinction and that the new isolates had not arisen by capsule replacement in Hib strains.

### Conclusion

In England, where cases of invasive Hia disease are rare, it is highly unusual to have 10 cases within 13 months. The recent cases were predominantly among older adults, with underlying comorbid conditions. This clinical picture is similar to two recent cases of Hia disease noted in Italy,<sup>3</sup> but contrasts with earlier reports of predominantly childhood cases in the North American Arctic and Brazil.<sup>4,5</sup> The geographical diversity and lack of an epidemiological link suggests widespread carriage of Hia. The clonality of the isolates around ST23 is similar to other studies. The unexpected recent increase and subsequent decline in cases due to this rare serotype highlights the importance in ongoing national surveillance.

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## OC - (EMGM2019-13210) - INVASIVE HAEMOPHILUS INFLUENZAE SEROTYPE A DISEASE—UNITED STATES, 2008–2017

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1 - Centers for Disease Control and Prevention; 2 - New York State Department of Health; 3 - New Mexico Department of Health; 4 - Johns Hopkins Bloomberg School of Public Health; 5 - Colorado Department of Public Health and Environment; 6 - Connecticut Department of Public Health; 7 - California Department of Public Health; 8 - Vanderbilt University School of Medicine; 9 - Minnesota Department of Health

### Introduction & Aims

*H. influenzae* serotype b (Hib) conjugate vaccines introduced in the United States during the 1980s dramatically decreased Hib incidence. Since then, the incidence of *H. influenzae* serotype a (Hia) disease has increased by an average of 13% annually from 2002–2015. Hia can cause invasive disease similar to Hib; however, no Hia vaccine is available. We describe the epidemiology and clinical severity of invasive Hia disease in the United States during 2008–2017.

### Materials and Methods

Active population- and laboratory-based surveillance for invasive Hia disease was conducted through Active Bacterial Core surveillance in 10 U.S. sites. Sterile-site isolates were serotyped via slide agglutination and real-time polymerase chain reaction. Projected nationwide annual incidences per 100,000 population were standardized for race and age; unknown race was multiply imputed. On a subset of Hia cases from 2011–2015, additional data were retrospectively abstracted from medical records to describe the clinical severity and adverse clinical outcomes.

### Results

From 2008–2017, 384 cases of invasive Hia disease (estimated national annual incidence: 0.1) were reported. Overall, 166 (43%) cases were in children aged <5 years (incidence: 0.65), with highest incidence among children aged <1 year (1.65). Incidence among children aged <5 years increased from 0.36 in 2008 to 0.79 in 2017. Among children aged <5 years, 44 (27%) cases were in American Indians and Alaska Natives (AI/AN) and disease incidence was 17 times higher among AI/AN than among all other races combined (8.35 vs. 0.50, respectively). Clinical presentation varied: among all patients, 40% had bacteremic pneumonia, 32% had bacteremia, and 24% had meningitis; among children aged <5 years, 48% had meningitis. From 2011–2015, 169 Hia patients had additional data abstracted from medical records: 95% were hospitalized, 28% required mechanical ventilation, 46% required intensive care, and 7% died. Overall, 17% of patients had adverse clinical outcomes at hospital discharge, as did 16% one-year after disease onset. At both time points, children aged <1 year had the highest proportion of cases with adverse clinical outcomes (34% and 36%, respectively), including hearing loss, developmental delay, and speech delay.

### Conclusion

Though overall Hia incidence remained low, the highest disease burden was among AI/AN children. The disease can be severe, causing short- and long-term adverse clinical outcomes, especially among infants. In the context of increasing Hia incidence and clinical severity similar to Hib, new prevention strategies, including development of a Hia vaccine, could prevent morbidity and mortality.

Session: Oral Session VIII

Room: Auditorium I

Meningococcal Vaccines

### OC - (EMGM2019-13221) - 4CMENB, A MULTICOMPONENT MENINGOCOCCAL VACCINE DEVELOPED FOR SEROGROUP B MENINGOCOCCI ELICITS CROSS-REACTIVE IMMUNITY ALSO AGAINST SEROGROUPS C, W AND Y

Alessia Biolchi (Italy)<sup>1</sup>; Gabriella De Angelis (Italy)<sup>1</sup>; Monica Moschioni (Italy)<sup>1</sup>; Sara Tomei (Italy)<sup>1</sup>; Brunella Brunelli (Italy)<sup>1</sup>; Maria Giuliani (Italy)<sup>1</sup>; Stefania Bambini (Italy)<sup>1</sup>; Ray Borrow (United Kingdom)<sup>2</sup>; Heike Claus (Germany)<sup>3</sup>; Maria Cecilia O. Gorla (Brazil)<sup>4</sup>; Eva Hong (France)<sup>5</sup>; Ana Paula S. Lemos (Brazil)<sup>4</sup>; Jay Lucidarme (United Kingdom)<sup>2</sup>; Muhamed-Kheir Taha (France)<sup>5</sup>; Ulrich Vogel (Germany)<sup>3</sup>; Maurizio Comanducci (Italy)<sup>1</sup>; Sonia Budroni (Italy)<sup>1</sup>; Marzia Monica Giuliani (Italy)<sup>1</sup>; Rino Rappuoli (Italy)<sup>1</sup>; Phillip Boucher (United States of America)<sup>6</sup>; Mariagrazia Pizza (Italy)<sup>1</sup>

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#### Introduction & Aims

Invasive meningococcal disease, mainly caused by 6 meningococcal serogroups (MenA, MenB, MenC, MenW, MenX and MenY), remains a major public health concern worldwide. The 4-component MenB vaccine (4CMenB) contains 4 main antigens (factor H binding protein [fHbp], Neisseria adhesin A [NadA], Neisserial heparin binding antigen [NHBA] and porin A [PorA]) that are also conserved in some non-MenB strains. This study evaluated the ability of sera from infants and adolescents vaccinated with 4CMenB to induce complement-mediated killing of MenC, MenW, and MenY strains collected in 3 European countries and Brazil.

#### Materials and Methods

227 non-MenB clinical isolates collected in 01/07/2007-30/06/2008 by reference laboratories in the UK, Germany and France (Euro-3 panel), and 41 non-MenB isolates collected in 2012 in Brazil were classified by serogroup, multilocus sequence typing (MLST) and antigen genotypes. 147 strains representative of STs and antigen genotypes were randomly selected and tested in a serum bactericidal antibody (SBA) assay using pooled immune sera from infants and adolescents immunized with 4CMenB.

#### Results

In the Euro-3 panel, MenC represented 57%, MenY 22% and MenW 16% of the isolates that mainly belonged to the ST-11, ST-23/ST-167 and ST-22 clonal complexes, respectively. In the Brazilian panel, MenY represented 49%, MenW 39% and MenC 12% of the isolates that belonged to the ST-22, ST-11 and ST-103 clonal complexes, respectively. The SBA assays with MenC, MenW, and MenY strains showed that 74.1% and 61.9% of the non-MenB strains tested were killed by infant and adolescent sera, respectively, with SBA titers ranging from  $\geq 4$  to  $\geq 128$ .

#### Conclusion

4CMenB can provide cross-protection against non-MenB strains in both infants and adolescents, which represents an added benefit of this vaccine.

#### References

Clinical Trial Registrations: NCT00518180, NCT00661713, NCT00944034, NCT00847145, NCT00657709.

## OC - (EMGM2019-13240) - GENETIC VARIABILITY OF THE MENINGOCOCCAL SEROGROUP B VACCINE ANTIGENS: ANALYSIS OF 2015-2016 INVASIVE MENB STRAINS IN SPAIN

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### Introduction & Aims

With the **aim** to analyze the diversity of Spanish invasive MenB strains, and genetic variability of the vaccine antigens, all MenB isolates received at National Reference Laboratory (NRL) in 2015 and 2016 were molecularly characterized.

### Materials and Methods

108 and 103 invasive MenB strains isolated during 2015-2016, respectively, were received at NRL. The strains were whole genome sequenced, and *porA*, *fetA*, MLST, *fHbp*, *nhba* and *nadA* variability was analyzed.

### Results

Fifty different PorA genotypes were identified, the most frequent being 22,14 (n=59, 28%) and 22,9 (28, 13.3%), predominant in cc213 and cc269 strains, respectively. The PorA VR2 variant 4, one of the 4CMenB vaccine components, was present in 17 (8.1%) of the total strains.

The *fHbp* gene was present in all isolates. Fifty seven different fHbp peptides were identified (29 subfamily A, 25 subfamily B, and 3 subfamily A/B hybrid), of which more than half (n=31, 54.4%) were present only in one isolate. FHbp subfamily A peptides were harboured by most of the strains (n=130, 61.6%), while fHbp subfamily B and A/B hybrid peptides were harboured by 76 (36.0%) and 5 (2.4%) isolates, respectively. Peptide 45, corresponding with rLP2086 vaccine variant A05, was the most prevalent (n=29, 13.7%), harboured by cc213 strains. The other rLP2086 vaccine variant, B01 (peptide 55) was not present in any isolate; and peptide 1 (variant B24), the fHbp peptide included in 4CMenB vaccine, was present in 11 strains (5.2%) belonging to different cc (cc32, cc269, cc162 and cc865).

All isolates were found to contain the *nhba* gene, however one of them presented an allele with a frameshift mutation. Thirty eight different NHBA peptides were found, of which 23 were only present in one isolate. The most frequent peptides were 18 (n=53, 25.1%) and 17 (n=33, 15.6%), harboured by strains belonging to cc213 and cc269, respectively. Peptide 2, 4CMenB NHBA peptide, was identified in 11 strains (5.2%) belonging to the 41/44cc.

The *nadA* gene was present in 80 strains (37.9%), but only 19 (9.0%) showed an intact NadA peptide. Eight cc32 isolates showed NadA variant 1 peptides, 8 isolates without any cc assigned presented NadA variant 4/5 peptides, and 3 cc11 strains harboured NadA variant 2/3 peptides.

### Conclusion

Due to invasive meningococcal strains temporal variability (eg prevalence of the cc213 increased from 3.6% in 2007 to 30% in 2016) affecting to the presence and distribution of the vaccine antigens, continuous detailed meningococcal surveillance and monitoring of the vaccine antigens is needed.

## OC - (EMGM2019-13254) - MODELLING OF LONG-TERM ANTIBODY PERSISTENCE FOLLOWING 4CMENB VACCINATION IN ADOLESCENTS

Lorenzo Argante (Italy)<sup>1</sup>; Ottavia Prunas (Italy)<sup>1</sup>; Patricia Novy (United States of America)<sup>2</sup>; Rob Mulder (Netherlands)<sup>3</sup>; Ellen Ypma (Netherlands)<sup>3</sup>; Kumaran Vadivelu (Italy)<sup>1</sup>; Philip Watson (United States of America)<sup>2</sup>; Duccio Medini (Italy)<sup>1</sup>

1 - GSK, Siena, Italy; 2 - GSK, Rockville, MD, Unites States; 3 - GSK, Amsterdam, the Netherlands

### Introduction & Aims

Protection from serogroup B meningococcal disease depends on both the presence of circulating bactericidal antibodies and the antigenic characteristics of the invasive strain. Predicting duration of protection after vaccination with the multicomponent, meningococcal serogroup B vaccine (4CMenB) is complex. The persistence of antibodies to each vaccine component differs, and MenB strains are antigenically diverse. Persistence of antibodies to individual components may not reflect overall vaccine performance. To help predict the duration of clinical disease protection, we modelled immunogenicity data from clinical studies in adolescents and integrated this with strain coverage data.

### Materials and Methods

Different mixed-effect models were fitted to human serum bactericidal activity (hSBA, the accepted surrogate of protection<sup>1</sup>) longitudinal data for each major antigenic component of 4CMenB, generated in four clinical trials<sup>2-7</sup> where adolescents were immunized with 2 doses of 4CMenB. Overall 4CMenB persistence profiles for the United States (US) were derived through computational simulations based on the 4 best-fitting curves (1 per antigenic component) integrated with Meningococcal Antigen Typing System (MATS) data from a panel of 442 invasive MenB strains, representative of US epidemiology.<sup>8</sup>

### Results

The power-law model fitted the data best. Unified decay curves for each antigenic component could not be derived because of inter-study variability in antibody titers immediately after series completion.

Using antibody decay curves from Canada and Australia (144 subjects, follow-up: 4 years) and MATS data from US, the predicted probability of protection against vaccine-covered MenB strains circulating in the US was 74.7% after 3 years and 73.6% after 5 years.

Using decay curves from the US and Poland (39 subjects, follow-up: 2 years) and MATS data from US, the predicted probability of protection against the same strains was 51.6% and 46.0% after 3 and 5 years, respectively.

### Conclusion

By combining modelled antibody decay curves with knowledge of the antigenic profile of circulating MenB strains in a given country or region, it is possible to estimate the duration of antibody persistence and possibly clinical disease protection. Modelling data suggest that adolescents vaccinated with 4CMenB at age 16-18 years may derive protection during their period of higher age-related disease risk.

Funding: GlaxoSmithKline Biologicals SA

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Session: Poster Session IV

Room: Auditorium III

Immunity, serology, vaccine development and implementation

**PO-051 - (EMGM2019-13309) - A ROUTINE SUCCESS: VERY LOW LEVELS OF HIB PARTICULARLY IN THE VACCINE ELIGIBLE COHORT (ENGLAND 2009-2018)**Sarah Collins (United Kingdom)<sup>1</sup>; David Litt (United Kingdom)<sup>1</sup>; Norman K Fry (United Kingdom)<sup>1</sup>; Shamez N Ladhani (United Kingdom)<sup>1</sup><sup>1</sup> - Immunisation and Countermeasures Division, Public Health England**Introduction & Aims**

The epidemiology of invasive *Haemophilus influenzae* serotype b (Hib) disease underscores the positive impact of a successful immunisation programme. Prior to routine vaccination, Hib was responsible for over 80% of invasive *H. influenzae* infections and was a major cause of acute bacterial meningitis, septicaemia pneumonia and epiglottitis, particularly in young children. The introduction of the Hib conjugate vaccine to the UK national immunisation programme in 1992 resulted in a rapid and sustained decline in invasive Hib disease incidence across all age groups.

**Aim:** To describe the epidemiology of invasive Hib disease focusing on the vaccine eligible cohort January 2009 – \*December 2018.

**Materials and Methods**

Public Health England (PHE) conducts enhanced national surveillance of invasive Hib disease in England, including the species confirmation and serotyping of cultures. Detailed clinical information was obtained for all laboratory-confirmed Hib cases during 2009-18.

**Results**

During the 10 years from 2009 to 2018, 167 Hib cases were reported. In 2017 incidence was at a low of 0.02/100,000, with an incidence of 0.06/100,000 (3 cases) among <5 year-olds, compared with 22.9/100,000 prior to the introduction of routine Hib vaccination. Most cases occurred in adults (median age=49.3 years, IQR=21.1-63.9) who had pre-existing medical conditions (56%) and presented with pneumonia (46%).

The overall case-fatality rate was 9.6% (16/167 cases); work is ongoing to identify the Hib-associated deaths.

Forty-two cases were eligible for vaccination, only four of whom had received the currently recommended four doses; there were 31 additional breakthrough cases who had received at least one dose of vaccine, and 11 were unimmunised. Eighteen (42.8%) of the vaccine eligible cohort presented with meningitis of which 72.2% (13/18) had no known comorbidities.

**Conclusion**

The introduction of the Hib conjugate vaccine has been a resounding success with extremely high levels of direct and indirect (herd) protection. Few cases are reported among the vaccine eligible cohort with only four cases of vaccine failure after the booster dose in 10 years. Now Hib is predominantly diagnosed among older adults, who often have concurrent medical conditions and present with pneumonia.

**References**

\*The abstract includes data up to November 2018 - this will be updated for the presentation

## PO-052 - (EMGM2019-13361) - FACTOR H BINDING PROTEIN DIVERSITY AND LEVEL OF SURFACE EXPRESSION AMONG MENINGOCOCCAL SEROGROUP B DISEASE ISOLATES IN THE NETHERLANDS

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### Introduction & Aims

*Neisseria meningitidis* is a commensal of the human upper respiratory tract but can cause life-threatening disease. Two serogroup B meningococcal (MenB) vaccines (MenB-fHbp and 4CMenB), both comprised of protein antigens, are approved for the prevention of disease. Factor H binding protein (fHBP) is an antigen component of both vaccines. We compared the genetic and antigenic diversity of meningococcal isolates collected from patients in the Netherlands with invasive meningococcal disease (IMD). The level of fHBP expression on the surface of the MenB subset of IMD isolates was also determined.

### Materials and Methods

IMD isolates were collected by the Netherlands Reference Laboratory for Bacterial Meningitis during mid-2012 thru 2014. All isolates were assessed by whole genome sequencing. Serogroup, clonal complex (CC) and meningococcal antigen sequence diversity was extracted from the genome sequence. Surface expression of fHBP was determined for MenB isolates using the flow cytometric MEningococcal Antigen SURface Expression (MEASURE) assay.

### Results

IMD isolates from 214 patients were available for analyses. The median patient age was 17.1 years ( $\pm$ SD28.3). MenB isolates were most prevalent (n=161, 75%), followed by MenY (14%), MenC (5%), MenW (4%), and MenE/MenX (both 1%). MenB isolates were distributed among 9 CCs; predominant CCs include CC41/44 (35%), CC32 (25%), CC213 (11%) and CC269 (11%). A total of 37 fHBP variants were identified among MenB isolates and 70% code for a subfamily B variant. Genes coding for the seven most prevalent variants (B03 – 24%, B24 – 18%, A22 – 10%, B133 - 8%, A05 – 6%, B44 – 6%, B09 – 3%) were identified in nearly 75% of isolates. Expression of fHBP was detected at the surface of all MenB isolates and 95% (152/161) of isolates expressed fHBP at levels sufficient to be susceptible to bactericidal killing by MenB-fHbp-elicited antibodies.

Relative to MenB, genetic and antigenic diversity was considerably different among the 53 non-MenB IMD isolates, with fHBP subfamily A variants being most common.

### Conclusion

This study illustrates the strain and fHBP antigen distribution among disease isolates from the Netherlands during the years 2012-2014. All MenB isolates expressed fHBP and 95% of isolates expressed at levels sufficient to be susceptible to bactericidal killing by MenB-fHbp-elicited antibodies.

## PO-053 - (EMGM2019-13208) - HUMAN FACTOR H BINDING PROTEIN (fHBP) PHYLOGENETIC ANALYSIS IN INVASIVE NEISSERIA MENINGITIDIS B STRAINS, ITALY, IN 4 YEARS PERIOD

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### Introduction & Aims

Vaccines against serogroup B *Neisseria meningitidis* strains target the factor H-binding protein (fHBP). Based upon sequence and phylogenetic analyses, fHBP can be classified into 3 variants (1, 2 or 3) or 2 subfamilies (A or B). Recombination at fHBP contributes to the antigenic diversity within some clonal complex of *Neisseria meningitidis* serogroup B strains (MenB).

To analyze the prevalence, distribution and phylogenetic analysis of *fhhp* gene and predicted proteins among invasive MenB in Italy, 2014–2017.

### Materials and Methods

fHBP nucleotide and protein sequence alignments were performed with ClustalW on 155 MenB. JModeltest and Smart Model Selection software have been used for the statistical selection of the best-fit substitution models for nucleotide and protein alignments, respectively. Maximum Likelihood (ML) phylogenetic reconstructions were carried out with Phyml, by using the GTR + I + G and the JTT + G models respectively for nucleotide and protein alignments. The statistical significance in the tree, has been evaluated by the bootstrap test.

### Results

ML trees, performed on nucleotide and protein sequence alignments, showed the same topology and supported internal clusters.

The subfamily A, clustering in the same clade, comprised three major subgroups (I, II, III). Subgroup I included a new variant, the A181\_001, closely related with variant A07\_ together with A10\_001, A12\_001, A15\_001, A78\_001. Subgroup II included only two variants, the new A184\_001 related to A22\_001. Meanwhile, subgroup III comprised a higher number of variants and many supported clusters, of which one included the new variant A182\_001 with variants A69 and A05\_001.

Within the subfamily B many statistically supported clusters were outlined with four major subgroups (I, II, III and IV). The new variant B257\_001 did not belong to any subgroups as well as the predominant B231\_001 variant.

MenB clustered in the two clades and their subgroups regardless to the year of isolation and patient's age.

### Conclusion

The phylogenic analysis identified different subgroups within the A and B subfamilies fHBP variants. The variant A05 belonged to the subgroup III. The predominant variant B231 did not belong to any subgroup. Follow the variability of the variant genes may be useful to consider how this gene and its predicted proteins may vary among the MenB population. Critically, though this supplies only a crude genotypic characterization is possible without the evaluation of vaccine antigens expression.

## PO-054 - (EMGM2019-13265) - NHBA INTERGENIC REGION CHARACTERIZATION AND IMPACT ON 4CMENB VACCINE COVERAGE

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### Introduction & Aims

Neisserial Heparin Binding Antigen (NHBA) is a protective antigen of *Neisseria meningitidis* that binds heparin, plays a role in adhesion and serum resistance of this pathogen. NHBA is one of the four components of the 4CMenB vaccine against serogroup B meningococcus (MenB). The prediction of coverage of the 4CMenB vaccine is performed through the Meningococcal Antigen Typing System (MATS), which evaluates antigen expression and genetic diversity of the vaccine components on circulating strains and requires culturable samples. To overcome this hurdle, a genetic MATS (gMATS), able to predict coverage based on antigen peptide sequences, has been proposed. However, gMATS does not consider promoter sequences and their role on protein expression. The aim of this study is the characterization of the intergenic region upstream of NHBA (NIR) by dissecting its distribution and diversity, its level of association to NHBA peptides and its influence on expression and vaccine coverage prediction.

### Materials and Methods

From a public collection of 3353 MenB strains (BIGSdb), we identified 42 unique NIR sequences, with the 5 most common NIRs covering 94% of the dataset. Genetic sequences are divided in one long (L) and two short classes (S1 and S2). Furthermore, NHBA peptides were found to be strongly associated to their preferential NIR.

MATS data of a panel of 919 strains showed that coverage rate for NHBA in the three NIR groups was 21.4%, 35.2% and 83.7% respectively in S2, L and S1 classes. MATS results are derived from the combination of expression level and antibodies affinity to NHBA peptide. Unfortunately, it is difficult to dissect the impact on MATS of these two components, due to the strong association of the NIR to NHBA peptides. To overcome this issue, we engineered isogenic recombinant strains where NHBA p3 expression was under the control of each of the five NIRs.

### Results

We observed some degree of variability in the expression between NIRs. NIR 29 resulted the least expressing by Western Blot and MATS. However, the decrease in NHBA levels did not impact the killing capability in rSBA.

### Conclusion

In conclusion, we found 42 NIR sequences, divided in three classes, that respond diversely to MATS assay on NHBA. NIR sequence resulted to affect NHBA expression levels in the recombinant strain tested, though not impacting the killing. NHBA peptides are strictly associated with their own promoters, suggesting that the NIR sequence itself is not required for 4CMenB vaccine coverage prediction, thus confirming the current gMATS implementation.

**PO-055 - (EMGM2019-13160) - SAFETY DATA FOR MENB-FHBP IN HEALTHY INDIVIDUALS 10 YEARS OF AGE AND OLDER: A REVIEW OF CLINICAL TRIALS**

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1 - Pfizer Ltd; 2 - Pfizer Inc

**Introduction & Aims**

The vaccine MenB-FHbp (Trumenba<sup>®</sup>; bivalent rLP2086; Pfizer Inc, Philadelphia, PA) is licensed to prevent meningococcal serogroup B disease in those aged  $\geq 10$  years in Europe and 10–25 years in the United States. The MenB-FHbp clinical development program in this age group included 11 completed trials in which a primary vaccination series was given. However, individual randomized clinical trials usually do not enroll enough subjects to detect rare events. Therefore, the current analysis assessed pooled safety data from all 11 clinical trials, allowing evaluation of MenB-FHbp safety in a large population and increasing the likelihood of detecting rare events or safety signals not identified during individual clinical trials.

**Materials and Methods**

The safety dataset included pooled adverse event (AE) data from all 11 trials involving individuals aged 10–65 years. AEs were categorized as immediate AEs (IAEs), medically attended AEs (MAEs), serious AEs (SAEs), newly diagnosed chronic medical conditions (NDCMCs), and autoimmune or neuroinflammatory conditions. Reactogenicity data were pooled for 7 of the 8 controlled trials.

**Results**

A total of 15,294 MenB-FHbp recipients from controlled and uncontrolled studies and 5509 control subjects were included. Local and systemic reactogenicity events were reported more frequently in the MenB-FHbp groups compared with controls, consistent with individual trial observations. The frequencies of grouped IAEs, SAEs, MAEs, NDCMCs, and autoimmune or neuroinflammatory conditions were similar between MenB-FHbp and control groups.

**Conclusion**

Pooled analysis of >15,000 vaccine recipients provided the opportunity to review rigorously collected clinical trial data to identify potential rare or very rare adverse events. No safety signals were identified in this pooled analysis that had not been identified in review of the individual studies; safety and tolerability findings from individual studies were confirmed. ClinicalTrials.gov: NCT00879814/NCT00808028/NCT01830855/NCT01323270/NCT01461993/NCT01352793/NCT01461980/NCT01352845/NCT00780806/NCT01299480/NCT01768117.

Funded by Pfizer.

**References**

## PO-056 - (EMGM2019-13191) - SAFETY AND TOLERABILITY OF THE MENINGOCOCCAL SEROGROUP B VACCINE MENB-FHBP IN CHILDREN 1 TO <10 YEARS OF AGE

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### Introduction & Aims

MenB-FHbp (bivalent rLP2086) is a serogroup B meningococcal vaccine licensed in multiple countries for adolescents and adults. Two recent phase 2 studies evaluated MenB-FHbp safety in younger children.<sup>1,2</sup>

### Materials and Methods

In an ongoing study, 352 toddlers 1–<2 years old were randomized to receive MenB-FHbp (120 µg at months 0,2,6) or hepatitis A virus vaccine (HAV; months 0,6)/saline (month 2).<sup>1</sup> Four hundred children 2–<10 years old were randomized 3:1 to receive 120 µg MenB-FHbp or HAV/saline.<sup>2</sup> Safety outcomes included local reactions, systemic events, and adverse events (AEs); AEs were also evaluated in a pooled analysis (children 1–<10 years old).

### Results

Across age groups, local reactions and systemic events, including fever, were more common among MenB-FHbp recipients than controls (local reactions: 82.3%–88.4% vs 39.4%–46.9%; systemic events: 71.1%–85.0% vs 51.9%–62.9%), mostly mild or moderate in severity, transient, and rarely associated with potentiation or study withdrawal (n=1, attributed to injection site pain, decreased appetite, irritability, and somnolence). One serious AE of transient hip synovitis was assessed as vaccine related (MenB-FHbp). Fever rates were higher in toddlers <2 years old vs children 2–<10 years old receiving MenB-FHbp (37.3% vs 24.5%) and declined with subsequent vaccinations; fever >40.0°C was rare (n=3 across age groups). Frequencies of various categories of AEs, newly diagnosed chronic medical conditions, and medically attended AEs were similar across treatment groups.

### Conclusion

MenB-FHbp recipients 1–<10 years old more frequently experienced redness, swelling, and fever compared with adolescents in previous studies. Although MenB-FHbp had an acceptable safety and tolerability profile in this age group, this analysis was not powered to detect uncommon AEs; continued safety monitoring of MenB-FHbp in children is warranted. Clinical Trial Registration: ClinicalTrials.gov, NCT02534935, NCT02531698. Funded by Pfizer.

### References

[1]H. Marshall, et al, A Phase 2 Study of the Immunogenicity, Safety, and Tolerability of the Meningococcal Serogroup B Vaccine MenB-FHbp (Bivalent rLP2086) in Healthy Toddlers ≥12 to <24 Months of Age. Presented at: European Society for Paediatric Infectious Diseases; May 28-June 2, 2018, Malmö, Sweden.

[2]T. Vesikari, et al, Phase 2 Study of the Safety and Immunogenicity of the Meningococcal Serogroup B Vaccine MenB-FHbp (Bivalent rLP2086) in Healthy Children between 2 and <10 Years of Age. Presented at: European Society for Paediatric Infectious Diseases; May 28-June 2, 2018, Malmö, Sweden.

**PO-057 - (EMGM2019-13360) - BREADTH OF THE HUMAN IMMUNE RESPONSE TO TRUMENBA: SUMMARY OF FHBP VARIANTS EXPRESSED BY MENB STRAINS SUSCEPTIBLE IN THE HSBA**

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**Introduction & Aims**

Trumenba (bivalent rLP2086), a vaccine for the prevention of *Neisseria meningitidis* serogroup B (MenB) disease, consists of two protein antigens, variants of meningococcal factor H binding protein (fHBP). fHBP exists as two subfamilies, A and B. Within each subfamily several hundred unique fHBP variants have been identified. Despite this sequence diversity, a vaccine containing one protein from each subfamily was demonstrated to induce broad coverage across MenB strains that represent the diversity of fHBP variants. Licensure was based on the ability of the vaccine to elicit antibodies that initiate complement-mediated killing of invasive MenB strains in a serum bactericidal assay using human complement (hSBA). Due to the endemic nature of meningococcal disease, it is not possible to predict to which fHBP variants individuals may be exposed. For this reason we have continued to explore the coverage conferred by Trumenba and present here additional evidence to illustrate the breadth of immune coverage.

**Materials and Methods**

MenB invasive strains (n=109) were selected to confirm Trumenba breadth of coverage. The strains encoded 22 and 16 unique subfamily A and subfamily B fHBP variants, respectively. The expression of fHBP at the bacterial surface was determined using the flow cytometric MENingococcal Antigen SURface Expression (MEASURE) assay. Exploratory hSBAs were performed using pre- and post-vaccination sera (subject-matched) from young adults. A strain was considered susceptible to Trumenba immune sera if a 4-fold rise in the hSBA titer was achieved between the pre- and post-vaccination serum samples.

**Results**

Of the 109 strains, 87 (nearly 80%) were susceptible to Trumenba immune serum in hSBAs. This included strains expressing fHBP variants A02, A28, A42, A63, A76, B05, B07, B08, B13, B52 and B107, in addition to variants that had been reported previously. The majority of strains that could not be killed had fHBP expression levels that were below the level considered sufficient to initiate bactericidal killing in an hSBA.

**Conclusion**

The hSBA is recognized as the surrogate of efficacy for meningococcal vaccines. Assay complexity prevents demonstration of the bactericidal activity of Trumenba immune sera against MenB strains that express each of the hundreds of unique fHBP sequence variants. To illustrate the breadth of immune coverage conferred by Trumenba, we show that MenB strains expressing additional diverse fHBP variants can be killed in hSBAs despite being heterologous to the vaccine antigens.

## PO-058 - (EMGM2019-13247) - GENETIC VARIABILITY OF THE MENINGOCOCCAL SEROGROUP B VACCINE ANTIGENS: ANALYSIS OF 2010-2012 CARRIERS MENB STRAINS IN SPAIN

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### Introduction & Aims

With the **aim** to assess the genetic variability of the vaccine antigens in MenB carried meningococcal population, a collection of meningococcal isolates from asymptomatic carriers in Spain was molecularly characterized.

### Materials and Methods

Both serogroup and genogroup were determined for the total of 278 carrier strains isolated from a survey carried out among 4 to 19 years old subject in Spain from 2010 to 2012. Serogroup and/or genogroup B isolates were whole genome sequenced, and *porA*, *fetA*, MLST, *fHbp*, *nhba* and *nadA* variability was analyzed.

### Results

A total of 125 MenB strains (45%) were found, of which 112 (89.6%) belonged to 13 different clonal complexes (cc) and remaining 13 strains did not belong to any assigned cc. The most frequent cc observed was cc213 (n=22, 17.6%), mainly associated with 22,14 PorA genotype and F5-5 FetA variant. Forty different PorA genotypes were identified, of which only 17 were present in more than one isolate. The most frequent PorA genotypes observed were 22,14 (n=19) and 7-2,4 (n=19). PorA genotype 7-2,4 was predominant in the cc162, the second most frequent cc observed (n=18, 14.4%). The PorA VR2 variant 4, one of the 4CMenB vaccine components, was present in 22 (17.6%) of the total strains.

The *fHbp* gene was present in all isolates. A total of 23 different fHbp peptides were identified (10 subfamily A and 13 subfamily B). FHbp subfamily A peptides were harboured by most of the strains (n=101, 80.8%), while fHbp subfamily B peptides were harboured by 24 (19.2%) isolates. The most prevalent fHbp peptides were 19 (n=22, 17.6%), 21 (n=20, 16%), 45 (n=19, 15.2%), corresponding with bivalent rLP2086 vaccine variant A05, and 16 (n=14, 11.2%). The other rLP2086 vaccine variant, B01 (peptide 55) was not present in any isolate; and peptide 1 (variant B24), the fHbp peptide included in 4CMenB vaccine, was present in 5 strains (4.0%) belonging to cc32.

All isolates were found to contain the *nhba* gene. Twenty five different NHBA peptides were found, of which 11 were only present in one isolate. The most frequent peptides were 20 (n=21, 16.8%) and 18 (n=20, 16.0%), harboured by strains belonging to cc162 and cc213, respectively. Peptide 2, 4CMenB NHBA peptide, was identified in 8 strains (6.4%) belonging to the 41/44cc.

The *nadA* gene was present in 35 strains (28.0%), but only 15 (12.0%) showed an intact NadA peptide. Ten cc32 isolates showed NadA variant 1 peptides and 5 isolates without any cc assigned presented NadA variant 4/5 peptides.

### Conclusion

MenB carriers strains presented great variability also affecting the vaccine antigens. Even without information about the potential impact of the MenB vaccines in carriers, it is of interest to know the degree of variability of the antigens, as well as the level of potential recognition of the antibodies generated by the vaccines.

## PO-059 - (EMGM2019-13204) - VARIABILITY OF MENB VACCINE COMPONENTS AMONG POLISH SEROGROUP B MENINGOCOCCI

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### Introduction & Aims

The purpose of the study was to evaluate variability of Polish invasive meningococci based on MLST analysis and sequencing of genes encoding proteins, used as vaccine antigens

### Materials and Methods

The study encompassed 662 invasive serogroup B meningococci (MenB) collected between 2010 and 2016 in Poland. MLST analysis and sequencing of *porA*, *fHbp*, *NHBA* and *nadA* genes were performed according to recommended protocols

### Results

Nineteen clonal complexes were detected, of which the most frequent were cc32, cc41/44, cc18, cc213 and cc269 accounting for 31.9%, 16.5%, 12.5%, 6.2%, and 3.5%, respectively. A significant part (21.0%) of MenB isolates did not belong to any assigned cc (no cc).

111 combinations of PorA variable regions (VR1/VR2) were found; the most common were: 7/16 (15.0%), 22/14 (13.6%), 7-2/16 (6.1%) and 5-2/10-1 (5.3%). The 4CMenB vaccine variant (VR2:4) was detected in 48 isolates (7.3%), mainly representing cc41/44 and no cc.

85 *fHbp* alleles encoding 74 peptide subvariants were revealed, half of which was represented by single isolates. Among 3 families (v1, v2, v3), most common was v1 (79.2%), followed by v2 (14.1%) and v3 (6.6%). Sub-variant 1.1, component of the 4CMenB, was prevalent (24.2%) and found generally in cc32 (mainly ST-32).

The *nhba* typing revealed 102 alleles and 87 peptide variants including 47 appearing only once. The most frequent was variant 3 (22.4%) followed by v6 (11.2%) and v20 (10.7%). The vaccine variant v2 was detected in 65 isolates (9.8%), mostly among cc 41/44.

The *NadA* was detected in 196 (29.7 %) isolates and the most prevalent was peptide 1 (79.6%), followed by peptide 21 (13.3%) and peptide 3 (5.1%). Variant 1 was found almost exclusively in cc32 meningococci (mainly ST-32), while variant 4/5 was associated mostly with cc213. Vaccine variant 8 was not detected.

Consequently, 39.7% of isolates had at least one 4CMenB vaccine variant, although if evaluation concerns gMATS predictors [1], the percentage of coverage increases twice, counting 86.6%.

### Conclusion

Polish MenB responsible for IMD in 2010-2016 are highly variable according to MLST and gene alleles encoding 4CMenB vaccine proteins. Some correlations between clonal complexes and variants of examined proteins were revealed. According to gMATS analysis high coverage almost 90% for Polish MenB was estimated

### References

[1] A. Muzzi et al., Genetic Meningococcal Antigen Typing System (gMATS): A genotyping tool that predicts 4CMenB strain Coverage worldwide. *Vaccine*, , January 17, doi: 10.1016/j.vaccine.2018.12.061, 2019.

## PO-060 - (EMGM2019-13282) - SAFETY AND IMMUNOGENICITY OF A QUADRIVALENT MENINGOCOCCAL CONJUGATE VACCINE (MENACYW-TT) ADMINISTERED AS SINGLE DOSE IN A BROAD AGE RANGE

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### Introduction & Aims

MenACYW-TT is an investigational quadrivalent meningococcal conjugate vaccine intended for use in a broad age population. We evaluated the safety and immunogenicity of MenACYW-TT compared to licensed quadrivalent conjugate meningococcal vaccines (MCV4-TT; Nimenrix®, MCV4-CRM; Menveo®, MCV4-DT; Menactra®) in toddlers (12-23 months), children (2-9 years), adolescents (10-17 years) and adults (18-55 years); and licensed quadrivalent meningococcal polysaccharide vaccine (MPSV4; Menomune®) in adults  $\geq 56$  years of age.

### Materials and Methods

A total of 3 phase II and 6 phase III studies, administering the vaccine as a single dose, were conducted globally (USA, Europe, South Korea, Thailand, Russia and Mexico) in a broad age range (12 months and above). Each of the studies evaluated MenACYW-TT vs a licensed standard of care comparator vaccine to demonstrate immune non-inferiority or describe the immunogenicity responses. Co-administration with age specific vaccines was also evaluated in adolescents [tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap) vaccine and Human Papillomavirus (4vHPV) vaccine] and toddlers [measles, mumps rubella (MMR), varicella (V), Pneumococcal 13-valent Conjugate Vaccine (PCV13), diphtheria, tetanus, acellular pertussis, poliomyelitis, Hepatitis B and *Haemophilus influenzae* type b conjugate vaccine (DTaP-IPV-HB-Hib)]. Serum bactericidal assays with human (hSBA) and baby rabbit (rSBA) complement were used to evaluate antibodies at baseline and 30 days after vaccination. Safety data were collected up to 30 days or 6 months post-vaccination.

### Results

Non-inferiority of immune responses was demonstrated between MenACYW-TT and comparator vaccines for all four serogroups across all ages, based on percentages of participants achieving hSBA vaccine seroresponse at Day 30 compared to baseline (children, adolescents, adults and elderly) or percentages of participants achieving hSBA  $\geq 1:8$  at Day 30 (toddlers). The percentages of participants with post vaccination rSBA  $\geq 1:128$  were higher for all serogroups in subjects vaccinated with MenACYW-TT. Co-administration of MenACYW-TT, Tdap and HPV4 vaccines did not generate evidence suggestive of clinically significant interference in adolescents. Overall, the safety profiles of MenACYW-TT and standard of care vaccines were comparable across all ages. There were no Adverse Events leading to study discontinuation and no related serious adverse events among MenACYW-TT recipients. Post-vaccination rates of severe reactions were low for all vaccines.

### Conclusion

MenACYW-TT was well tolerated and demonstrated a non-inferior immune response compared to the standard of care quadrivalent conjugate or polysaccharide meningococcal vaccines in a broad age range of 12 months and above. This vaccine will be another option for the prevention of invasive meningococcal disease in different areas of the world.

**PO-061 - (EMGM2019-13158) - A REVIEW OF IMMUNOGENICITY AND SAFETY OF MENACWY-TT IMMUNIZATION IN INFANTS AND TODDLERS**

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1 - Pfizer Ltd; 2 - Pfizer Inc

**Introduction & Aims**

The quadrivalent meningococcal conjugate vaccine MenACWY-TT is licensed to protect those  $\geq 6$  weeks of age against serogroup A, C, W, or Y meningococcal disease. Four clinical studies in infants and toddlers established the immunogenicity and safety of MenACWY-TT administered with or without routine childhood vaccines, summarized herein.

**Materials and Methods**

In 4 phase II, III, or IIIb studies, infants aged 6–12 weeks (NCT01144663, NCT01340898) and toddlers aged 12–14 or 15 months (NCT01939158, NCT01994629) received MenACWY-TT given on various primary and booster schedules with or without routine childhood vaccines. Coadministered vaccines included a 10- or 13-valent pneumococcal polysaccharide conjugate vaccine (PCV10 or PCV13) and DTPa-IPV/Hib or DTPa-HBV-IPV/Hib. Immunogenicity was measured by serum bactericidal assays using rabbit complement (rSBA) to evaluate percentages of subjects achieving titers  $\geq 1:8$  1 month after the last primary and booster doses. Safety was assessed.

**Results**

In total, 2845 infants and 1003 toddlers were vaccinated. Among infants given MenACWY-TT on a 2+1 or 3+1 schedule,  $\geq 93.1\%$  of subjects had rSBA titers  $\geq 1:8$  for all serogroups after the last primary dose; for other infant groups evaluating a 3+1 or 1+1 schedule,  $\geq 93.9\%$  had rSBA titers  $\geq 1:8$  for all serogroups after the last primary dose. In all groups, immune responses to a booster dose were robust. Among toddlers receiving 1 or 2 doses of MenACWY-TT,  $\geq 89.0\%$  of single-dose recipients and  $\geq 98.0\%$  of 2-dose recipients had rSBA titers  $\geq 1:8$  for all serogroups 1 month after the last dose. Coadministration of MenACWY-TT with other vaccines did not affect immunogenicity of MenACWY-TT or the other vaccines, and all studies reported acceptable safety profiles.

**Conclusion**

MenACWY-TT is immunogenic and safe in infants and toddlers with or without coadministration of routine childhood vaccinations.

Funded by Pfizer.

## PO-062 - (EMGM2019-13188) - CLINICAL DEVELOPMENT OF A MENINGOCOCCAL GROUP A, C, W, AND Y TETANUS TOXOID CONJUGATE VACCINE

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1 - Pfizer Inc; 2 - Pfizer Ltd UK

### Introduction & Aims

Increased numbers of meningococcal serogroup W (MenW) disease cases have emerged globally; in Europe in 2016, infants were at particular risk. The associated cc11 MenW strain is hypervirulent and demonstrates atypical clinical characteristics. In response, several countries updated their immunization programs to include quadrivalent meningococcal (MenACWY) vaccines. To understand clinical use of specific MenACWY vaccines, data for MenACWY-TT (Nimenrix<sup>®</sup>), a MenACWY tetanus toxoid conjugate vaccine licensed in the European Union and 48 other countries for individuals aged  $\geq 6$  weeks, are reviewed.

MenACWY-TT is given as a 2-dose primary series plus 1-dose booster to infants (6–12 weeks) and as a single dose from age 12 months. Booster dosing can be given from age 12 months if previously vaccinated with another conjugated or plain polysaccharide meningococcal vaccine.

### Materials and Methods

MenACWY-TT clinical studies supporting licensure are summarized.

### Results

Across studies and age groups, MenACWY-TT elicited comparable antibody responses against the 4 vaccine meningococcal groups compared with meningococcal C vaccines in infants/toddlers and MenACWY vaccines in other groups and robust antibody responses after booster dosing. Antibody persistence up to 5 years after primary vaccination was demonstrated.

In infants, MenACWY-TT can be concomitantly administered with combined diphtheria, tetanus, acellular pertussis/hepatitis B/inactivated poliomyelitis virus/*Haemophilus influenzae* type B (DTaP-HBV-IPV-Hib) and 10-valent pneumococcal conjugate vaccines (PCV10). From age  $\geq 1$  year, MenACWY-TT can be given with hepatitis A (HAV), HBV, measles-mumps-rubella (MMR), MMR-varicella, PCV10, or unadjuvanted seasonal influenza vaccines. MenACWY-TT can be administered with DTaP combination vaccines and 13-valent PCV in the second year of life and with bivalent human papillomavirus vaccine at age 9–25 years.

Safety of a single dose of MenACWY-TT was evaluated in a pooled analysis of data from 3079 toddlers, 1899 children, 2317 adolescents, and 2326 adults. Safety was also assessed in 274 older adults (>55 years), 1052 infants receiving  $\geq 1$  dose (beginning at 6–12 weeks), and 1008 toddlers (12–14 months) receiving a booster. Across studies, MenACWY-TT had an acceptable safety/reactogenicity profile. The safety profile in adults aged >55 years was similar to younger adults. Both infant doses and primary and booster dosing (12 months–30 years) were associated with generally similar reactogenicity.

### Conclusion

The MenACWY-TT clinical study program demonstrated consistency of vaccine-induced immunogenicity and safety across age groups. These data support MenACWY-TT licensure and current recommendations to prevent meningococcal group A/C/W/Y disease from  $\geq 6$  weeks of age. This includes disease caused by MenW, for which infants in Europe are at particular risk.

Funded by Pfizer.

## PO-063 - (EMGM2019-13357) - IMMUNE PERSISTENCE MEASURED BY HUMAN COMPLEMENT SERUM BACTERICIDAL ACTIVITY IN PEDIATRIC POPULATIONS IMMUNIZED WITH MENAFRIVAC

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### Introduction & Aims

*Neisseria meningitidis* causes endemic and epidemic meningitis and sepsis resulting in high morbidity and mortality. Introduction of PsA-TT conjugate meningococcal vaccine, MenAfriVac®, through large-scale vaccination campaigns in Africa led to significant decreases in serogroup A (MenA) meningococcal disease. Antibody persistence following immunization is important for continued control of MenA disease. Here, bactericidal antibody is measured using human complement (hSBA) in sera from two pediatric persistence studies conducted in Bamako, Mali following the national MenAfriVac® campaign.

### Materials and Methods

Pers-007 examines the persistence of MenA antibodies 4-5 years following study PsA-TT-007 in which infants were immunized with one or two doses of PsA-TT (5µg or 10 µg). A representative subset of PsA-TT-007 participants (165 from four original study arms, n=660) and an unimmunized age-matched control group (n=165) were enrolled. Sera were obtained from all participants prior to a MenAfriVac® catch-up campaign conducted in 2017, and from a subset of enrollees (56 from each study group, n=280) 28 days and 180 days following receipt of the catch-up campaign dose. The NIH MenAfriVac® Antibody Persistence Study (MAP) conducted in 2012 enrolled a household-based, age stratified sample of 800 residents of Bamako, Mali who were 1-29 years of age at the time of the 2010 MenAfriVac® campaign. In 2014, MAP re-enrolled subjects (with age- and sex-matched replacements as needed) and unvaccinated children born since 2010 to compare with persistence following vaccination in infancy.

### Results

hSBA was detectable in sera collected from children 4-5 years following MenAfriVac® vaccination in infancy, with antibody persistence being greatest in those who received two doses (hSBA titer  $\geq 4$  in 70% vs. 42% of subjects, two vs. one dose 10 µg,  $p < 0.0001$ ). All previously vaccinated subjects developed high-titer hSBA responses to a booster dose administered at approximately five years of age, irrespective of their infant dose or regimen. At six months following the catch-up campaign vaccination, 98-100% of previously vaccinated subjects maintained titers  $\geq 8$ , compared with 64% of age matched controls ( $p < 0.0001$ ). hSBA assays of sera from the 2014 MAP participants who were 1 year to 17 years of age at the time of vaccination (n=600) are being initiated to determine hSBA persistence in children and adolescents 3.5 years following vaccination.

### Conclusion

Bactericidal antibody measured by hSBA was detectable in children 4 to 5 years following MenAfriVac® vaccination in infancy. By monitoring hSBA immune responses following MenAfriVac® immunization over time we can address questions regarding antibody decline and immune persistence across pediatric age groups.

### References

**PO-064 - (EMGM2019-13231) - TOOLS TO STUDY INVASIVENESS OF CLINICAL MENINGOCOCCAL ISOLATES AND PROTECTION BY SPECIFIC ANTIBODIES**

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**Introduction & Aims**

Recently the incidence of serogroup W invasive meningococcal disease increased in the Netherlands. We hypothesize that clinical invasiveness associates with increased ability to invade into respiratory epithelial cells. Therefore, we aim to develop tools to test different isolates for their ability to adhere to and cross the respiratory epithelium as proxy for invasiveness. Moreover, we want to test the ability of antibodies in serum or saliva samples to inhibit epithelial infection.

**Materials and Methods**

Men A, C, W and Y isolates were allowed to bind to nasopharyngeal (RPMI2560) epithelial cell monolayers (500,000 cells/well) for 2h at 37°C at a multiplicity of infection of 100. Then cells were washed and colony forming units (CFUs) of total cell-associated meningococci enumerated by serially diluting the cell lysates and plating on Columbia blood agar. Alternatively, cells were incubated for an additional 2h in the presence of the non-cell-permeable antibiotic gentamicin, lysed and intracellular CFUs determined. To test the ability of antibodies to agglutinate meningococci and thereby prevent epithelial infection a FACS-based agglutination assay was developed. In FACS, light scattering increases due to the increased size of agglutinated bacteria. Suspensions of MenC or MenW bacteria (100,000 CFU/50µl) were incubated with commercial polyclonal Intravenous Immunoglobulin (IVIg) preparation (20µg/µl), washed and assessed by FACS.

**Results**

Binding to the epithelial cells was similar between the four different meningococci at about  $2 \times 10^6$  CFU of the  $50 \times 10^6$  bacteria added. However, numbers of intracellular bacteria were the lowest for MenC (50 +/-28SEM CFU/well), and the highest for the MenY (3259 +/-734 SEM CFU/well) isolate used. Cellular invasion of MenW (298 +/-62SEM CFU/well) was higher ( $p < 0.001$ ) than of MenC and similar to MenA (227 +/-61 SEM CFU/well). 19% and 7% of suspensions of a MenC isolate and a MenW isolate, respectively were converted to aggregates.

**Conclusion**

In subsequent studies the epithelial cell binding and invasion assay will be used to compare binding ability and invasiveness of clinical isolates, including clonal complex 11 MenC and MenW isolates. Serum and saliva samples from individuals of different age groups and with different period post MenACWY vaccination will be evaluated for the ability to agglutinate meningococci. Finally, we will assess these samples for their ability to prevent meningococcal binding and invasion of epithelial cells.

Together, these assays provide a set of tools to analyse invasiveness of clinical isolates and the ability of antibodies to protection against meningococcal infection.

## PO-065 - (EMGM2019-13337) - STRUCTURE-IMMUNOGENICITY STUDIES OF MENC-TT CONJUGATE VACCINES SHOW ADVANTAGE OF LARGER CONJUGATES

Kay Lockyer (United Kingdom)<sup>2</sup>; David Eastwood (United Kingdom)<sup>1</sup>; Robert Francis (United Kingdom)<sup>1</sup>; Bhagwati Khatri (United Kingdom)<sup>1</sup>; Fang Gao (United Kingdom)<sup>1</sup>; Richard Stebbings (United Kingdom)<sup>1</sup>; Jeremy Derrick (United Kingdom)<sup>3</sup>; Barbara Bolgiano (United Kingdom)<sup>1</sup>

1 - NIBSC; 2 - NIBSC, University of Manchester; 3 - University of Manchester

### Introduction & Aims

The relationship between conjugate size and immune response was quantitatively assessed by evaluating how saccharide chain length influences immune response.

### Materials and Methods

A panel of four glycoconjugate meningococcal serogroup C (MenC) vaccines of different size (molar mass and radii) and polysaccharide (PS) chain length was prepared. It comprised conjugates from 191,500 to 2,348,000 g/mol, with hydrodynamic radii from 12.1 nm to 47.9 nm formed through conjugation of a monomeric tetanus toxoid (TT) to MenC PS of varying chain lengths (24 to 442 kDa).

### Results

The two larger panel vaccine conjugates produced higher anti-MenC IgG titres, with IgG1>IgG2b. Larger vaccine conjugate size similarly stimulated greater T cell proliferative responses in an *in vitro* recall assay. *In vitro* innate cytokine responses (RANTES, MIP-2 and MIP-1a) were also greater with larger conjugates.

### Conclusion

In conclusion, larger MenC-TT conjugate size correlates with greater humoral, cellular and innate murine immune responses. This is the first study looking at a quantitative assessment of MenC-TT conjugate size and the effect of structural properties on the immune response generated. Further work could be undertaken to determine whether there is an optimum vaccine size or an upper size limit for efficacious MenC conjugates, other conjugates and different vaccine types. Additionally analysis could be undertaken to determine whether these identified trends are translatable into superior vaccine protection for humans. This could result in vaccine manufacturers choosing to adapt vaccine conjugates to a required size or with selected structural properties.

## PO-066 - (EMGM2019-13195) - INVASIVE MENINGOCOCCAL DISEASE IN PATIENTS WITH COMPLEMENT DEFICIENCIES IN ENGLAND

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### Introduction & Aims

To describe cases with inherited and acquired complement deficiency who developed invasive meningococcal disease (IMD) in England over the last decade.

### Materials and Methods

We retrospectively identified patients with complement deficiency who developed IMD in England during 2008-2017 from the Public Health England enhanced surveillance system. Information was retrieved on their clinical presentation, vaccination status, medication, recurrence of infection and outcomes, as well as characteristics of the infecting meningococcal strains.

### Results

A total of 16 patients with 20 IMD episodes were identified. Four patients had two episodes. Six patients had inherited complement deficiencies, two had immune-mediated conditions associated with complement deficiency (glomerulonephritis and vasculitis), and eight others were on Eculizumab therapy, five for paroxysmal nocturnal haemoglobinuria and three for atypical haemolytic uraemic syndrome. The age range for those with inherited complement deficiencies or immune-mediated conditions was 4 to 42 years with a median age of 15 years. The age range of patients on Eculizumab therapy was 20 to 40 years with a median age of 22 years. Meningococcal cultures were available for 7 of 11 episodes for those with inherited complement deficiencies/immune-mediated conditions and the predominant capsular group was Y (7/11), followed by B (3/11) and non-groupable (NG) (1/11). Among patients receiving Eculizumab therapy, 3 of the 9 episodes were due to capsular group B (3/9), three others were NG but genotypically group B, and there was one case each for groups E, W and Y.

### Conclusion

Even in patients with IMD, acquired and inherited deficiencies of the terminal complement pathway are rare. Most of these cases occur during adolescence. Health care professionals should consider the possibility of underlying inherited complement deficiency in any patient with recurrent IMD or in those who develop IMD due to unusual capsular groups such as Y (unless an elderly patient), E or NG meningococci, especially in previously healthy adolescents. The management of such patients is challenging because of the limited protection offered by the current vaccines. In addition to vaccination, antibiotic chemoprophylaxis should be strongly considered but rare cases of penicillin-resistant group B disease highlight the need to raise awareness of IMD risk among patients and healthcare professionals. This includes the use of information cards to be carried by patients and their care givers, as well as the need to seek early medical attention for prompt investigation and treatment in unwell patients.

## PO-067 - (EMGM2019-13174) - PERSISTENCE OF IMMUNE RESPONSE POST-4CMENB PRIMARY VACCINATION, AND RESPONSE TO A BOOSTER DOSE IN INFANTS, CHILDREN, ADOLESCENTS AND YOUNG ADULTS

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### Introduction & Aims

*Neisseria meningitidis* serogroup B (MenB), the main cause of invasive meningococcal disease (IMD) in many countries, has incidence peaks in infancy and adolescence. The multicomponent 4CMenB vaccine has demonstrated real-life effectiveness. However, the need for and timing of booster doses are not yet established, and this remains a significant issue for start-up funding and future risk management for national programs. We studied the available data on antibody persistence and booster after 4CMenB priming across different age groups.

### Materials and Methods

We analyzed the available data (8 studies – 9 cohorts) assessing antibody persistence after 4CMenB priming and the immunogenicity of a booster dose in infants, children, adolescents and young adults.

### Results

Seroprotective hSBA (serum bactericidal assay using human complement) titres were demonstrated in  $\geq 76\%$  of infants for at least one 4CMenB vaccine antigen 2-3 years after 3 or 4 doses of 4CMenB.

7.5 years after two 4CMenB doses,  $\geq 84\%$  of adolescents showed seroprotective hSBA titres against at least 1 vaccine antigen.

The declining trend of vaccine-induced antibodies to 4CMenB antigens varies, with antibodies to NHBA (Neisserial heparin binding antigen) and NadA (*Neisseria* adhesin A) persisting longer than antibodies to PorA (porin A) and fHbp (factor H binding protein).

A booster dose significantly and rapidly increased antibody levels to all 4 vaccine components, showing that primary 4CMenB vaccination induced robust immunologic priming irrespective of the schedule.

### Conclusion

Primary vaccination with 4CMenB induced robust immunologic priming, as demonstrated by the rapid onset of an anamnestic response to re-vaccination. A booster dose induced marked rises in antibody levels to all 4 vaccine components.

However, the precise level and combination of protective antibodies raised from the different antigens in 4CMenB that are responsible for real-life impact and effectiveness is not yet clear.

Real-life data will further contribute to understanding correlations between immune patterns of 4CMenB-induced antibody persistence and long-term clinical protection against IMD, as well as the potential need for booster doses.

**Funding:** GlaxoSmithKline Biologicals SA

### References

## PO-068 - (EMGM2019-13358) - PROTOCOL SUMMARY: CASE-CONTROL STUDY TO EVALUATE THE EFFECTIVENESS OF 4CMENB VACCINE IN THE PREVENTION OF INVASIVE MENINGOCOCCAL DISEASE IN PORTUGAL

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### Introduction & Aims

4CMenB vaccine (Bexsero®, GSK) is licensed in Europe based on immunogenicity and safety data and was first used universally in the UK where ecological evidence of impact in target age groups has been reported in the context of already falling rates of disease. To date no direct evidence of effectiveness by case control methodology has been reported. In Portugal the vaccine has been widely used in the private market since 2014. With limited use of vaccine in our setting a sufficient number of cases of invasive disease have since occurred to permit evaluation using density case-control methodology.

### Materials and Methods

A case control protocol has been designed and has been given ethical approval. All cases of culture and/or PCR-confirmed cases of invasive meningococcal disease in children aged 2 months and 18 years are being identified from hospital coding, microbiology laboratory records and public health data between October 2014 and December 2018. Demographic, clinical and microbiological data, including meningococcal capsular group from each confirmed case along with linked immunisation records are being entered into an anonymous case report form. For each case, two controls are identified from the emergency service log of the admitting hospital on the same or adjacent days, matched for sex, age and postcode and data on immunisation status collected in the same anonymised fashion. The primary end point is to calculate vaccine effectiveness against meningococcus group B disease while other capsular groups will be included in a secondary analysis.

### Results

Assuming 40% vaccine coverage (based on national sales data) and a vaccine effectiveness of 80% (based on UK impact data), with 2 controls per case, for 80% power at a 5% level of significance, we require 32 cases and 64 controls. To date 91 cases have been identified and the collection of data is in progress.

### Conclusion

Data collection for this pan-Portugal study will be done in February – April 2019. The results will provide the first data globally on direct effectiveness of a protein antigen meningococcal vaccine in children.

This study is being conducted in collaboration with Direção Geral da Saúde e Comissão Técnica de Vacinação.

## PO-069 - (EMGM2019-13199) - PRODUCTION AND EVALUATION OF A RECOMBINANT MENINGOCOCCAL PORA VARIANT P1.4 MONOCLONAL ANTIBODY

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### Introduction & Aims

Recombinant antibodies (rAbs) are monoclonal antibodies (mAbs) which are generated *in vitro* using synthetic genes. Traditional production of mAbs involves the immunisation of mice and fusion of spleen cells with myeloma cells to produce hybridomas. Cold storage, revival and prolonged culture of hybridoma cells is required to maintain stocks of these mAbs and this can lead to loss of mAb expression or changes to its properties. Making recombinant versions of these mAbs gives control of the genetic content of the expressed mAb ensuring less batch-to-batch variability. Manipulation of the antibody genes also makes it possible to generate new antibodies and antibody fragments which are tailor-made to a particular application. NIBSC holds a panel of hybridoma cell lines which express mAbs specific for different meningococcal surface antigens. The multi-component Meningococcal B vaccine Bexsero contains PorA P1.4 as the main antigen of Outer Membrane Vesicles (OMV). The NIBSC catalogue currently contains meningococcal PorA variant P1.4 mAb which is freeze dried powder of cell supernatant (NIBSC Cat No. 02/148). To ensure future supply of this important antibody we set about making a recombinant anti-P1.4 mAb.

### Materials and Methods

The material is produced from a hybridoma cell line (MN20B9.34) which was donated to NIBSC by The Netherlands National Institute for Public Health and the Environment (RIVM).

The heavy and light chain variable domains were sequenced from the hybridoma mRNA, synthesised with mouse IgG2a and kappa light chain constant regions respectively and cloned into a mammalian expression vector. Antibody was expressed in ExpiCHO-S cells. IgG was purified from the culture supernatant and purity was determined using SDS-PAGE and analytical size exclusion chromatography (SEC).

### Results

The recombinant antibody was dispensed into ampoules at a concentration of 0.5mg/ml and freeze dried. It was tested in a range of immunological assays and has shown to be fit for purpose. The results show that it is a suitable replacement for the hybridoma derived mAb (02/148).

### Conclusion

This demonstrates that antigen specific recombinant mAb with defined sequence was successfully expressed and purified from transfected ExpiCHO-S cells. In conclusion this study shows that production of well characterised recombinant antibodies can be successfully performed to ensure future supply of our antibodies.

## PO-070 - (EMGM2019-13248) - INVESTIGATION OF THE PROTECTIVE MECHANISMS OF NEISSERIAL HEPARIN BINDING ANTIGEN (NHBA) INDUCED ANTIBODIES

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1 - GSK, Siena and University of Siena; 2 - GSK, Siena; 3 - GSK, Siena and University of Florence

### Introduction & Aims

Neisserial Heparin Binding Antigen (NHBA) is a surface-exposed lipoprotein ubiquitously expressed by *Neisseria meningitidis* strains and is one of the three main protein antigens of the Bexsero vaccine. NHBA binds heparin and heparan sulfates through an arginine-rich region, it is cleaved by meningococcal and human proteases, its expression is upregulated at 32°C<sup>[1]</sup> and it appears to be sparsely distributed on the bacterial surface. Additionally, recent evidence suggests that NHBA plays a key role in bacterial adherence mediated by the arginine-rich region<sup>[2]</sup>.

NHBA induces bactericidal antibodies in humans and confers protective immunity in the infant rat model. Anti-NHBA monoclonal antibodies from mice and humans are functional, being able to induce complement-mediated bacterial killing, in presence of rabbit complement.

The aim of this study is to further elucidate the functional properties of the anti-NHBA monoclonal antibodies, using a strain engineered to express higher amount of NHBA.

### Materials and Methods

An NHBA overexpressing strain was generated and used to characterize a panel of anti-NHBA monoclonals isolated from Bexsero immunized adults<sup>[3]</sup> that target different regions of the protein.

### Results

The monoclonals selected recognize different NHBA epitopes. All monoclonals tested are functional, inducing a strong bactericidal activity in presence of human complement.

### Conclusion

These data are providing an important outlook on the immunological properties of NHBA, demonstrate that NHBA contains multiple functional epitopes inducing functional antibodies in humans immunized with Bexsero.

**Funding:** GlaxoSmithKline Biologicals SA

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## PO-071 - (EMGM2019-13178) - USE OF SALIVA TO MONITOR MENINGOCOCCAL VACCINE RESPONSES: PROPOSING A THRESHOLD IN SALIVA AS SURROGATE OF PROTECTION

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### Introduction & Aims

Mucosal antibodies against capsular polysaccharides offer protection against acquisition and carriage of encapsulated bacteria like *Neisseria meningitidis* serogroup C. Measurements of salivary antibodies as replacement for blood testing has important (cost-effective) advantages, particular in studies that assess the impact of large-scale vaccination or in populations in which blood sampling is difficult. This study aimed to estimate a threshold for meningococcal IgG salivary antibody levels to discriminate between unprotected and protected vaccinated individuals.

### Materials and Methods

MenA-, MenC-, MenW- and MenY-polysaccharide (PS) specific IgG levels in serum and saliva from participants in a meningococcal vaccination study were measured using the fluorescent-bead-based multiplex immunoassay. Functional antibody titers in serum against the four serogroups were measured with serum bactericidal assay using rabbit complement (rSBA). A threshold for salivary IgG was determined by analysis of ROC curves using a serum rSBA titer  $\geq 128$  as correlate of protection. The area under the curve (AUC) was calculated to quantify the accuracy of the salivary test and was considered adequate when  $\geq 0.80$ . The optimal cut-off was considered adequate when salivary IgG cut-off levels provided specificity of  $\geq 90\%$ . True positive rate (sensitivity), positive predictive value, and negative predictive value were calculated to explore the possible use of salivary antibody levels as a surrogate of protection.

### Results

The best ROC curve (AUC of 0.95) was obtained for MenC, with an estimated minimum threshold of MenC-PS specific salivary IgG  $\geq 3.54$  ng/mL as surrogate of protection. An adequate AUC ( $> 0.80$ ) was also observed for MenW and MenY with an estimated minimal threshold of 2.00 and 1.82 ng/mL, respectively. When applying these thresholds, all (100%) samples collected 1 month and 1 year after the (booster) meningococcal vaccination, that were defined as protective in the saliva test for MenC, MenW and MenY, corresponded with concomitant serum rSBA titer  $\geq 128$  for the respective meningococcal serogroups.

### Conclusion

The saliva test offers an alternative screening tool to monitor protective vaccine responses up to one year after meningococcal vaccination against MenC, MenW and MenY. Future (large) longitudinal vaccination studies evaluating also clinical protection against IMD or carriage acquisition are required to validate the currently proposed threshold in saliva.

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**PO-072 - (EMGM2019-13253) - SET UP OF A HIGH-THROUGHPUT KINETIC-BASED SERUM BACTERICIDAL ASSAY TO ASSESS IMMUNOGENICITY OF MENINGOCOCCAL VACCINES IN PRECLINICAL**

Cristiana Balocchi (Italy)<sup>1</sup>; Daniele Casini (Italy)<sup>1</sup>; Maria Stella (Italy)<sup>1</sup>; Brunella Brunelli (Italy)<sup>1</sup>; Marzia Monica Giuliani (Italy)<sup>1</sup>; Elena Mori (Italy)<sup>1</sup>

1 - GSK, Siena, Italy

**Introduction & Aims**

Complement-mediated serum bactericidal activity (SBA) assay is the well-known, widely accepted serological correlate of protection against *Neisseria meningitidis*. The conventional assay procedure has remained largely the same since its introduction by Goldschneider *et al.* in 1969 [1] and involves surviving bacterial colony count on agar plates as readout, which is time-consuming and subjects to inter-operator variability. For this reason, a kinetic-based high-throughput SBA (HT-SBA) for human sera has been developed (Mak *et al.*, 2011) [2]. It follows the same principles of the classical format for the bactericidal phase but differs from the conventional method in how surviving bacteria are quantified.

**Materials and Methods**

The readout is based on the fluorescent signal generated by the oxidative respiration of surviving bacteria in presence of the fluorescence dye Alamar Blue. The reciprocal serum dilution giving a 50% reduction of the fluorescence signal is used for bactericidal titer calculation. Moreover, the assay format has been miniaturized to a 384-well microtiter plate to reduce the amount of test sera and complement increasing at the same time the number of samples that can be analyzed onto one plate. The assay has been implemented through a fully-automated robotic platform which includes an automatic liquid handling and automated plate incubation and reading steps.

**Results**

Here we describe the preclinical work done to set up and optimize a HT-SBA assay to test sera from mice immunized with Bexsero\*, using baby rabbit serum as complement source.

\*Bexsero is a trademark of the GSK group of companies

**Conclusion**

A bridging study with the manual assay has been carried out and results demonstrate that the automated format is robust and reproducible and titers strongly correlate with those obtained with the conventional method. The system is highly flexible and easy adaptable to different bacterial serotypes and strains together with sera from different animal models and shows a great potential as a high-throughput screening tool.

**References**

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## PO-073 - (EMGM2019-13206) - COMPARING CULTURE AND NON-CULTURE MENINGOCOCCAL STRAINS IN ENGLAND AND WALES FOLLOWING INTRODUCTION OF 4CMENB INTO THE NATIONAL INFANT IMMUNISATION SCHEDULE.

Stephen Clark (United Kingdom)<sup>1</sup>; Laura Willerton (United Kingdom)<sup>1</sup>; Aiswarya Lekshmi (United Kingdom)<sup>1</sup>; Steve Gray (United Kingdom)<sup>1</sup>; Ray Borrow (United Kingdom)<sup>1</sup>

<sup>1</sup> - Public Health England

### Introduction & Aims

In September 2015, the UK included 4CMenB meningococcal vaccine into the national routine immunisation programme on a 2, 4 and 12 month schedule. Assessing the ongoing impact of the vaccine requires enhanced surveillance of invasive meningococcal strains, especially those causing group B disease in the vaccinated cohort. As part of this enhanced surveillance programme, whole genome sequencing of invasive isolates is routinely performed, whilst non-culture cases (PCR only) are characterised using individual gene sequencing from clinical specimens. Assessments of vaccine strain coverage continue to be performed using analyses of cultured isolates only; despite the possibility of culture bias in the data. Analyses of strains from previous years (2011-2013) showed limited differences between culture and non-culture group B strains in terms of antigen distribution. The aim of this work was to provide an updated comparison of these two datasets for recent years following vaccine introduction.

### Materials and Methods

Capsular group, Factor H-Binding Protein (fHbp) and PorA typing data were compiled for all English and Welsh IMD cases confirmed between 1<sup>st</sup> Sept 2015 and 31<sup>st</sup> January 2018. Invasive isolates were initially characterised using phenotyping (dot blot ELISA) before undergoing whole genome sequencing. Genomic data were uploaded to the Meningococcus Genome Library hosted at PubMLST.org, in which meningococcal genes were annotated and indexed. Non-culture strains were characterised through gene sequencing of fHbp and PorA from PCR-positive clinical specimens. Nested PCR was used to amplify the gene targets prior to Sanger (chain-termination) sequencing.

### Results

Throughout period analysed, approximately one third of disease cases were confirmed using PCR only. Substantially more group W and Y cases are observed among isolates compared to non-culture. Group W and Y strains were largely homogenous in terms of fHbp and PorA genotyping. Group B strains were more diverse although no consistent differences were observed between culture and non-culture strains for either fHbp or PorA.

### Conclusion

Whilst differences continue to exist in the proportion of group W and Y strains among the two datasets, the distribution of antigenic variants among group B culture and non-culture strains remain largely similar. These data suggest that group B isolates are reasonably representative of group B strains as a whole and these findings support the continued use of isolate-based strain coverage assessments as part of enhanced surveillance activities.

## PO-074 - (EMGM2019-13300) - PRODUCTION AND QUALITY CONTROLS IN PROCESS OF A MENINGOCOCCAL W CONJUGATE VACCINE USING MODIFIED REDUCTIVE AMINATION

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1 - Oswaldo Cruz Foundation; 2 - Federal University of Rio de Janeiro

### Introduction & Aims

*Neisseria meningitidis* is classified by their capsular polysaccharide composition in 12 different serogroups, however only six are responsible for the majority of cases. Meningococcal W produces a polysaccharide capsule composed of galactose and sialic acid. Several outbreaks caused by this serogroup were registered in Asia and South America and currently was observed an increase of these cases. The aim of this study is to obtain bulks of meningococcal W conjugate vaccine by modified reductive amination.

### Materials and Methods

Meningococcal W strain 2467, from Adolfo Lutz Institute, was cultivated using Frantz medium in a 150 l bioreactor with controlled pH and temperature for 4h. After that period, 10% of this culture was inoculated in another 150 l culture for 16h. Cell growth, glucose consumption and polysaccharide production were evaluated during this step. After bacterial cells inactivation the supernatant was concentrated to 10% of initial volume. Supernatant was submitted to precipitation with anionic detergent and an inert support was used as filtration assistant. Extractive solution was used to reach polysaccharide fraction that was precipitated two times with ethanol to obtain a polysaccharide as required by WHO. Purified polysaccharide was dialyzed against EDTA to improve solubility and evaluated by <sup>1</sup>H nuclear magnetic resonance (NMR). Reductive amination assays started with polysaccharide oxidation reaction studies using different sodium periodate (NaIO<sub>4</sub>) concentrations and reaction times. Using the best condition found for polysaccharide oxidation some conjugate bulks were obtained with different reactant ratios (oxidized polysaccharide:activated tetanus toxoid; ratios 1:2, 1:1, 2:1). Obtained molecules were evaluated using different size exclusion chromatography (SEC) columns.

### Results

Bioreactor growth showed that cells reached stationary phase in 6h with continuous glucose consumption and polysaccharide production. Glucose consumption was about 95% after 16h of culture. NMR assays showed no differences between peaks after and before dialysis with EDTA. All native polysaccharide was consumed using NaIO<sub>4</sub> for 17h as observed by a homogeneous chromatographic peak. SEC assays demonstrated lower elution times in all conjugate batches suggesting that there is a polysaccharide:protein linkage. Increasing the reactant ratio revealed a tendency to observe chromatographic profiles with only one peak at ratios above 1:1, suggesting the presence of more homogenous products. SEC analysis using TSK G5000PWXL showed a better discrimination between protein, polysaccharide and conjugate samples. A method is being developed by Capillary Electrophoresis to evaluate conjugates batches.

### Conclusion

Produced conjugate bulks were formulated and inoculated intramuscularly in mice in order to obtain immunized serum for ELISA and bactericidal assays.

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Session: Oral Session IX  
Room: Auditorium I

Carriage

### **OC - (EMGM2019-13345) - AN ALTERNATIVE APPROACH TO STUDYING MENINGOCOCCAL PROTEIN-ANTIGEN VACCINES' EFFECTS ON CARRIAGE AND TRANSMISSION**

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#### **Introduction & Aims**

Meningococcus(Nm) conjugate vaccines can have powerful indirect effects. Whether protein-antigen vaccines similarly reduce transmission population-wide when used in teenagers has not been tested in any population although this is underway in South Australia. Recent attempts to answer this question have been studying throat carriage rates in individuals and groups immunised 6-12 months earlier compared to controls. So far, results seem to indicate minimal effects if any. We have conducted longitudinal studies which take a different approach.

#### **Materials and Methods**

917 16-17 year old school students had throat swabs(TS) taken at one month intervals through wintertime. 416 students had 4CMenB vaccine 2 doses one month apart with TS at immunisation and 3 months later. This group also gave weekly saliva samples throughout the study. Samples were analysed for Nm and capsular genogroups (B,C,Y,W,X) by qPCR of DNA extracts of samples and of products of culture on selective media. In study 1 a panel of respiratory viruses were also detected by PCR.

#### **Results**

Nm throat carriage episodes were significantly shorter than previously reported (median 29 days, 95%CI 26-32) with spikes in carriage density crossing 2-4 decile logs and often associated with respiratory viral infection ( $p<0.03$ ). Observed weekly in saliva, colonisation persisted for >20 weeks in 5 individuals. Among carriers (6.3-8.7%), high density carriage in the throat (>300 gene copies/ml) was seen before but not 3 months after Bexsero administration ( $n=4$  vs 0, NS). Combining the area-under-the-curve of salivary meningococcal density in carriers over time permitted an estimation to be made of trends in overall circulating meningococcal mass in the schools studied over the sampling time period.

#### **Conclusion**

Nm carriage is usually brief and dynamic. Saliva sampling used alongside throat swabbing increases detection rates by PCR, especially if samples are culture-amplified before DNA extraction. Saliva sampling is quick, easy and not uncomfortable, permitting frequent sampling to be done. Mucosal immune responses to protein-antigen vaccines may impact on carriage density, duration and efficiency of onward transmission but, unlike conjugate vaccines, may not reliably prevent acquisition. As an alternative to population-wide experiments (as conducted with MenA and MenC vaccines), studies to evaluate protein antigen vaccines should measure carriage duration, density and rates of onward transmission rather late carriage rates in vaccine recipients. Additionally, if well-demarcated populations can be identified and studied, it is feasible to monitor the overall mass of circulating meningococci over time by frequent saliva sampling and the effect of vaccine at different levels of coverage.

## OC - (EMGM2019-13222) - PREVALENCE, SEROGROUP DISTRIBUTION AND RISK FACTORS FOR MENINGOCOCCAL CARRIAGE AMONG CHILDREN AND ADOLESCENTS IN TURKEY-2018: UNEXPECTED-HIGH SEROGROUP X CARRIAGE

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1 - Eskisehir Osmangazi University Faculty of Medicine; 2 - Hacettepe University Faculty of Medicine; 3 - 4Okmeydanı Training and Research Hospital; 4 - Ege University Faculty of Medicine, Izmir; 5 - Uludag University Faculty of Medicine; 6 - Antalya Muratpaşa Çaybaşı No:1 Family Health Center; 7 - Konya Training and Research Hospital; 8 - Mersin University Faculty of Medicine; 9 - Erciyes University Faculty of Medicine, Kayseri; 10 - Adnan Menderes University Faculty of Medicine; 11 - Diyarbakır Children Hospital; 12 - Trabzon Kanuni Training and Research Hospital; 13 - Karadeniz Technical University Medical Faculty

### Introduction & Aims

Invasive meningococcal disease (IMD) is associated with high case-fatality rates and long-term sequelae all around the world. Transmission modeling can be used to inform IMD control strategies and predict IMD epidemiology, including the impact of proposed vaccination programs. Sero-epidemiology of IMD and nasopharyngeal carriage of *Neisseria meningitidis* (*Nm*) in Turkey is quite different from other countries. Our previous multicenter study about meningococcal study in Turkey showed that carriage rate among 1518 adolescents and young adults, aged between 10-24 years, has been shown to be 6.3%, with peak ages at 17 years (11%), and 65% of carriers having serogroup W. In this multicenter study, we aimed to re-determine the prevalence nasopharyngeal *Nm* carriage, serogroup distribution and related risk factors in same geographical area in Turkey, in 2018.

### Materials and Methods

Nasopharyngeal samples were collected from a total of 1267 cases (643 girls and 624 boys) at 12 cities in Turkey, and tested for *Nm* with rt-PCR and evaluated for serogroup distribution. Previously described risk factors for *Nm* carriage have been recorded.

### Results

Meningococcal carriage rate was 7.6% (n=96, 49 girls and 47 boys) among children 0-18 years old, with a peak age at 13 years (12.5%) and higher in 15-18 years old group (9.3%). Among 96 *Nm* samples, the serogroup distribution were as follow: 25% for serogroup X, 9.4% for serogroup A, 9.4% for serogroup B, 2.1% for serogroup C, 3.1% for serogroup W, 2.1% for serogroup Y and 48.9% for non-groupable. Meningococcal carriage rate was positively correlated with previous month upper respiratory tract infections ( $p<0.05$ ) and presence of the impact high number of household members ( $p<0.05$ ), while negatively correlated with antibiotic use at last one month ( $p<0.05$ ).

### Conclusion

In this study, serogroup X carriage rate was higher than expected, and low serogroup W carriage has been seen comparing the 2015 study results. In this study, we did not observe serogroup C carriage, while we did not observe IMD or carriage related with serogroup C since 2005 in Turkey. The geographical distribution of *Nm* strains differs, however, serogroup distribution might be change in the same country within years. Adequate surveillance and/or proper carriage study is paramount for accurate/dynamic serogroup distribution and potential vaccine strategies. Immunization strategies against all clinically relevant *Nm* serogroups (A, B, C, W, X, Y) should be developed and country-specific approaches to vaccine prevention are needed.

## OC - (EMGM2019-13245) - RISK FACTORS ASSOCIATED WITH MENINGOCOCCAL CARRIAGE AMONGST THIRD-LEVEL STUDENTS IN THE REPUBLIC OF IRELAND.

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### Introduction & Aims

The main reservoir for *Neisseria meningitidis* is asymptomatic colonisation of the oropharynx, a phenomenon known as carriage. Older adolescents and young adults tend to be the highest carriers and transmitters of meningococci. Monitoring the prevalent serogroups and determinants of carriage in this population demographic aids disease epidemiology prediction and guides infection prevention measures such as vaccination.

The objective of this study was to perform a nationwide survey of *N. meningitidis* strains being carried by third-level students in the Republic of Ireland (RoI) and to evaluate the potential risk factors associated with meningococcal colonisation in this cohort.

### Materials and Methods

Subjects were recruited on a voluntary basis from 12 third-level institutions located throughout the RoI during Winter 2016/Spring 2017. A single oropharyngeal swab was collected from each participant and paired with a self-administered questionnaire capturing baseline demographic data plus information on general health and social practices. Meningococcal genogroups were identified using a multiplex PCR assay, and risk factor analysis undertaken using univariate and multivariate statistical modelling.

### Results

We analysed genogroup and risk factor data from 1,755 study participants. A total of 398 meningococcal isolates were recovered from the cohort, giving an overall carriage prevalence of 22.6%. Genogroup distribution analysis revealed a majority of non-groupable meningococci (n=189, 47.5%), while genogroup B predominated amongst the remainder (n=123, 31.2%), followed by Y (n=41, 10.3%), W (n=22, 5.5%), C (n=18, 4.5%), and X (n=4, 1%). Significantly associated risk factor variables were included in the multivariate model, of which, age<20 years, living in campus accommodation, recent travel abroad, Irish nationality and, inversely, antibiotic consumption remained independently associated with carriage.

### Conclusion

This study provides valuable carriage data on meningococcal carriage in Irish young adults attending third-level institutions. We report a predominance of non-groupable meningococci, followed by genogroup B and Y. Low prevalence of MenC and MenW carriage is demonstrated, which contrasts with current disease trends in the country. Multivariate analysis suggests a strong link between the behavioural patterns and living arrangements of this cohort and their propensity for carrying *N. meningitidis* strains. These findings, coupled with recent increases in MenC and MenW IMD cases, may have implications for public health management of this vulnerable cohort in the RoI.

## OC - (EMGM2019-13270) - IRON STATUS AND CARRIAGE OF *N. MENINGITIDIS* IN THE AFRICAN MENINGITIS BELT

Maria Sundaram (United States of America)<sup>1</sup>; Nicole Basta (United States of America)<sup>2</sup>; Caroline Trotter (United Kingdom)<sup>3</sup>; Sarah Cusick (United States of America)<sup>2</sup>; Julian Wolfson (United States of America)<sup>2</sup>; Abraham Aseffa (Ethiopia)<sup>4</sup>; Jean-Marc Collard (France)<sup>5</sup>; Aldiouma Diallo (France)<sup>6</sup>; Abraham Hodgson (Ghana)<sup>7</sup>; Jean-François Jusot (France)<sup>5</sup>; Babatunji Omotara (Nigeria)<sup>8</sup>; Samba Sow (Mali)<sup>9</sup>; Brian Greenwood (United Kingdom)<sup>10</sup>

1 - Emory University Rollins School of Public Health; 2 - University of Minnesota School of Public Health; 3 - University of Cambridge; 4 - Armauer Hansen Research Institute; 5 - Centre de Recherche Médicale et Sanitaire; 6 - Institut de Recherche pour le Développement; 7 - Navrongo Health Research Centre; 8 - Department of Community Medicine, University of Maiduguri; 9 - Centre pour les Vaccins en Développement; 10 - London School of Hygiene and Tropical Medicine

### Introduction & Aims

*Neisseria meningitidis* (Nm) carriers are the primary transmission source of the bacterium. Nm requires human iron to replicate and survive. Many questions remain about biological risk factors for susceptibility to Nm carriage. The availability of iron may increase risk of carriage. We investigated whether there is an association between body iron status and asymptomatic nasopharyngeal Nm carriage among individuals of all ages.

### Materials and Methods

We conducted a retrospective, matched case-control study nested within a cohort study led by the MenAfriCar Consortium during 2010-2012. Cases were Nm carriers (any serogroup) based on bacterial culture and confirmed via molecular methods at any study visit. Controls were participants who tested negative for carriage. Cases were matched to up to two controls based on age, sex, study site, and visit date. Iron status was determined by serum ferritin (an iron storage protein that increases with inflammation and body iron stores) and soluble transferrin receptor (sTfR, a measure that increases with iron deficiency). We stratified by age group (<5, 5-11, 12-17, and ≥ 18 years). We used conditional logistic regression to assess the association between serum ferritin or sTfR and Nm carriage, using continuous  $\log_{10}$  ferritin and  $\log_{10}$  sTfR. We excluded individuals with high C-reactive protein (an inflammation marker), since ferritin and sTfR are acute phase proteins, and we adjusted for number of members in household.

### Results

In total, 194 cases were matched to 332 controls. Conditional logistic regression suggested that higher  $\log_{10}$  serum ferritin was associated with increased odds of carriage in the youngest children and decreased odds of Nm carriage in all other age groups; the association was statistically significant for 5-11 years olds (OR: 0.30, 95% CI: 0.12 - 0.78). In addition, higher  $\log_{10}$  sTfR was associated with increased odds of carriage in 5-11 year olds and adults and decreased odds of carriage in the youngest children and teenagers; this association was not statistically significant in any age group.

### Conclusion

Our results do not suggest a clear relationship between iron and Nm carriage across all age groups. However, we found evidence that young children with low serum ferritin and teens with high sTfR, both reflective of poorer iron status, are less likely to be carriers. Future studies could evaluate these relationships by conducting longitudinal studies that assess iron status prior to identifying carriers, and considering other markers of local iron availability, including human nasal lactoferrin (needed by Nm to replicate).

Session: Oral Session X  
Room: Auditorium I

Immunology and Immunity

### OC - (EMGM2019-13326) - POTENTIAL COVERAGE OF MENB-FHBP VACCINE (TRUMENBA™) TO MENB PATIENT ISOLATES: RESULTS FROM THE GREEK STUDY DURING THE PERIOD 2010-2017

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#### Introduction & Aims

The estimation of vaccine strain coverage among meningococcal isolates is a crucial element for predicting the effectiveness of non-capsular meningococcal antigen vaccines. For this purpose, the Meningococcal Antigen Surface Expression (MEASURE) assay was established in order to quantify the *in vitro* surface expression of FHBP on meningococcal serogroup B (NmB) isolates [1]. The aim of this study was to evaluate the potential of the MenB-FHbp vaccine against Greek invasive MenB strains.

#### Materials and Methods

A total of 68 MenB strains isolated from patients with invasive meningococcal disease (IMD) during the period 2010–2017 were studied. The strain set was composed of: 14 clinical strains (first subset) isolated from adolescent patients (11-17 years of age) during 2010-2014, and, 54 strains (2<sup>nd</sup> subset) isolated from patients of all ages during a 3-year period (2015–2017). All isolates were cultured and identified as described previously [1]. The MEASURE assay was performed as previously described [2]. Isolates producing a mean fluorescent intensity (MFI) of >1,000 (corresponding to approximately 30pg of FHBP pergram of NmB whole-cell extract) are considered as susceptible to bactericidal killing by antibodies induced by MenB-FHbp.

#### Results

Sixty-five out of 68 (95.6%) isolates produced an MFI above the putative threshold for susceptibility to bactericidal killing by vaccine-induced antibodies. Specifically, for the two consecutive periods the percentages were a) **2010-2014**: 100% (14/14 isolates from adolescents), b) **2015-2017**: 94.4% (51 /54 from all age groups). Of note, comparing patients aged 0-19 years and >20 years of age, the percentages were 100% (46/46), and 86.4% (19/22), respectively.

#### Conclusion

To our knowledge, this is the first report on the application of the MEASURE assay to a local panel of fully representative isolates for a country. According to the results, MenB-FHbp has the potential to protect against the vast majority of Greek invasive MenB isolates and is in agreement with previously published data for a representative panel of isolates from EU and USA [2].

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## OC - (EMGM2019-13220) - IMMUNOGENICITY OF THE MENINGOCOCCAL SEROGROUP B VACCINE MENB-FHBP IN CHILDREN 1 TO <10 YEARS OF AGE

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### Introduction & Aims

MenB-FHbp (bivalent rLP2086) is a serogroup B meningococcal (MenB) vaccine licensed in multiple countries for adolescents and adults. Two recent phase 2 studies evaluated MenB-FHbp immunogenicity in younger children.<sup>1,2</sup>

### Materials and Methods

In an ongoing study, 352 toddlers 1–<2 years old were randomized to receive MenB-FHbp (120 µg at months 0, 2, 6) or hepatitis A virus vaccine (HAV; months 0, 6)/saline (month 2).<sup>1</sup> Four hundred children 2–<10 years old were randomized 3:1 to receive 120 µg MenB-FHbp or HAV/saline.<sup>2</sup> Immune responses were evaluated in serum bactericidal assays using human complement (hSBA) against 4 diverse, vaccine-heterologous MenB test strains; the lower limits of quantitation (LLOQs; 1:8 or 1:16) exceeded the accepted correlate of protection (hSBA titers ≥1:4). The current analysis evaluated pooled immune responses in 120-µg MenB-FHbp recipients (1–<10 years old) from the evaluable immunogenicity populations of both studies.

### Results

One month postdose 3, 71.6%–100% of toddlers 1–<2 years old receiving 120 µg MenB-FHbp had hSBA titers ≥LLOQ against each of the 4 test strains; percentages were 79.1%–100% in children 2–<10 years old and 81.4%–100% in the pooled analysis (individuals 1–<10 years old). Percentages of subjects in the pooled analysis achieving ≥4-fold rises from baseline in hSBA titers were 74.7%–95.3% at 1 month following dose 3 and were similar across age groups. Geometric mean titers (GMTs) in the pooled analysis increased from 4.0–8.6 before vaccination to 19.0–178.4 at 1 month postdose 3.

### Conclusion

MenB-FHbp administered on a 0-,2-,6-month schedule induced protective bactericidal antibody responses against diverse MenB strains in subjects 1–<10 years old, supporting its potential for providing children with broad protection against MenB disease. Clinical Trial Registration: ClinicalTrials.gov, NCT02534935, NCT02531698. Funded by Pfizer.

### References

[1]H. Marshall, et al, A Phase 2 Study of the Immunogenicity, Safety, and Tolerability of the Meningococcal Serogroup B Vaccine MenB-FHbp (Bivalent rLP2086) in Healthy Toddlers ≥12 to <24 Months of Age. Presented at: European Society for Paediatric Infectious Diseases; May 28-June 2, 2018, Malmö, Sweden.

[2]T. Vesikari, et al, Phase 2 Study of the Safety and Immunogenicity of the Meningococcal Serogroup B Vaccine MenB-FHbp (Bivalent rLP2086) in Healthy Children between 2 and <10 Years of Age. Presented at: European Society for Paediatric Infectious Diseases; May 28-June 2, 2018, Malmö, Sweden.

## OC - (EMGM2019-13184) - ANTIBODY PERSISTENCE UP TO 26 MONTHS POSTBOOSTER DOSING IN ADOLESCENTS 4 YEARS FOLLOWING 2- AND 3-DOSE PRIMARY SERIES OF MENB-FHBP

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### Introduction & Aims

Antibody persistence after booster vaccination with MenB-FHbp (bivalent rLP2086) has not been previously described. This adolescent study evaluated antibody persistence following a MenB-FHbp booster dose administered 4 years after primary vaccination.

### Materials and Methods

This phase 3 open-label extension of a phase 2 randomized study included adolescents 11-18 years of age who received MenB-FHbp on 2- and 3-dose schedules (including licensed 0-,6-month and 0-,2-,6-month schedules). Booster vaccination was administered 48 months after the primary series. Immune responses were evaluated in serum bactericidal assays with human complement (hSBAs) using 4 vaccine-heterologous meningococcal serogroup B (MenB) test strains. Immunogenicity endpoints included percentages of subjects with hSBA titers  $\geq$  the lower limit of quantitation (LLOQ; 1:8 or 1:16; titers  $\geq$ 1:4 correlate with protection) at 1 and 48 months postprimary and 1, 12, and 26 months postbooster. Post-booster safety was evaluated.

### Results

The booster stage included 58 and 62 subjects on 0-,2-,6-month and 0-,6-month primary schedules, respectively. Persistence data following primary vaccination and through 26 months postbooster indicated that percentages of subjects with protective hSBA titers were similar across primary series. Percentages at 1, 12, and 26 months after boosting (93.4%–100%, 59.0%–89.1%, and 57.5%–82.8%, respectively) were similar or higher compared with 1, 12, and 24 months after primary vaccination (77.9%–99.1%, 16.5%–76.1%, and 15.7%–68.6%, respectively). No safety concerns were identified with up to 26 months of postbooster follow-up.

### Conclusion

A booster dose given 4 years after a licensed 2- or 3-dose MenB-FHbp schedule can be used to elicit robust anamnestic immune responses, providing broad protection for at least 2 additional years to a large proportion of recipients reaching college age who are at continued risk of meningococcal disease. Clinical Trial Registration: NCT01543087. Funded by Pfizer.

## OC - (EMGM2019-13179) - DOES 4CMENB VACCINE-INDUCED IMMUNITY AGAINST A MENINGOCOCCAL B OUTBREAK STRAIN PERSIST 20 MONTHS AFTER VACCINATION?

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### Introduction & Aims

Meningococcal B (MenB) vaccination presents an important opportunity to prevent meningococcal disease and control outbreaks. However, questions remain about the persistence of vaccine-induced immunity against the diversity of MenB isolates causing invasive disease. Additional evidence is needed to further develop recommendations for vaccinating target age groups, including teens and young adults, in both high-risk and routine settings. We aimed to assess whether 4CMenB (Bexsero®) vaccine-induced immunity against a MenB outbreak strain persisted up to 20-months after vaccination among adults.

### Materials and Methods

In 2013-14, 4CMenB vaccine was used to control a MenB outbreak at a university in New Jersey caused by a ST 409 [cc41/44/lineage3], PorA P1.5-1,2,2, fHbp 1.276, NHBA p0002, NadA- strain. We previously conducted a seroprevalence study 2 months after 4CMenB vaccination to evaluate short-term immune responses among vaccinated and unvaccinated students [1]. We subsequently enrolled these participants into a follow-up study to assess longer-term persistence of immunity against the outbreak strain. Participants still enrolled at the university 20 months post-vaccination were invited to provide a blood sample. We measured serum bactericidal antibodies using human complement (hSBA) among both vaccinated and unvaccinated participants. We compared changes in the proportion seroprotected (hSBA titre  $\geq 4$ ) against the outbreak strain and in the geometric mean titres (GMTs) from 2 months to 20 months post-vaccination among both vaccinated and unvaccinated participant.

### Results

Among the 173 young adults who provided blood samples at both 2-months and 20-months post-vaccination, 170 received 2 doses of 4CMenB vaccine spaced 2 months apart and 3 remained unvaccinated. While 61% (95% CI: 53% to 68%) of 2-dose vaccinees were seroprotected against the outbreak strain at 2 months (previously reported [1]), only 24% (95% CI: 18% to 31%) maintained an hSBA titre 4 or greater against the outbreak strain 20-months after vaccination, representing a significant decline in seropositivity among vaccinees (37 percentage point decline [95% CI: 27 to 47,  $p < 0.001$ ]). hSBA GMTs against the outbreak strain among vaccinees declined from 6.5 (95%CI: 5.3 to 8.0) 2 months-post to 1.9 (95% CI: 1.6 to 2.4) 20-months post-vaccination. None of the unvaccinated participants had detectable hSBA titres 20 months after the vaccination was offered (0% seroprotected; hSBA GMT = 1).

### Conclusion

While nearly two thirds of young adults vaccinated with 2 doses of 4CMenB exhibited hSBA immune responses of 4 or greater 2 months after vaccination, immunity against the outbreak strain (hSBA $\geq 4$ ) persisted only among a quarter of vaccinees after 20 months.

### References

[1] Basta et al. Immunogenicity of a Meningococcal B Vaccine during a University Outbreak. NEJM. 2016 Jul 21;375(3):220-8.

Session: Oral Session XI  
Room: Auditorium I

Thinking outside the box

## OC - (EMGM2019-13342) - THE ZEBRAFISH EMBRYO AS AN INFECTION MODEL FOR NEISSERIA MENINGITIDIS

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<sup>1</sup> - Amsterdam UMC

### Introduction & Aims

The host innate immune system is the first barrier to overcome in order to develop invasive meningococcal disease. The zebrafish embryo has a fully functioning innate immune system from 2 days post fertilization onward which resembles that of mammals (1). In addition, zebrafish have a functional blood-brain barrier similar to that of mammals (2). Due to its transparency and the availability of a wide range of fluorescent tools, the zebrafish embryo infection model offers the ability to study host-pathogen interaction in real time. The aim of this study was to explore the zebrafish embryo as a potential meningococcal infection model to study host-pathogen interaction.

### Materials and Methods

We used H44/76 (wild type, wt) and the H44/76 isogenic variant HB-1 which is unencapsulated and an H44/76 *lpxL1* knock-out ( $\Delta lpxL1$ ). All three strains were transformed to express Mcherry from the chromosomal location between *recC* and *mtrF*. Zebrafish embryos were collected within the first hours post fertilization and kept at 28 °C in embryo medium. Meningococci were cultured according standard culture techniques. Bacteria were injected in the fish caudal vein at 28 hours post fertilization and zebrafish embryos were monitored for survival up to 72 hours post infection. Location of meningococci in the fish embryos were assessed by fluorescence microscopy.

### Results

At 72 hours post infection,  $55.4 \pm 4.505\%$  of the fish embryos had died when infected with wt H44/76, while only  $15.75 \pm 4.973\%$  had died when the unencapsulated strain was used.  $\Delta lpxL1$  showed a similar phenotype with  $16.67 \pm 6.667\%$  killing of the fish embryos, while  $6.667 \pm 3.727\%$  of the fish embryos survived when mock infected. At 24 hours post infection, H44/76 wt could be cultured from the fish embryos, while the cultures of HB-1 and the  $\Delta lpxL1$  were below the detection limit. At 24 hpi with wt H44/76, 85% of the living embryos showed meningococci throughout the body, while in 15% meningococci were absent in the head. 48% showed pericardial edema analogous to what was reported for *Pseudomonas aeruginosa* LPS injected fish embryos. When infected with  $\Delta lpxL1$  these numbers were 26%, 67% and 26%, respectively.

### Conclusion

Our data suggest that the zebrafish embryo is a promising infection model to study the pathogenesis of invasive meningococcal disease. This model may potentially be useful for medium-throughput screening to evaluate the virulence capacity of clinical isolates, to identify bacterial mutants with altered virulence or medium-throughput screening of pharmacological compounds.

### References

1. Lam SH, Chua HL, Gong Z, Lam TJ, Sin YM. Development and maturation of the immune system in zebrafish, *Danio rerio*: a gene expression profiling, in situ hybridization and immunological study. *Dev Comp Immunol.* 2004;28:9-28.
2. Jeong JY, Kwon HB, Ahn JC, Kang D, Kwon SH, Park JA, Kim KW. Functional and developmental analysis of the blood-brain barrier in zebrafish. *Brain Res Bull.* 2008;75:619-28.

## OC - (EMGM2019-13187) - CULTURE-FREE METAGENOMIC SHOTGUN SEQUENCING OF URINE TO IDENTIFY MENINGOCOCCAL COINFECTION WITH URETHRITIS PATHOGENS.

Adam Retchless (United States of America)<sup>1</sup>; Mark Itsko (United States of America)<sup>1</sup>; Jose Bazan (United States of America)<sup>2</sup>; Abigail Norris Turner (United States of America)<sup>2</sup>; Brandon Snyder (United States of America)<sup>2</sup>; Morgan Brown (United States of America)<sup>2</sup>; Sandeep Joseph (United States of America)<sup>1</sup>; Xin Wang (United States of America)<sup>1</sup>

1 - Centers for Disease Control and Prevention; 2 - Ohio State University

### Introduction & Aims

Over 200 cases of *Neisseria meningitidis* (Nm) urethritis have been reported in the United States since 2015 involving a clade of nongroupable Nm (the "U.S. NmNG urethritis clade") [1]. These cases have not been thoroughly evaluated for coinfection by other pathogens that could contribute to the development of urethritis.

### Materials and Methods

We used Nm-specific real-time PCR (rt-PCR) and metagenomic shotgun sequencing to detect microbial species by evaluating DNA in 51 urine specimens collected from male patients at a U.S. sexual health clinic that had recently reported a urethritis outbreak attributable to the U.S. NmNG urethritis clade [2]. Specimens were categorized according to patient symptoms, urethral Gram Stain results, urine nucleic acid amplification testing (NAAT) results for *Neisseria gonorrhoeae* (Ng) and *Chlamydia trachomatis* (Ct), and urethral culture for *Neisseria* species. The specimens were from patients with the following diagnoses: 13 Nm urethritis (2 of which were positive for Ct by NAAT); 10 Ng urethritis; 9 Ct urethritis; 9 non-Ng, non-Ct urethritis; and 10 without urethritis.

### Results

Nm was detected by rt-PCR in urine specimens from all 13 Nm urethritis cases. Metagenomic sequencing detected Nm in 12 of those 13 specimens, but detected no other urethritis pathogens. Two Nm urethritis specimens contained JC polyomavirus, and one contained small proportions of several bacteria commonly found on skin. The Nm DNA sequences identified in Nm urethritis specimens were most similar to a genome representing the U.S. NmNG urethritis clade among a collection of 222 diverse Nm genomes. Nm was not detected by rt-PCR or metagenomic sequencing in the 28 urine specimens from non-Nm urethritis cases. None of 10 specimens from asymptomatic patients was positive for Nm by PCR; only one had any evidence of Nm based on metagenomic sequencing data. However, Nm was estimated to be only 10% of the bacteria in this specimen, and the sequences did not clearly match any specific Nm reference genome. Metagenomic sequencing detected Ng only in the 10 specimens from patients with Ng urethritis, and Ct only in 3/9 specimens from patients with Ct urethritis. Several additional bacteria and DNA viruses were detected in the remaining specimens from both symptomatic and asymptomatic patients, the most common being *Gardnerella vaginalis* (8 specimens), *Atopobium vaginae* (6 specimens) and the JC polyomavirus (6 specimens).

### Conclusion

These findings suggest that urethral infection with the U.S. NmNG urethritis clade is sufficient to cause urethritis, independent of other microbes.

### References

1. Retchless AC, Kretz CB, Chang HY, et al. Expansion of a urethritis-associated *Neisseria meningitidis* clade in the United States with concurrent acquisition of *N. gonorrhoeae* alleles. *BMC genomics* **2018**; 19:176.
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Session: Oral Session XII  
Room: Auditorium I

## Prevention and Control Measures and Public Health Management

### OC - (EMGM2019-13348) - DEFEATING MENINGITIS BY 2030: A GLOBAL ROADMAP

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1 - WHO

#### Introduction & Aims

Meningitis is a devastating disease affecting all populations and remains a major public health challenge in regions and countries around the world. Cases and outbreaks continue to be highly feared.

The aim is to agree a global roadmap to defeat meningitis by 2030.

#### Materials and Methods

The roadmap is being developed by a multi-organization partnership led by WHO. It covers the organisms responsible for the majority of acute bacterial meningitis, namely *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus agalactiae* (Group B Streptococcus).

#### Results

The vision is a world free of meningitis. The provisional goals to be achieved by 2030 are: (i) eliminate meningitis epidemics (ii) reduce cases and deaths from vaccine-preventable meningitis by 80% (iii) decrease the impact of sequelae by 50%

The roadmap is based on five axes:

1. Prevention and epidemic control - through development and enhanced access to affordable vaccines, effective prophylactic measures and targeted control interventions
2. Diagnosis and treatment - achieving access to the right diagnostic test from remote health facilities to city hospitals, to enhance surveillance and ensure patients can be promptly treated through effective antibiotics and adjunctive care
3. Disease Surveillance - encompassing all main causes of bacterial meningitis and their sequelae in order to guide meningitis control policies and accurately monitor progress
4. Support and aftercare for survivors and their families - so that the heavy burden of meningitis sequelae is recognized and alleviated in every community around the world
5. Advocacy and Information - to raise public and political awareness of meningitis as a health priority and improve health-seeking behavior and access to control measures

#### Conclusion

The objective is to submit the roadmap for adoption at the seventy-second World Health Assembly in May 2020. Major steps include publication of a baseline situation analysis, extended consultation with stakeholders and technical advisory groups, recommendations from the Strategic Advisory Group of Experts on Immunization.

#### References

This abstract is submitted by the authors on behalf of the Technical Task Force on Defeating Meningitis by 2030

## OC - (EMGM2019-13212) - FIRST EVIDENCE OF BEXSERO VACCINE IMPACT ON MENINGOCOCCAL SEROGROUP W CC11 DISEASE IN ENGLAND

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<sup>1</sup> - Public Health England

### Introduction & Aims

An outbreak of a hypervirulent serogroup W meningococcal (MenW) strain belonging to sequence type 11 clonal complex led to the introduction of teenage MenACWY vaccination from August 2015. The programme directly protects teenagers and young adults but also aims to induce population-wide herd protection by reduction of carriage.

Bexsero (4CMenB) vaccine was included in the routine UK infant programme from September 2015, at 8 and 16 weeks and 12 months of age. 4CMenB contains NHBA (Neisserial heparin binding antigen), NadA (Neisseria adhesin A) and fHbp (factor H binding protein) with MenB outer membrane vesicles (PorA) from an outbreak strain. Whilst 4CMenB is licensed for prevention of MenB disease, the vaccine antigens are also in some non-MenB meningococci. Cross-protection against the circulating MenW:cc11 strain has been shown using serum samples from 4CMenB-immunised children [1].

### Materials and Methods

Vaccine impact was estimated using confirmed MenW cases from 2011/12 to 2017/18 by ages 0-17 weeks, 18-52 weeks and 1-4 years. Those aged 0-17 weeks were assumed to have no protection. Those aged 18-52 weeks were 2-dose vaccine eligible, 1-year olds were partly eligible in 2016/17 and fully in 2017/18 and the 2-year olds partly eligible in 2017/18. As teenage MenACWY was introduced concurrent to infant 4CMenB the impact of MenACWY vaccination was also assessed.

To estimate impact a Poisson model was constructed on incidence rates with a factor for; year, age group and the six vaccine eligible periods with non-vaccine eligible as baseline. This interrupted time series model uses rates in the non-vaccine targeted aged groups to predict changes in vaccine targeted ages. ONS population denominators (England) were used as offsets.

### Results

This model showed no lack of fit (goodness of fit test  $p=0.67$ ). It is therefore reasonable to use changes in the non-vaccinated age cohorts to predict what would have happened in vaccinated cohorts in the absence of vaccination. Reductions were seen in most post 2-dose targeted cohorts; when fully eligible cohorts were combined, there was a 65% reduction (95% CI: 33% to 82%). No reductions were seen in non-eligible or 1-dose 4CMenB cohorts.

### Conclusion

This impact analysis demonstrates evidence of lower levels of MenW in cohorts targeted with 4CMenB than those not targeted. The analyses are based on small numbers and assumes that MenACWY herd effects would apply equally to all <5 years. Additional impact of MenACWY vaccine needs assessing across all ages.

### References

[1] LADHANI, S. N., GIULIANI, M. M., BIOLCHI, A., PIZZA, M., BEEBEEJAUN, K., LUCIDARME, J., FINDLOW, J., RAMSAY, M. E. & BORROW, R. 2016. Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England. *Emerg Infect Dis*, 22, 309-11.

## OC - (EMGM2019-13180) - CHARACTERISTICS OF AND MENINGOCOCCAL DISEASE PREVENTION STRATEGIES FOR COMMERCIALY INSURED PATIENTS RECEIVING ECULIZUMAB IN THE UNITED STATES

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### Introduction & Aims

Ecuzumab, a terminal complement inhibitor, is licensed to treat paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG). Ecuzumab use is associated with an approximate 2,000-fold increased incidence of meningococcal disease. Meningococcal vaccines are recommended for ecuzumab recipients in the United States; long-term antibiotic prophylaxis is recommended in some countries but not in the United States. We describe characteristics of and meningococcal vaccine and antibiotic receipt for ecuzumab recipients in the United States to inform meningococcal disease prevention strategies for this population.

### Materials and Methods

Using the 2007–2016 IBM® MarketScan® Research Databases, ecuzumab recipients were identified as persons with  $\geq 1$  claim for ecuzumab injection during 2007-2016 and  $\geq 30$  days continuous health plan enrollment prior to first ecuzumab treatment date. Indication for ecuzumab use was assessed using International Classification of Diseases-9/10 diagnosis codes for PNH, aHUS, typical HUS, and gMG. Median therapy duration was estimated using Kaplan-Meier survival curves. Serogroup B meningococcal (MenB) and serogroup A, C, W, Y conjugate meningococcal (MenACWY) vaccine receipt was assessed using vaccine administration procedure codes. Antibiotic receipt was assessed using antibiotic codes from pharmacy claims.

### Results

Overall 630 persons met the inclusion criteria; mean age was 40 years (range: 0-88), 59% were female. PNH and aHUS were the most common indications for ecuzumab use (42% and 35%, respectively); 21% had an undetermined indication. For aHUS, median therapy duration was 633 days (95% CI: 453, 1617). For undetermined indication, median duration was 0 days: 68% of these patients received only one injection. Treatment duration was longest for PNH, but median duration could not be calculated, as 72% of these patients were receiving ecuzumab at the end of follow-up. From publication of US MenB recommendations in June 2015 through December 2016, 19% (29/155) of continuously-enrolled patients received  $\geq 1$  MenB dose, and 10% (16/155) received a complete series. For MenACWY, 45% (78/173) of patients received  $\geq 1$  dose within five years of their most recent ecuzumab dose. Of ecuzumab recipients with outpatient prescription data, 43% (222/516) received penicillin or macrolide antibiotics at any time during ecuzumab therapy; only 6% (32/516) received antibiotics for the duration of ecuzumab therapy.

### Conclusion

Most patients receiving ecuzumab appeared to have aHUS or PNH. Low MenB and MenACWY receipt suggests many ecuzumab recipients may not be up-to-date on meningococcal vaccines. More information is needed about people receiving ecuzumab for undetermined indications, as appropriate prevention strategies may differ for them.

### References

## OC - (EMGM2019-13200) - VACCINATION CAMPAIGN AS RESPONSE TO INCREASE OF SEROGROUP W MENINGOCOCCAL DISEASE IN THE NETHERLANDS

Mirjam Knol (Netherlands)<sup>1</sup>; Hester de Melker (Netherlands)<sup>2</sup>; Helma Ruijs (Netherlands)<sup>2</sup>; Arie van der Ende (Netherlands)<sup>3</sup>  
1 - National Institute for Public Health and the Environment; 2 - National Institute for Public Health and the Environment; 3 - Amsterdam University Medical Center

### Introduction & Aims

In the Netherlands, an increasing incidence of invasive serogroup W meningococcal disease (IMD-W) has been observed since 2015. As a response, the MenC vaccination at 14 months of age has been replaced by the MenACWY vaccination in May 2018 and a vaccination campaign targeting 14-year-olds was started in October 2018. In Spring 2019, the campaign will be extended to all 14-18-year-olds. We describe the current IMD-W outbreak in terms of incidence, clinical characteristics and microbiological typing, and present preliminary vaccination uptake for the adolescent campaign.

### Materials and Methods

All microbiological laboratories in the Netherlands submit *Neisseria meningitidis* isolated from blood or cerebrospinal fluid to the Netherlands Reference Laboratory for Bacterial Meningitis for serogrouping, fine typing and whole genome sequencing. Cluster analysis using *N. meningitidis* core genome v1.0 application was performed through the PubMLST Genome Comparator tool at <https://pubmlst.org/neisseria/>. Demographic and clinical data from IMD patients were obtained from the mandatory notifications. Vaccination uptake data were obtained from the national vaccination register.

### Results

The incidence of IMD-W increased from 0.02/100,000 during 2005-2014 (~4 cases/year) to 0.6/100,000 in 2018 (103 cases). From January 2015 to December 2018, 242 cases have been reported. IMD-W incidence was highest in children <2 years of age (1.3/100,000; n=18), 14-18 year olds (0.8/100,000; n=32) and 80+ year olds (1.2/100,000; n=36). The majority of cases was female (65%) and had no underlying condition (75%). Cases were diagnosed with septicaemia (51%), meningitis (19%), septicaemia and meningitis (6%), pneumonia (14%), or septic arthritis (7%). The case fatality rate was 17% (39/233) and was highest in 14-18 year olds (28%; 9/32). There were no epidemiologically related cases. Almost all IMD-W strains had finetype P1.5,2:F1-1 (209/239; 87%). Of 219 isolates analysed by whole genome sequencing, 205 (94%) belonged to clonal complex 11 (cc11). Virtually all cc11 isolates (198/205; 97%) belonged to the UK 2013 sublineage. The isolates tended to cluster by year, but no geographic clusters were found. As of mid-January 2019, the vaccination uptake among 14-year-olds was 84% (110,395/132,015).

### Conclusion

In the Netherlands, a rapid increase of IMD-W disease caused by meningococci belonging to the cc11 UK 2013 sublineage has been observed since 2015, which was associated with a high case fatality rate and relatively high occurrence of atypical disease manifestations. A vaccination campaign has been started among adolescents to give direct protection to this age group, but also to prevent meningococcal transmission and thereby indirectly protecting other age groups.

## OC - (EMGM2019-13175) - LIFETIME COSTS OF INVASIVE MENINGOCOCCAL DISEASE: A MARKOV MODEL APPROACH

Bing Wang (Australia)<sup>1</sup>; Hossein Afzali (Australia)<sup>1</sup>; Lynne Giles (Australia)<sup>1</sup>; Helen Marshall (Australia)<sup>1</sup>

<sup>1</sup> - University of Adelaide

### Introduction & Aims

Invasive meningococcal disease (IMD) is an uncommon but life-threatening infectious disease associated with high sequelae rates in young children and an increased risk of mortality in adolescents and young adults. Funding decisions to reject inclusion of new meningococcal serogroup B vaccines on national immunisation schedules have been criticised by IMD patients, their families, paediatricians and charity organisations. We aim to estimate the lifetime costs of IMD with the best available evidence to inform cost-effectiveness analyses.

### Materials and Methods

A Markov model was developed taking healthcare system and societal perspectives. A range of data including age-specific mortality rates, and probabilities of IMD-related sequelae were derived from a systematic review and meta-analysis. All currencies were inflated to year 2017 prices by using consumer price indexes in local countries and converted to US dollars by applying purchasing power parities conversion rates.

### Results

The estimated lifetime societal cost is US\$319,896.74 per IMD case including the direct healthcare cost of US\$65,035.49. Using a discount rate of 5%, the costs are US\$54,278.51 and US\$13,968.40 respectively. Chronic renal failure and limb amputation result in the highest direct healthcare costs per patient. Patients aged <5 years incur the higher healthcare expenditure compared with other age groups. The costing results are sensitive to the discount rate, disease incidence, acute admission costs, and sequelae rates and costs of brain injuries and epilepsy.

### Conclusion

IMD can result in substantial costs to the healthcare system and society. Understanding the costs of care can assist decision-making bodies in evaluating cost-effectiveness of new vaccine programs.

### References

## OC - (EMGM2019-13183) - GLOBAL MENINGOCOCCAL INITIATIVE 2018: CURRENT SITUATION OF MENINGOCOCCAL DISEASE AND FURTHER RECOMMENDATIONS/STRATEGIES

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### Introduction & Aims

The Global Meningococcal Initiative (GMI) was established in 2009 with a goal to prevent invasive meningococcal disease (IMD) worldwide through education, research, and cooperation. After 10 global/regional roundtable meetings, a global GMI Meeting was held in Zurich-Switzerland, 19-21 March 2018.

### Materials and Methods

The main objectives of this symposium are to provide an update on meningococcal surveillance, epidemiology, prevention, and control strategies from a global perspective; to share lessons learned from immunisation programmes; to highlight the importance of conjugate vaccines; to discuss the emergence of antibiotic resistance; to discuss the potential risk of IMD in high-risk groups, and recommendations for immunisation.

### Results

Meningococcal surveillance and control strategies vary between the countries. Global incidence of IMD ranged between 0.01-3.6/100 000 persons. The predominating serogroups globally were B/C, while A predominates in Russia, India, and Angola; W/B in Turkey, and W/Y in Japan and Mozambique. The emergence and spread of serogroup ST-11 complex (cc11) W and C was evident worldwide. The W isolates in South Africa likely originated from the Hajj strain which likely originated in sub-Saharan Africa. The European W cc11 isolates likely originated from South America. New-hypervirulent UK strain has since been found in France, The Netherlands, and Sweden. Clonal complex 11 continues to cause outbreaks of IMD with high case fatality rates and atypical presentations, e.g. gastrointestinal findings. The spread of serogroups X and C within Africa was extensive due to cross-border transmission, but the risk of transmission to other continents seems low. *Neisseria meningitidis* was still susceptible to the antibiotics that were currently used; however, reduced susceptibility to penicillin was increasing. In China, the susceptible rates of meningococci to nalidixic acid, sulfamethoxazole and ciprofloxacin were 21.2%, 5.5% and 27.5%, respectively. Global antibiotic resistance surveillance was therefore warranted. High risk of IMD has been defined in patients with asplenia, complement deficiencies including eculizumab, HIV, MSM and laboratory workers; routine immunisation has been recommended for these groups. IMD outbreaks have also been observed during mass gathering events such as the World Scout Jamboree (Japan-2015) and the Norwegian Russefeiring (2017). Whilst immunisation is recommended for Hajj and Umrah mass gatherings; in future, recommendations for other mass gatherings, such as sports events (e.g. Olympics), music festivals, high-profile funerals and military camps is required.

### Conclusion

In 2018, IMD remains an important public health problem, surveillance and case definitions should be globally harmonised, and further immunisation strategies are needed at the country-level and for newly-defined risk groups.



