Meningitis and Septicaemia 2019

Poster Abstract Book

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Meningitis and Septicaemia 2019 – Poster abstract book

Prevention and epidemic control

#P1 Application of whole genome sequence analysis tools to analyse meningococcal vaccine antigens in routine public health microbiology in Scotland

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Keywords: Meningococcal disease, outbreaks, public health, vaccination, whole genome sequencing

Background: Invasive meningococcal disease (IMD) occurs due to infection with *Neisseria meningitidis*, predominantly affecting young children. Public health management of IMD cases, clusters/outbreaks requires rapid meningococcal characterisation to advise prophylactic measures for contacts, including vaccination. Since 2013, vaccines were available against serogroups A, B, C, W, and Y meningococci through direct protection, with some polysaccharide vaccines inducing herd immunity. Assessing the bacterial coverage of protein-based vaccines, targeting serogroup B, is problematic due to surface protein variation amongst circulating meningococcal strains. Therefore, serogroup B cluster/outbreak strains were typed using PCR methods to determine vaccine antigenic variants.

Aim: To introduce novel genomic tools, in real-time analysis of meningococcal whole genome sequences (WGS) to inform public health decisions in Scotland.

Methods: In Scotland, all culture-confirmed meningococcal cases from April 2018 onwards were sequenced using standard protocols, and raw reads assembled and uploaded onto PubMLST.org/neisseria. Genomic typing tools were previously established for analysis of protein sequence variation of the key antigens in protein-based vaccines, 4CMenB (Bexsero®) and rLP2086 (Trumenba®). The Bexsero® Antigen Sequence Typing (BAST) scheme, available on PubMLST.org/neisseria, combines the antigenic variants of factor H binding protein (fHbp), Neisserial heparin binding protein (NHBA), Neisseria adhesion A (NadA), and Porin A (porA). The BAST scheme was adapted into vaccine coverage algorithms for use at NHS Health Protection Scotland, for real-time analysis of meningococcal WGS. These algorithms were incorporated into existing public health microbiology platforms.

Results: From Autumn 2018, meningococcal genomes could be analysed by frontline public health microbiologists, providing information regarding which antigenic variants of fHbp, NHBA, NadA and PorA were present in a given isolate. The potential genomic coverage estimates for both Bexsero® and Trumenba® were determined using published data on putative cross-reactivity of antigenic variants. The outputs were communicated through a traffic light system providing each isolate the tag of green (exact vaccine antigen matches), amber (putative cross-reactive vaccine antigen matches), red (no vaccine antigen matches).

Discussion: Public health microbiologists rely on clinical, epidemiological, and microbiological data to make informed decisions regarding disease prevention. As the availability of WGS increases and platforms for analysing these improve, this information must be accessible and understandable to non-bioinformaticians. This study demonstrates the adaptation of genomic analysis tools to function in a clinical public health microbiology

setting and will be used to provide additional guidance on suitability of protein-based vaccines that may be effective for use in contacts of cases in meningococcal clusters/outbreaks.

Funding source: Wellcome Trust

#P2 A New Strategy is Needed to Prevent Pneumococcal Meningitis

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Keywords: *Streptococcus pneumoniae*, pneumococcal meningitis, serotype replacement, conjugate vaccine, colonization

Objectives: Evaluation of the inability of polysaccharide-conjugate vaccines (PCVs) to adequately protect against total pneumococcal meningitis.

Methods: Review of the literature

Results: PCVs target the pneumococcal capsular types in the US and Europe that were the most common causes of fatal pneumonia and sepsis. As these types were eliminated by the vaccines, it became apparent that in immunized populations, most invasive diseases caused by pneumococci, including bacteraemia, sepsis, and complicated pneumonia, were greatly reduced. However, the protective effects of PCVs against another invasive disease, meningitis, showed much less, or no decrease in disease incidence. Even in the presence of the PCVs, meningitis rates in children have been reported globally to be as high as 13 per 100,000 annually. The PCV type strains, which had been largely eliminated from carriage, were replaced by a broad diversity of new capsular types that generally failed to cause sepsis but were able to cause meningitis at levels similar to, or in excess of, prior pneumococcal meningitis rates. We suspect that this occurred because of a direct transmission of the non-PCV strains from the nasopharynx to the brain through non-hematogenous routes.

Conclusions: Since virtually all cases of pneumococcal meningitis lead to either permanent neurological sequelae or death, it would be well worth the effort to develop a new vaccine capable of preventing pneumococcal meningitis. Such a vaccine would need to protect against colonization with most, if not all, types of pneumococci.

Funding source: National Institutes of Health, USA

#P3 Group B Streptococcal colonization dynamics and serotype distribution in Japanese mother-infant pairs

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Background: In Japan, universal screening for group B streptococcal (GBS) colonization in pregnant woman and intrapartum antibiotic prophylaxis (IAP) have been recommended to prevent neonatal GBS infection. The object of this study was to describe GBS colonization dynamics and serotype distribution in Japanese mother-infant pairs under universal screening.

Methods: We conducted a prospective cohort study during the period of July 2018 to March 2019 in Japan. Rectovaginal swabs were taken from 251 pregnant women between 33 0/7 and 37 6/7 weeks of gestation. Nasopharyngeal and rectal swabs were taken from 251 infants at birth, 1 week of life and 1 month of life. All specimens were subjected to GBS identification using our in-house real-time polymerase chain reaction (PCR) method as well as bacterial culture. GBS-positive isolates subsequently underwent capsular typing and multilocus sequence typing.

Results: The overall maternal GBS colonization rate was 22.7% (57/251). 55 colonized mothers (96.5%) were given IAP. 34 of 55 women colonized (61.8%) were given IAP initiated 4 hours or more before birth. The overall infant GBS colonization rate was 8.8% (22/252). 11 of 57 infants born to colonized mothers were colonized. These 11 mothers were exposed IAP before delivery. In single analysis, maternal age, maternal GBS colonization, maternal fever at delivery and maternal intrapartum antibiotics administration were found to be significantly associated with infants GBS colonization. The number of colonized infants at birth, 1 week of life, and 1 month of life is 6, 6, and 13 infants, respectively. Capsular types Ib (22.8%), III (19.3%), V (17.5%%), and Ia (15.8%) were predominant among the isolates from pregnant women. On the other hand, V (27.3%), Ib (22.7%) and III (18.2%) were predominant among the isolates from infants. Capsular typing analysis (available for 10 of 11 pairs) confirmed the same serotypes in all mother-baby pairs. Moreover, multilocus sequence typing analysis (available for 4 of 11 pairs) confirmed the same sequence types. No infants developed invasive GBS disease during the period of this study.

Conclusion and future work: Even if GBS-positive mothers receive IAP, the risk of GBS carriage among their neonates is likely to be high. We will measure antibody concentration distribution among these mothers and infants

Funding source: N/A

#P5 MenACWY vaccine impact in Scotland

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Keywords: Meningococci, surveillance, vaccination, ACWY

Background: MenACWY vaccine was recommended by the UK Joint Committee on Vaccination and Immunisation (JCVI) for 14 to 18 year olds as a measure to address an increasing number of meningococcal serogroup W cases in this age group. A phased catch-up programme ran in Scotland between August 2015 and March 2016. MenACWY vaccine continues to be offered routinely to those in secondary school year 3 (S3; age 13-14 years).

Study objective: To evaluate the impact of MenACWY vaccine through routine surveillance.

Results: The impact of MenACWY vaccine in the target population is striking. Since the beginning of 2018, there have been no cases of MenW disease in the age group at greatest risk of disease (age 15-24 years). It was in this target age group that disease declined first following the introduction of vaccination, despite contemporary increases in the < 5 and > 25 year age groups. Disease in these age groups also declined markedly from 2016 onwards. Rates in the 5-14 year age group remained low throughout.

Conclusion: Rapid declines in disease in the target age group, followed by other population groups potentially point toward a population protection effect. This is plausible since the large scale immunisation programme was offered across Scotland to the age groups with highest carriage rates over a relatively short period of time (8 months).

Funding source: NHS Scotland

#P6 Epidemiology of invasive meningococcal disease and vaccination strategy in the Czech Republic

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Keywords: invasive meningococcal disease; epidemiology; vaccination strategy; Czech Republic;

Background: Invasive meningococcaůl disease (IMD) has a decreasing trend in the Czech Republic in the last years. However, it still has a high case fatality rate. For this reason, the recommendation for the optimal vaccination strategy is required.

Methods: IMD is a notifiable disease in the Czech Republic and the incidence data have been available since 1943. Active surveillance of IMD was introduced in the Czech Republic in 1993, when a hypervirulent meningococcal clone (cc11) emerged and caused increased incidence and case fatality rate in the country. The IMD case definition used matches the 2012 ECDC case definition, i.e. confirmation of *Neisseria meningitidis* from normally sterile site. Laboratory confirmation of cases is based on culture and PCR. Notification is compulsory and *N. meningitidis* isolates from IMD cases are referred to the National Reference Laboratory for Meningococcal Infections (NRL) to be characterized by serogrouping and molecular methods.

Results: The overall incidence of IMD ranged between 0.4 and 2.2/100 000 in the period 1993-2018 and has a decreasing trend since 2003. IMD showes the highest incidence in infants under one year of age, ranging from 5.4 to 38.7/100 000. The overall case fatality rate (CFR) ranged between 4.7 and 16.4 %, and the highest figures were found in infants. Serogroup B was mostly prevalent over the whole period of surveillance, with the exclusion of the years 1994-1998, when serogroup C (cc11) prevailed. In comparison to previous years, there was a decline in cases caused by *N. meningitidis* B since 2016 while the proportion of cases caused by *N. meningitidis* C increased. Serogroups Y and W increased in recent years.

Recommendation for vaccination against invasive meningococcal disease is updated regularly according to the actual epidemiological situation of invasive meningococcal disease in the country and availability of a new meningococcal vaccines. The last update was made in January 2018: http://www.szu.cz/uploads/IMO/Recommendation_for_vaccination_IMD.pdf Meningococcal vaccines are recommended but not included in the NIP. Combination of conjugate tetravalent vaccine and MenB vaccine is recommended. Some insurance companies reimburse vaccination. Vaccination is free of charge for patients with underlying diseases since January 2018.

Conclusions: As the incidence of IMD in the Czech Republic is low, there is no indication for the implementation of mass vaccination. However, the need for individual protection of persons at increased risk of IMD is emphasised. The combination of the conjugate tetravaccine A, C, W, Y and vaccine MenB is recommended.

Funding source: N/A

#P7 An audit of the public health management of meningococcal disease in the South West, May 2016 – April 2017

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Keywords: Meningococcal disease, notifications, audit, chemoprophylaxis, vaccinations, health care systems

Aim: This audit examined the public health management of meningococcal disease in the South West over a period of 12 months to identify areas for improvements across the wider healthcare system.

Background: National guidance outlines the key role of public health following the notification of suspected cases of meningococcal disease.

Method: The audit criteria and standards were developed using national guidance and the Centre's local Standard Operating Procedure. A total of 161 cases of possible, probable and confirmed meningococcal disease notified to the South West PHE centre between 1st May 2016 and 31st April 2017 were included. An electronic data collection tool was used, and the data analysed using Excel.

Results: Sample demographics and disease epidemiology were consistent with the national picture. Early notification, i.e. within 24 hours, occurred in 61% of cases. 10% of cases were notified more than 3 days late, up to 10 days in a few cases. The audit identified specific hospitals where delayed notification was a concern. Actions relating to laboratory investigation of cases were well completed. Chemoprophylaxis was arranged for contacts within 24 hours in 89% of cases along with information on signs and symptoms. The audit also identified a number of contacts who had not received vaccinations where indicated, and these were followed up. Incomplete documentation of HPZone records was also identified as a concern, particularly with regards to pre-admission antibiotics and vaccination status.

Recommendations: Ten recommendations were proposed which have led to actions across the system. Electronic reminders regarding notification and investigations have been implemented in various trusts. Clinical leads have committed to continuously raising awareness, particularly amongst junior staff, of the responsibility to notify. This together with importance of early notification and investigation, and awareness of unusual presentations has also been raised at a strategic level. Internally, the HPT have implemented changes to improve and standardise documentation.

Funding source: N/A

#P8 Quality evaluation of clinical consistency lots of MenFive, a pentavalent (A, C, W, X, Y) meningococcal serogroup conjugate vaccine

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Keywords: MenAfriVac, Meningitis, polysaccharide, quality, vaccine

Introduction: Following success with MenAfriVac in protecting sub-Saharan populations from invasive group A- meningococcal disease, a multivalent vaccine was developed to protect against four additional circulating meningococcal serogroups, where protection was feasible by a glycoconjugate approach. Three consistency batches of the pentavalent Meningococcal groups A, C, W, X and Y conjugate vaccine, MenFive, were manufactured by the Serum Institute of India Private Limited (SIIPL) for phase III clinical trials in West Africa and India. In addition to performing lot release testing at SIIPL, further independent evaluation was performed at the National Institute for Biological Standards and Control, U.K.

Methods: Analytical and ELISA-based methods were performed on purified polysaccharides (PS), conjugate bulk components as well as final product to confirm the structural and serological identity, safety by endotoxin content along with tests such as sterility, pyrogen content, size, integrity, purity and polysaccharide content, according to WHO Recommendations.

Results: All lots of purified polysaccharides, carrier proteins (TT and $rCRM_{197}$), bulk conjugate, and freeze-dried single-dose and multi-dose fills with saline diluent, conformed to designated specifications. Polysaccharide O-acetylation levels were on average, 85 % in group A, 72 % in group C; 35 % in group Y; and, 45 % in group W lots, thus meeting WHO guidelines. The size of the PSs ranged Y > X > C > W > A, based on elution volume. Endotoxin (LAL) levels determined on the PS by kinetic turbidometric and gelation clot methods were < 10 IU/μg for groups C and Y; and < 45 IU/μg for groups A, W and X. A sensitive measure of consistency, the sizing profiles of individual lots of the conjugated TT (to groups A and X) and rCRM197 (to groups C, Y and W) were generally superimposable, and free of measurable contaminants in 280 nm and RI traces. Size distributions were as expected for TT conjugates and $rCRM_{197}$ conjugates. Non-conjugated polysaccharide determined following separation by deoxycholate precipitation of the conjugated saccharide was < 30% for all groups and did not rise significantly during freeze-drying. The target dose of 5 □g/dose of each polysaccharide was confirmed by HPAEC-PAD using WHO International Standards.

Conclusion: The quality evaluation of this pentavalent vaccine developed by PATH and SIIPL has concluded. With the successful completion of ongoing clinical and stability evaluation, the vaccine is expected to progress to licensure and WHO Pre-qualification in 2021 for use on the African continent to eliminate disease caused by five serogroups of meningococcus.

Funding source: U.K. Department for International Development

#P9 Uptake of the MenACWY vaccine and vaccination views among first-year students at a London university

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Keywords: MenACWY, vaccination, university, vaccination views, meningitis

Background New university students are at particular risk of invasive meningococcal disease (IMD). Group W, a particularly aggressive strain, is increasing in prevalence and the high case-fatality rate is concerning. This age group has been offered the MenACWY vaccine since 2015. National uptake has been low, leaving students vulnerable to infection.

Aims To investigate MenACWY uptake, knowledge of and attitudes towards vaccination among first-year students, with the aim of informing university vaccination policy and practice.

Methods A mixed methods approach was used, involving a questionnaire (response rate = 4.4%, *n* = 144) and follow-up interviews (*n* = 13). Eligibility criteria were first year students, undergraduates and over the age of 18. Statistical tests, including multiple logistic regression, were carried out and interviews were analysed thematically.

Results: MenACWY uptake was 84%, higher than at other universities in previous studies, with more socioeconomically disadvantaged students less likely to be vaccinated (aOR = 0.117, *p* = 0.006). International students had equal uptake to UK-based students (95% CI = -12.2% to 19.5%). Most students thought vaccines were safe (95.1%) and important (97.2%). Students with above average knowledge were more likely to be vaccinated (OR = 3.057, *p* = 0.019). Students unaware that meningitis can be fatal were less likely to be vaccinated (aOR = 0.173, *p* = 0.035). Vaccination views were positive and knowledge level was moderate to high. Reasons for vaccination include influence of authority figures and peers, to avoid disease and due to an inherent trust of vaccines. Reasons for non-vaccination included temporary illness, laziness, forgetfulness and difficulty with GP access. Opinions regarding the university's vaccination campaign were positive, and in particular there was praise for the university's awareness campaign. Issues raised by this study include difficulty in accessing GP services and the belief that the vaccine prevents any cause of meningitis.

Conclusion: High vaccine uptake is essential to protect students. Uptake was higher than at other universities in previous studies, suggesting the university's vaccination campaign was successful, in particular its targeting of international students. These results highlight several areas requiring further study, including the association between uptake and socioeconomic group and understanding of post-vaccination risk of meningitis. This research has implications for vaccination policy at UK universities.

Funding source: UCL Great Ormond Street Institute of Child Health

#P10 Impact of meningococcal vaccination timing on Neisseria meningitidis carriage: A cross-sectional study of pilgrims traveling to Mecca, Saudi Arabia

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Keywords: Antibiotic, Hajj, meningococcal, pharyngeal carriage, vaccination

Background: Hajj, the spiritual journey that Muslims undertake to Mecca in Saudi Arabia is one of the largest annual events to occur globally. Pilgrims from different ethnicities, age groups and socioeconomic status were reported to have come from more than 183 nations worldwide in previous Hajj seasons. Overcrowding during the Hajj has, in the past, facilitated the spread of meningococcal disease, and there have been several meningococcal outbreaks during Hajj pilgrimage. Consequently, the Saudi authorities made it obligatory for all Hajj pilgrims to receive the quadrivalent meningococcal vaccine at least 10 days before the Hajj in order to obtain a visa and for all pilgrims coming from Africa's meningitis belt to receive ciprofloxacin tablets (500 mg) as a chemoprophylaxis on arrival in Saudi Arabia.

Method: A cross-sectional study was conducted among 2,973 Hajj pilgrims in 2017 to investigate the association between time of meningococcal vaccination and carriage of *N. meningitidis* pathogenic serogroups A, C, W, and Y. Pilgrims were selected by using two-stage sampling method. First stage was done by selecting flights from the daily Hajj flight schedule and second stage by selecting pilgrims from each selected flight. Oropharyngeal swabs were collected from pilgrims and were inserted into a transport medium containing skimmed milk, tryptone, glucose and glycerin (STGG). An electronic data collection tool, 'Open Data Kit' (ODK) was used to collect survey data from pilgrims. Real-time polymerase chain reaction (rt-PCR) for diagnosing *Neisseria meningitidis* and PCR-based assays for the identification of serogroups were used to identify *Neisseria meningitidis* from the oropharyngeal swabs.

Results: Overall *N. meningitidis* carriage prevalence was 4.6%. Meningococcal carriage of pathogenic serogroups A, C, W, and Y was not significantly associated with time of meningococcal vaccination. More than half of the pilgrims (55.8%) reported taking antibiotics during and after the Hajj. A majority of pilgrims (77 %) were vaccinated with the meningococcal quadrivalent vaccine, however 22.58 % said they were not vaccinated.

Conclusion: Excessive use of antibiotic during the Hajj and the issue of unauthorised vaccination cards by Hajj pilgrims highlights an urgent need to re-assess the current Hajj policy to prevent meningitis outbreaks.

Funding source: Royal Embassy of Saudi Arabia Cultural Bureau in London, United Kingdom.

#P11 Molecular basis for the interaction between Haemophilus influenzae type b capsular polysaccharide and a protective monoclonal antibody

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Keywords: Hib, Glycoconjugate, minimal epitope, STD-NMR, SPR

Haemophilus influenzae infections are a major cause of bacterial respiratory tract morbidity and can lead to severe diseases such as pneumonia, sepsis, and meningitis.[1] *H. Influenzae* type b (Hib) is coated with a capsular polysaccharide (CPS) made up of polyribosyl-ribitol-phosphate (PRP) repeating units (RUs) that has been conjugated to carrier proteins for efficacious vaccination.[2] Mapping of epitopes recognized by protective antibodies is crucial for understanding the mechanism of action of vaccines and for enabling antigen design. It has been demonstrated that an octasaccharide antigen (containing 4 RU) resembles PRP polysaccharide in terms of immunogenicity and recognition by anti-Hib antibodies.[2] Identifying the minimal epitope directly involved in the antibody binding can facilitate vaccine design. For this purpose short Hib oligosaccharide (OS) fragments (2 to 5 RU), obtained from acid hydrolysis of natural polysaccharide,[3] were used to characterize the interaction with the human protective anti-Hib monoclonal antibody (hmAb)[4] by STD-NMR (Saturation Transfer Difference NMR). A Fab fragment from the hmAb digestion was obtained and its interaction with the Hib OS fragments were characterized by SPR (Surface Plasmon Resonance). Attempts to achieve X-ray crystallography of the Fab complex with Hib OS are underway.

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Funding source: This work was funded by GlaxoSmithKline Biologicals SA

#P12: 4CMenB, a multicomponent meningococcal vaccine developed for serogroup B meningococci elicits cross-reactive immunity against serogroups C, W and Y

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Keywords: 4CMenB, meningococcal vaccine, non-serogroup B strains, cross-protection, vaccine coverage

Background: 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.

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 antigenic sequence typing (ST). 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 clonal ST-22 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 ≥4 to ≥128.

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

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

Funding source: GlaxoSmithKline Biologicals SA

#P13 Performance of licensed meningococcal vaccines against hypervirulent MenC strains: An interesting post-hoc analysis

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Keywords: hypervirulent MenC strains, cc11 and cc334 clonal complexes, outbreak, MenACWY-CRM conjugate vaccine, MenC-CRM conjugate vaccine

Background and aim: This *post-hoc* analysis was triggered by evidence of an increase in invasive meningococcal disease incidence in Tuscany in 2015/16, with the most common bacterial isolates being hypervirulent strains belonging to clonal complexes cc11 and cc334. The goal of this analysis was to assess, in sera from children primed with MenACWY-CRM or MenC-CRM conjugate vaccines and who received a MenACWY-CRM booster dose, antibody responses against 5 meningococcal C (MenC) hypevirulent field strains (FI001 to 005).

Methods: Sera collected from 90 children who participated in a phase III, open-label, multicentre study (NCT00667602) and its extension (NCT01345721) were analysed for antibody responses. Children were primed in the initial study with either 2 MenACWY-CRM doses at 6–8 and 12 months of age (MOA) (group MenACWY_2doses, N=30), 1 MenACWY-CRM dose at 12 MOA (group MenACWY_1dose, N=30), or 1 MenC-CRM dose at 12 MOA (group MenC_1dose, N=30). All primed children received a MenACWY-CRM booster dose at 22–45 MOA in the extension study. Sera from these children were tested using a serum bactericidal activity assay with human complement (hSBA). Seroresponse rates (1 month post-primary vaccination; hSBA titre ≥8 if pre-vaccination titre <4 or a ≥4-fold increase in titre if pre-vaccination titre ≥4), geometric mean titres (GMTs), and percentages of children with hSBA titres ≥4 and ≥8 (pre-vaccination, 1 month post-primary and post-booster vaccination) were calculated.

Results: Of the tested strains, 4 (FI001 to FI004) were C:P1.5-1,10-8:F3-6:ST-11(cc11) and 1 (FI005) was C:P1.7-4,14-3:F3-9:ST-1031(cc334). Seroresponse rates tended to be higher in the MenC_1dose (range: 33.3% [FI005]–93.3% [FI004]) than in the MenACWY_1dose group (range: 16.7% [FI005]–73.3% [FI004]). This was expected since MenC-CRM contains twice as much MenC antigen (10 µg) per dose as MenACWY-CRM and is also adjuvanted with aluminium hydroxide. GMTs were high in the MenACWY_2doses group (range: 94.8 [FI005]–588.1 [FI004]) and very high after a MenACWY-CRM booster dose in all groups (range: 176.9 [FI005]–3911.0 [FI004]). Irrespectively of the strain tested or the identity and number of doses of priming vaccine, hSBA titres ≥4 and ≥8 were detected in almost all sera (≥96.7%) following MenACWY-CRM booster dose. Overall, there was a tendency for higher immune responses against FI002, FI003 and FI004 than against FI001 and FI005.

Conclusions: This *post-hoc* analysis shows that both MenACWY-CRM and MenC-CRM conjugate vaccines are able to elicit immune responses and immunological memory against hypervirulent cc11 and cc334 MenC strains responsible for outbreaks of invasive meningococcal disease.

Funding source: GlaxoSmithKline Biologicals SA

#P14 Evaluating the use of digital methods to distribute public health information

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Keywords: Meningococcal infection; Health messaging; Educational setting; Digital communication; Public health

Aim/Objective: To evaluate the acceptability of using digital communication methods to distribute health information in response to single cases of invasive meningococcal disease [IMD] associated with educational settings.

Methods: A digital communications toolkit was created, containing template text for short, medium and long health messages to be distributed by educational settings. The short message was less than 280 characters, suitable for use in text and social media messages; the medium message was suitable for emails and website statements; and the long message was a single-sided A4 page with graphics.

Upon notification of a case of IMD associated with an educational setting, health protection teams contacted settings and provided our digital communications toolkit, requesting that they distribute the health messages via their usual communication channels. Two weeks later, settings participating in the study were asked to distribute a link to all those who received our digital messages, requesting feedback via an online survey.

Results: The study ran from October 2018 to July 2019. Completed surveys (n=38) were received for 4 educational settings: 3 primary schools and 1 university.

Email was reported as the most acceptable means of receiving health messages (by 89% of respondents), followed by letter and text message (at 78% and 65% respectively). 49% and 46% disagreed with receiving health communications via a WhatsApp message or social media.

58% of respondents said they would prefer to receive health messaging using a combination of digital and paper communications. 36% preferred to receive health messaging solely via digital methods.

Most respondents (95%) agreed that receiving messaging made them feel fully or somewhat informed about the situation. 58% reported the messaging prompted them to check they or their children were up-to-date with their vaccinations against meningococcal disease.

The study also found that universities were less willing to distribute messaging not curated by their own communications teams.

Conclusion: The study demonstrates that digital methods are acceptable to parents of school-age children as a means of receiving health information, with a preference for a combination of digital and paper methods.

Funding source: All funding has been provided at a local centre level by Public Health England

#P15 Safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine (MenACWY-TT) administered as a single dose in a broad age range (12 months and above)

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Keywords: Meningococcal, Neisseria, Vaccine, Meningitis, Trial

Background: 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 ≥ 56 years of age.

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. 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 at Day 30 post vaccination (toddler, children, adolescents, adults and elderly). The percentages of participants with post vaccination hSBA ≥ 1:8 (seroprotection) were higher or comparable to comparator for all serogroups in subjects vaccinated with MenACYW-TT. The percentages of participants with post vaccination rSBA ≥ 1:128 were comparable or higher for all serogroups in subjects vaccinated with MenACYW-TT vs the comparator vaccine. Co-administration of MenACYW-TT with age specific vaccines did not generate evidence suggestive of clinically significant interference. Overall, the safety profiles of MenACYW-TT and standard of care vaccines were comparable across all ages. There were no related serious adverse events among MenACYW-TT recipients. Post-vaccination rates of severe reactions were low for all vaccines.

Conclusions: MenACYW-TT was well tolerated and demonstrated higher or comparable seroprotection rates 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 global option for the prevention of invasive meningococcal disease in a broad age range.

Funding source: Sanofi Pasteur

#P16 Multicomponent meningococcal serogroup B vaccine (4CMenB) may elicit functional immunity against serogroup A strains

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Keywords: 4CMenB meningococcal vaccine; non-serogroup B strains; cross-protection; MenA; vaccine coverage and immunogenicity

Background and aim: 4CMenB vaccine (*Bexsero*, GSK) is currently indicated for immunisation against invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B (MenB). However, genes encoding the 4CMenB vaccine antigens are also present and expressed in strains belonging to other meningococcal serogroups. We have recently demonstrated that sera from infants immunised with 4CMenB were able to kill 109 out of 147 genetically diverse isolates (collected in Europe and Brazil) belonging to meningococcal serogroups C, W and Y. In this study, we investigated the coverage mediated by 4CMenB against meningococcal serogroup A (MenA) strains.

Methods: Sera derived from adolescents vaccinated with 2 doses of 4CMenB (NCT02212457) were tested in serum bactericidal antibody assay using human complement (hSBA) against a panel of strains representative of the current MenA epidemiology. The strain panel was selected based on the frequency of genetic profiles (clonal complex and 4CMenB antigen typing) in a dataset of MenA isolates, collected in different countries between 2000–2016, and available in PubMLST.

Results: Of the 1046 MenA isolates from PubMLST, the genetic profile of the 4CMenB antigens was available for approximately 300 of them. All MenA strains were highly clonal, with 77.0% of the 1046 isolates belonging to the ST-5 complex/subgroup III and 20.8% belonging to the ST-1 complex/subgroup I/II. The isolates of the ST-5 complex/subgroup III carried the genes encoding for factor H-binding protein (fHbp) variant 1.5, *Neisseria* adhesin A (NadA) and porin A (PorA) VR2 10. The isolates belonging to the ST-1 complex/subgroup I/II harboured the genes encoding for fHbp variant 1.4 and PorA VR2 9 but did not harbour the *nadA* gene. 95.6% of the isolates (almost all from the ST-5 complex) for which the Neisserial heparin-binding antigen (*nhbA)* gene was sequenced had alleles encoding for the NHBA peptide 126. Three strains from the ST-5 complex/subgroup III and 1 strain from the ST-1 complex/subgroup I/II were selected for hSBA testing. The percentage of adolescent sera with hSBA titre ≥4 (accepted correlate of protection) against the MenA strains ranged between 58.3% and 91.7%, while 45.8% to 83.3% had hSBA titre ≥8. The percentage of adolescents with ≥4-fold rise in hSBA titres at one month post-dose 2 *versus* baseline ranged between 45.8% and 83.3%.

Conclusions: Sera from adolescents vaccinated with 4CMenB showed hSBA activity against MenA strains. These results further support the evidence that 4CMenB vaccination may have an impact on meningococcal disease caused by serogroups other than MenB.

Funding source: GlaxoSmithKline Biologicals SA

#P17 Kinetic study of Streptococcus pneumoniae invasion and immune responses of the central nervous system in a non-hemotogeneous meningitis model

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Keywords: *Streptococcus pneumoniae***,** Pneumococcal meningitis, Invasion route, Intravital imaging

Further understanding of the invasion mechanism is a necessary step towards the development of novel and more efficient preventive or therapeutic strategies against meningitis. Transport from the nasal cavity to the meninges is a route of invasion that has been underinvestigated in the context of bacterial meningitis. In this project, we have developed and exploited a non-bacteremic meningitis mouse model where Streptococcus pneumoniae (S.p.), a major cause of severe bacterial meningitis, was administered intranasally. Viable counts were determined in the cortical meninges and in the nasopharynx between 0 and 72 hours after nasal instillation. Interestingly, we observed a steady decrease in bacterial density with a pseudo-clearance at 30 minutes post-infection occurring in the cortical meninges but not in the nasopharynx. This was then followed by a re-emergence of viable counts at 10 hours post-infection in both tissues. FACS analysis of tissue adhering to the skull after removal of the brain also showed increase in the expression of the neutrophil marker, Ly6G, peaking at 12 hours post infection. These results were corroborated by Intravital two-photon imaging of LysM+ GFP reporter mice showing increased numbers and speed of LysM + cells. Altogether, the increased number of viable bacteria and the local recruitment of immune cells provide supportive evidence that pneumococci are capable of translocating from the nasal cavity to the cortical meninges resulting in a local inflammatory response.

Funding source: Meningitis now, MRC

#P18 Strains from prevalent pathogenic Group B Streptococcus serotypes show reduced binding of complement factor C3b and greater resistance to opsonic killing

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Keywords: Group B Streptococcus, complement evasion, factor H, opsonophagocytic killing

Objective: Group B Streptococcus (GBS) is a leading cause of neonatal septicaemia worldwide with adverse neurodevelopmental outcomes in many survivors. GBS is a Gram-positive diplococcus that forms part of the microbiota in the lower gastrointestinal and vaginal tract in approximately 30% of women and transmission mainly occurs from mother to infant during the peripartum period. To aid its colonisation and persistence, GBS employs several mechanisms to disrupt and evade host immunity. There are reports that some GBS strains bind complement regulatory protein factor H (FH) via the β and streptococcal histidine triad (SHT) proteins to evade the complement system. These studies have used laboratory GBS strains and a limited number of current clinical isolates. To fully understand the mechanisms of complement evasion, we have investigated antibody-independent binding of complement proteins (C3b and FH) to a panel of 55 recent and historic isolates representing serotypes Ia, Ib, II, III, IV and V; and compared complement binding with survival in the presence of HL60 cells with IgG and IgM-depleted human plasma and genomic data.

Methods & Results: Using flow cytometry, we have assessed surface binding of C3b on GBS isolates in the absence of antibody using IgG and IgM-depleted human plasma. Binding of C3b was observed to be lowest in serotypes Ia, III and V and higher in serotypes Ib, II and IV. In particular, significantly higher levels of C3b binding were observed with serotype II isolates compared to all except for serotype IV. Binding of purified FH was also measured by flow cytometry. Few strains were found to bind FH with no serotype specificity observed. Where FH binding was observed, genomic analysis showed good correlation with presence of the β protein gene. We have also investigated resistance to killing by HL60 cells in the presence of IgG and IgM-depleted human plasma. Resistance to killing varied by serotype, with greatest to least resistance observed in serotypes III, V, Ia, Ib, IV to II.

Conclusions: Serotypes with the least C3b binding are the most prevalent disease serotypes globally and this is also reflected in our survival data where these serotypes are the most resistant to opsonophagocytic killing. Although FH binding was not common among the isolate panel, association with the presence of beta protein suggests it may play a role in complement evasion and would warrant further study.

Funding source: UK Department of Health Grant in Aid funding

#P19 Cryptococcal Meningitis is a Cause of Death Among HIV-Infected Adults Despite Cryptococcal Antigen Screening and Pre-emptive Fluconazole Treatment

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Keywords: Cryptococcal meningitis; Cryptococcus; Acquired Immunodeficiency Syndrome; AIDS-related opportunistic infections; autopsy

Background: Cryptococcal antigen (CrAg) screening and treatment with pre-emptive fluconazole reduces the incidence of clinically-evident cryptococcal meningitis in individuals with advanced HIV-disease. However, mortality remains higher in CrAg-positive than in CrAg-negative patients with similar CD4+ T-lymphocyte counts. Causes of death among CrAg-positive patients are unclear.

Methods: We conducted a cohort study to investigate causes of morbidity and mortality during six-months following routine CrAg screening, among asymptomatic CrAg-positive and CrAg–negative HIV-infected patients with CD4 counts <100 cells/μL (ratio of 1:2), attending two hospitals in Johannesburg, South Africa. CrAg-positive patients were offered lumbar punctures (LPs), and pre-emptive fluconazole (800 mg daily for two weeks, 400 mg for two months, 200 mg pending immune reconstitution and for at least one year) if subclinical cryptococcal meningitis was excluded. Causes of death were attributed by an expert panel using clinical information, interviews with family members, and the results of minimally-invasive autopsies (MIA), when possible.

Results: Sixty-seven CrAg-positive and 134 CrAg-negative patients were enrolled in the study. At baseline 17/67 (25%) asymptomatic CrAg-positive patients were found to have subclinical cryptococcal meningitis (n=11), cryptocccaemia (n=11) or pulmonary cryptococcosis (n=2). Although recommended antifungal (62/67 (93%)) and antiretroviral therapy (53/63 (84%)) was commenced for CrAg-positive patients, ART initiation was delayed for 36 days (compared to 17 days for CrAg-negative patients (p<0.001)).

Death occurred in 17/67 (25%) CrAg-positive and 12/134 (9%) CrAg-negative participants within 6 months (hazard ratio for death adjusted for CD4 count, 3.0, 95% CI 1.4–6.7, p=0.006). Cryptococcal disease was an immediate or contributing cause of death in 12/17 (71%) CrAg-positive participants; 8 had cryptococcal meningitis. Post-mortem cryptococcal meningitis and pulmonary cryptococcosis were identified in all four CrAg-positive participants who had

autopsies, three of whom had negative cerebrospinal fluid CrAg tests from LPs performed at the time of screening.

Blood CrAg titre (>160 vs. ≤160) was predictive of subclinical cryptococcal disease at the time of screening (OR 17.6 (95% CI 4.6-67.7)), and of death within 6 months (HR 3.5, 95% CI 1.4–9.2, p=0.009).

Conclusions: Cryptococcal disease remained an important cause of morbidity and mortality among asymptomatic CrAg-positive patients despite routine LPs to identify and treat those with subclinical cryptococcal meningitis, and pre-emptive treatment with fluconazole. Patients with higher blood CrAg titres were at greater risk of subclinical cryptococcal disease and death. Thorough investigation for cryptococcal disease, prompt initiation of antiretroviral treatment and more intensive antifungal treatment may reduce mortality among asymptomatic CrAg-positive patients identified through screening.

Funding source: Meningitis Research Foundation

#P20 Critical assessment of economic evaluations on protein-based meningococcal vaccines in developed countries

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Keywords: meningococcal vaccine, systematic review, economic evaluation, Serogroup B

Background: Invasive meningococcal disease (IMD) is a rare and severe condition with a high probability of complications, mortality and long-term sequelae. Most IMD cases in developed countries are now caused by serogroup B strains, which has prompted the licensing of two protein-based meningococcal vaccines and implementation of publicly-funded immunization programs using 4CmenB vaccine in a few jurisdictions. Economic evaluations used to inform decisions on these vaccines should be transparent, based on rigorous analytical methods, balanced and impartial.

Objectives: To review published economic evaluations and available reports on protein-based meningococcal vaccines for developed countries to characterize and critically assess these studies with the aim of identifying main factors influencing their results and the conditions under which acceptable cost-effectiveness ratios are generated.

Methods: We conducted a comprehensive search in four journal-indexing databases and grey literature available up to June 2018 to retrieve, select and review only full economic evaluations of a protein-based meningococcal vaccine against IMD-B licensed for use in the general population in high-income countries. Careful analysis of model structure, parameters and vaccine/disease related assumptions was undertaken.

Results: 16 studies were identified, fifteen pertaining to 4CMenB and one to MenB-fHBP, conducted for nine developed countries between 2013 and 2018. Our critical appraisal shows considerable differences in model characteristics, main assumptions and parameters used across assessments. Most evaluations are limited by key methodological constraints, some of which include: using a static model (8/16); limited range of immunization strategies (5/16); lack of consideration of program planning and evaluation costs (1/16); and uncertainty analyses mostly confined to parameter and methodological/normative uncertainty, with only 6/16 studies reporting exploring a few sources of structural/model uncertainty. Overall, ICERs were most sensitive to vaccine price, disease incidence, herd effect and discount rate applied; yet, the relative importance of variables differed across studies. Although structural and parameter differences complicate direct comparisons between studies, it is only under high IMD incidence scenarios or unlikely favorable conditions (e.g., very low vaccine prices), that these programs could produce ICERs below the cost-effectiveness threshold selected.

Conclusions: Since economic analysis can have a considerable impact on immunization policy-making, the data and methodological constraints identified in this review should be addressed in future evaluations. Updated methodological guidelines that account for the particularities of vaccination programs targeting rare and severe diseases could certainly assist health economists/researchers and decision-makers.

Funding source: This study was funded by the Public Health Agency of Canada and the Centre de Recherche Clinique du Centre Hospitalier Universitaire de Sherbrooke.

#P21 Impact of a mass vaccination campaign against Serogroup B meningococcal disease in the Saguenay-Lac-Saint-Jean region of Quebec four years after its launch

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Keywords: Meningococcal B vaccine, effectiveness, outbreak control, herd effect, mass campaign

Background: In the Saguenay-Lac-Saint-Jean region (SLSJ) of Quebec, 83% of the population ≤20 years (n≅59,500) was immunized in 2014 with the four-component Serogroup B meningococcal vaccine (MenB-4C) to control an outbreak caused by a Serogroup B ST-269 *Neisseria meningitidis* (*Nm*) clone.

Objective: To evaluate the impact of the campaign four years after its initiation.

Methods: Analysis of 448 cases of Serogroup B invasive meningococcal disease (B-IMD) reported in Quebec from July 2006 to June 2018. Population denominators were derived from census data and the QLSJ immunization registry. Univariate and multivariate Poisson regression models used to compare rates and assess their predictors.

Results: Following the campaign, 5 B-IMD cases occurred in the SLSJ region, including one vaccinated child, one unvaccinated young adult and 3 unvaccinated elderly adults. B-IMD incidence in the SLSJ population fell from 3.4/100,000 in 2006-2014 to 0.5/100,000 in 2014-2018 (p<0.0001); from 11.4/100,000 to 0.4/100,000 (p<0.0001) in the target age-group and from 1.1/100,000 to 0.5/100,000 (p=0.1) in the older age-group. Estimate of direct vaccine protection was 79% [95%CI:-231%;99%]. Taking into account the decrease in B-IMD incidence at provincial level in 2014-2018, the age-adjusted campaign impact was a 86% [95%CI:-2%;98%; p=0.05] lower B-IMD risk among vaccinees and a 52% [95%CI:-35%;83%; p=0.17] lower risk in the unvaccinated fraction of the SLSJ population.

Conclusions: Results suggest direct protection provided by MenB-4C but no herd effect in the older age-group that could be explained by a low vaccine uptake among targeted individuals 17 to 20 years of age (47%) and a weak effect of MenB-4C on *Nm* carriage. They support current recommendations for MenB-4C use for controlling IMD outbreaks caused by *Nm* clones covered by the vaccine.

Funding source: Ministère de la Santé et des Services sociaux du Québec

#P22 GBS6: A Vaccine Designed to Prevent Group B Streptococcal Disease in Infants

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Keywords: **GBS, vaccines, maternal immunization, prevention**

Group B streptococcus (GBS; *Streptococcus agalactiae*) is an important cause of invasive disease in young infants. Early studies have demonstrated a correlation between low GBS specific IgG antibody levels in mothers and susceptibility to GBS disease in infants. There are 10 capsular polysaccharide serotypes of GBS. We conducted an extensive global surveillance study to confirm the appropriate vaccine serotype composition which resulted in the design of a six-valent capsular polysaccharide conjugate vaccine (GBS6) which covers the majority of infant GBS disease. GBS6 is being developed for immunization of pregnant women to protect their infants against invasive GBS disease via placental transfer of vaccine induced antibodies.

Prior to initiating clinical studies, preclinical animal trials demonstrated that GBS6 was well tolerated without evidence of systemic toxicity and resulted in a strong functional antibody response to each of the 6 serotypes in the formulations. GBS6 formulations with 5 µg, 10 µg, or 20 µg with and without aluminum phosphate were then tested in a Phase 1/2 randomized clinical dose escalation trial in non-pregnant adults. The vaccine was well-tolerated with a safety profile consisting primarily of mild-moderate pain at the injection site. GBS6 IgG geometric mean concentrations (GMCs) increased rapidly at 1-week post vaccination and peaked by 2-week for all 6 dose/formulations evaluated. IgG GMCs remained elevated through 6 months. There were no apparent differences observed by dose/formulation. Based on the safety and tolerability data observed, a Phase 1/2 study in nonpregnant and pregnant women in South Africa was initiated in January 2019.

Data from pregnant women in our ongoing Phase 1/2 clinical trial will provide the opportunity to confirm that GBS6 elicits a robust immune response beyond what is observed from natural exposure and that those antibodies are transferred to infants of vaccinated mothers. These data will inform ongoing work to identify a protective antibody threshold in pregnant women and infants against GBS disease.

Funding source: Pfizer, Inc

#P23 Can Current Health Economic Modelling Approach Capture Unpredictability of Invasive Meningococcal Disease?

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Keywords: Health Economic model, Meningococcal, Unpredictability, Literature review, Vaccination

Background Invasive meningococcal disease (IMD) is predominantly caused by five serogroups: A, B, C, W and Y. Although overall incidence of IMD is low, incidence of the different serogroups can be erratic and unpredictable. Even with appropriate treatment, IMD still causes substantial mortality and morbidity. In order to introduce new vaccines into national immunization programs, many countries have instituted health technology assessments requiring a cost-effectiveness analysis (CEA). The health economic model used in these evaluations typically requires an assumption of endemic disease epidemiology, which has thus far been incompatible with variable and unpredictable IMD. Our objective is to review and assess disease incidence inputs to meningococcal vaccine CEAs and their influence on predicting meningococcal vaccine impact.

Methods: A targeted literature review of published meningococcal vaccine CEAs (serogroup B, C or ACWY combined) was conducted. Data on inputs of disease incidence and modelling methodology were extracted from selected articles, specifically considering stochasticity of epidemiology inputs.

Results: 25 articles or conference presentations were reviewed. Of these, 4 CEAs evaluated MenC, 10 for MenB, and 11 for MenACWY. Nineteen publications considered average incidence rates observed over 1 to 13 years (median =5 years) prior to the publication time as model inputs, and 5 parameterized disease incidence rates either based on experts' opinions or assuming probabilities of endemic episodes following a fixed pattern. Twenty-four models conducted sensitivity analyses and indicated that model results were highly influenced by incidence assumptions. Despite the incidence input used, all analyses predicted implementation of a vaccination program could reduce disease caused by the serogroup(s) targeted by the vaccine. However, model predictions were under the condition that baseline incidence rates over the model time horizon would not change and probabilities of changes in disease-causing serogroups (e.g., recent emerging cases caused by serogroup W) or natural fluctuations in disease incidence were not taken into consideration.

Conclusion: IMD is unpredictable and life threatening. Current modelling approaches to assess vaccination strategies against one or more serogroups may follow good modelling practice, no CEAs have yet determined a methodology sufficient to capture the value of preventing a rare but unpredictable disease. More research is needed to understand how to capture variable disease incidence considering emergent clones of IMD.

Funding source: Pfizer Inc.

#P24 Stoichiometric modelling of MenC-TT conjugates

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Keywords: MenC-TT, SEC-MALS, conjugate, hydrodynamic radius, viscometry

A panel of meningococcal serogroup C (MenC) glycoconjugate vaccines were made differing in chain length, molar mass and hydrodynamic volume. The MenC-tetanus toxoid (TT) conjugate vaccines had their molecular properties examined using size exclusion chromatography with inline multi angle light scattering and viscometry detectors (SEC/MALS/Viscometry). Different measurements of radius obtained from light scattering and viscosity detectors were compared with molecular mass (Mw) for the MenC-TT conjugates. An exponential relationship between Mw and hydrodynamic radius (Rh) was observed. By contrast, the relationship between Mw and RMS radius moments (Rn) was linear. When the relationship between Rh and Rn was explored two of the smaller conjugates had similar Rh and Rn values, suggesting a spherical morphology, whereas the larger conjugates had a much larger average radius (Rn) relative to Rh, suggesting a less symmetrical, and more ellipsoidal configuration.

Further mathematical modelling, using measured physical data obtained from SEC-MALS, functional weights and concentration determinations, was performed by allowing possible configurations to include true monomer (1 PS plus 1 protein), true dimers (2 + 2), and higher oligomers, or other stoichiometries. Molar mass values for the PS chains and conjugates, and PS loading ratios were used to explore models with varying stoichiometry. Data for the largest MenC-TT conjugate (2,348,000 g/mol) fitted well to a model consisting of 3 PS and 5 TTs, while the smaller MenC-TT conjugate (191,500 g/mol) fitted best to a model of 2 PS and 1 TT. These results support the data showing a more symmetrical arrangement for the smaller conjugates, and a more asymmetrical arrangement for the larger ones. The larger vaccine more asymmetrical conjugates correlated with greater humoral and cellular murine immune response.

Funding source: N/A

#P26 Safety and immunogenicity of a single dose of meningococcal ACYWX conjugate vaccine in Malian children aged from 12-16 months

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Keywords: Trial, NmCV-5, Reactogenicity, Immunogenicity, Meningitis

In regions where MenAfriVac® has been introduced since 2010, meningococcal serogroup A disease has been virtually eliminated; however, disease due to other serogroups, including X, remains. A pentavalent meningococcal conjugate vaccine against serogroups A, C, Y, W and X (NmCV-5) has been developed in India.

Twelve- to sixteen-month old Malian toddlers who had not previously received MenAfriVac were randomized to receive non-adjuvanted (group 1) or adjuvanted (Group 2) NmCV-5 or the control vaccine, Menactra® (Group 3) at day 0 and day 84. Reactogenicity was assessed for 7 days after each vaccination. Serum bactericidal activity (rSBA) for serogroups A, C, Y, W and X was measured prior to each dose and 28 days later.

From 15 November 2017 to 10 March 2018, 379 participants were screened and 375 were randomized. On day 7 after the first dose, the percentage of participants with any solicited adverse event was similar across all 3 groups (5.3%, 6.6% and 6.0%), as were the percentages of participants who experienced an unsolicited adverse event within 28 days (26%, 30.3% and 24.8%). Serogroup A rSBA titers ≥8 were observed in 11.6%, 12.8%, and 13.5% of subjects at baseline, and in 100%, 100%, and 98.6% 28 days after vaccination, in groups 1, 2 and 3, respectively. Serogroup C rSBA titers ≥8 were observed in 2%, 0%, and 0% of subject at baseline and in 99.3%, 99.3%, and 78.4% 28 days after vaccination in group 1,2 and 3 respectively. Serogroup W rSBA titers ≥8 were observed in 6.1%, 4.1%, and 2.7% of subjects at baseline, and 98.6%, 98%, and 90.5% 28 days after vaccination in group 1, 2 and 3 respectively. Serogroup X rSBA titers ≥8 were observed in 10.2%, 8.1%, and 8.1% of subjects at baseline and 100%, 99.3%, and 20.3% 28 days after vaccination in groups 1, 2 and 3 respectively. Serogroup Y rSBA titers ≥8 were observed in 11.6%, 15.5%, and 13.5% of subjects at baseline and 98%, 99.3%, and 87.8% 28 days after vaccination in groups 1, 2 and 3 respectively. Similar trends were observed for the percentages of subjects with rSBA titers ≥ 128 and four-fold increases in rSBA titer from day 0 to 28. Although there was no difference in the percentage of subjects with rSBA titers ≥128 across all serogroups in groups 1 and 2, they were similar for serogroup A and higher for all other serogroups when compared to Group 3. Moreover, geometric mean rSBA titers were superior in groups 1 and 2 compared to group 3 across all serogroups. (*Interim report after a single dose. Full data set including two dose results will be presented at the conference.)*

Non-adjuvanted and adjuvanted NmCV-5 formulations were safe and equally immunogenic. Immune responses to each were similar or superior to those observed with Menactra®

Funding source: PATH

Diagnosis and treatment

#DT1 Role of exposed sialic acid in the interaction between meningococci and neuronal cells in the invasive meningococcal disease

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Keywords: *Neisseria meningitidis*; Meningitis mouse model; CNS infection; Sialic acids; Serogroup C

Neisseria meningitidis is a leading cause of human sepsis and meningitis worldwide but unfortunately the lack of valuable animal model of disease due to the narrow host range has greatly hindered progress in understanding meningococcal disease pathogenesis. It is known that serogroups B, C, Y and W-135 carry sialic acids in their capsular polysaccharide. The large abundance of surface-exposed sialic acids is associated to virulence and serum resistance to phagocytosis, resulting in enhanced survival into bloodstream and central nervous system (CNS). Our aim was to evaluate the role of surface-exposed sialic acids in an experimental murine model based on intracisternal infection of BALB/c adult mice, using the reference serogroup C meningococcal strain 93/4286 (ET-37) and an isogenic knockout mutant 93/4286Ω*cssA*. In *N. meningitidis* serogroup C, *cssA* gene encodes an UDP-N-acetylglucosamine 2-epimerase enzyme required for the biosynthesis of polysialic acid capsular and for lipooligosaccharide sialylation. Before starting *in vivo* experiments, we developed a serogroup C *cssA*-defective isogenic mutant and its characterization under *in vitro* conditions. In order to study the infectious dynamics of meningococcal disease in the mouse model, survival and microbiological analyzes of the brain and peripheral organs of infected mice were performed. Afterwards, to analyze the histopathological characteristics of the disease, histological evaluation, analysis of cerebral bleeding and localization of bacteria in brain structures were carried out. The mutant exhibited a relative fitness of 108% compared to wild type in *in vitro* conditions. The 50% lethal dose of the reference strain was about four orders of magnitude lower than that of *cssA* mutant. Compared to the wild-type strain, the mutant's ability to replicate in brain and spread systemically was severely impaired. Evaluation of brain damage highlighted a significant reduction in cerebral haemorrhages in mice infected with the mutant strain compared to levels of those challenged with the wild-type strain. Histological analysis of mice infected with wild type strain showed the typical features of bacterial meningitis. Noticeably, 80% of mice infected with the wild-type strain presented massive bacterial localization and inflammatory infiltrate in the *corpus callosum*, indicating a specific involvement of this area in the mouse model of meningococcal meningitis. Our study further expands the knowledge about CNS infection dynamics. Histological analysis and

bacterial immunostaining indicate surface exposed sialic acid as a main determinant for meningococcal intracellular growth/survival and also as a possible mediator in the interaction between meningococci and neuronal cells in the pathogenesis of invasive meningococcal disease.

Funding source: This research was supported in part by PRIN 2012 [grant number 2012WJSX8K]: “Host-microbe interaction models in mucosal infections: development of novel therapeutic strategies”.

#DT2 Factor H binding protein (fHbp) mediated differential complement resistance of a Serogroup C Neisseria meningitidis isolate from CSF of a patient with Invasive Meningococcal Disease

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During an outbreak of meningococcal disease at Southampton University in 1997, two *Neisseria meningitis* MenC isolates were retrieved from a person who died (Case) and one who performed mouth to mouth resuscitation on the case (Carrier), without contracting the disease (1). Serological and genomic analyses (2) showed the isolates to be almost identical. Here, we further interrogate these isolates through proteomic and phenotypic characterisation.

Comparative proteomics identified six proteins differentially expressed between the isolates, five upregulated and one downregulated in the Case. One of these proteins was factor H binding protein (fHbp), a major virulence factor involved in bacterial survival in human serum, which was expressed by the Case isolate only. Sequence analysis detected a one base deletion (ΔT366) in the Carrier *fHbp* causing a frameshift mutation which resulted in lack of fHbp expression in this isolate, also demonstrated by absence of fHbp peptides in mass spectrometry. In contrast, a full-length fHbp is expressed by the Case.

Serum survival assays were performed to investigate isolates' ability to survive in human serum. The Case isolate showed increased survival in human serum compared to the Carrier presumably as it is more resistant to complement killing. The Carrier strain was genetically modified to express fHbp which enhanced its survival in serum and its resistance to complement killing.

The impact of fHbp expression was also assessed via Serum Bactericidal Antibody (SBA) assay using mouse sera raised against Bexsero (GSK), a MenB vaccine containing fHbp, NadA and NHBA recombinant proteins and Outer Membrane Vesicles (OMVs). Bexsero mouse sera demonstrated significant killing against both MenC Carrier and Case isolates due to cross-reacting NadA and NHBA. However, increased SBA titres were seen against the Case, presumably because of antibodies directed against fHbp.

This study demonstrated that fHbp mediates differential complement resistance between the Carrier and the Case isolates. Expression of fHbp in the Case probably resulted in its increased survival in human serum and thus played a role in the virulence of the isolate obtained from the deceased student. In addition, sera from mice vaccinated with Bexsero killed both MenC isolates, mostly due to cumulative effect of antibodies directed against NadA and NHBA antigens (and possibly OMV minor antigens), with fHbp providing additional killing activity in the Case due to anti-fHbp antibodies present in Bexsero sera.

Funding source: NIBSC Bacteriology and TDI Divisional budgets

#DT3: Streptococcus anginosus Infections Clinical and Bacteriologic Characteristics A 6-year Retrospective Study of Adult Patients in Qatar

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Keywords: Streptococcus anginosus, bacterial infection, abscess, meningitis, bacteremia

Background: The aim of this study was to assess clinical presentation and antimicrobial susceptibility of Streptococcus (S.) anginosus group infections in Hamad General Hospital, a tertiary care hospital in the state of Qatar, which is a multinational community. The S. anginosus group is a subgroup of viridans streptococci that consist of 3 different species: S. anginosus, S. constellatus, and S. intermedius. Although a part of the human bacteria flora, they have potential to cause suppurative infections.

Method: We studied a total of 101 patients with S. anginosus group infections from January 2006 until March 2012 by reviewing medical records and identification of organisms by VITEK 2 and MALDI-TOF.

Results: The most common sites of infection were skin and soft tissue, intra-abdominal, and bacteremia (28.7%, 24.8%, and 22.7%, respectively). Abscess formation was seen in approximately 30% of patients. Streptococcus constellatus was the most common isolated species (40%) followed by S. anginosus(30%) and S. intermedius(7%). In 23% of specimens, the species was unidentified. The most common type of specimen for organism isolation was blood followed by pus and tissue (50%, 22%, and 8%, respectively). Streptococcus constellatus was more frequently associated with abdominal and skin and soft tissue infections than the other 2 species, whereas S. anginosus was isolated more frequently from blood. All isolates were susceptible to penicillin, ceftriaxone, and vancomycin. Susceptibility to erythromycin and clindamycin was also good, reaching 91% and 95%, respectively. Forty percent of patients needed surgical drainage along with antibiotic therapy.

Conclusions: Identification of S. anginosus group to species level is helpful in clinical practice because different species exhibit different pathogenic potentials

Funding source: none

#DT4 Pneumococcal Meningitis Complicated by Cerebral Vasculitis, Abscess, Hydrocephalus, and Hearing Loss

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Keywords: Bacterial meningitis, pneumococcal meningitis, cerebral vasculitis, intracranial abscess, postinfectious vasculitis

Intracranial abscesses, postinfectious vasculitis, and hydrocephalus are rare complications of Streptococcus pneumoniae (S. pneumoniae) meningitis, and to our knowledge, there have been no case reports where all these 3 complications occurred in a single patient with Streptococcus pneumoniae meningitis. Here, we report a case of a 48-year-old male who developed postinfectious vasculitis, abscess, hydrocephalus, and hearing loss after S. pneumoniae meningitis. Clinicians ought to be aware of the possible adverse outcomes of S. pneumoniae meningitis and the limitations of current treatment options.

Funding source: none

DT5: Systematic review on the acute cost-of-illness of sepsis and meningitis in neonates and infants:

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Keywords: neonate, infant, sepsis, meningitis, costs

Objectives: Sepsis and meningitis in neonates and infants are a source of substantial morbidity, mortality and economic loss. The objective of this review is to estimate the acute costs associated with treating sepsis, meningitis and meningococcal septicaemia, in neonates and infants, worldwide.

Methods: The electronic databases Medline, Embase, and EconLit were searched and exported on November 24, 2018. Studies that reported an average hospitalization cost for confirmed cases of sepsis, meningitis, or meningococcal septicaemia were eligible for our review. Descriptive data were extracted and reported costs were inflated and converted. A narrative synthesis of the costs was conducted.

Results: Our review identified 20 studies reporting costs of sepsis, meningitis, and/or meningococcal septicaemia. Costs ranged from $55 to $129,632 for sepsis and from $222 to $33,635 for meningitis (in 2017 USD). One study estimated the cost of meningococcal septicaemia to be $56,286. All reported costs were estimated from the perspective of the healthcare provider or payer. Most studies were from the United States, which also had the highest costs. Only a few studies were identified for low- and middle-income countries, which reported lower costs than high-income countries for both sepsis and meningitis.

Conclusion: Sepsis and meningitis in neonates and infants are associated with substantial costs to the healthcare system and showed a marked difference across global income groups. However, more research is needed to inform costs in low- and middle-income settings and to understand the economic costs borne by families and wider society.

Funding source: The Bill & Melinda Gates Foundation, Seattle, WA (OPP1180644 and OPP1157270)

#DT6 The interplay between pneumococci and microglia during bacterial meningitis:

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Keywords: *Streptococcus pneumoniae,* microglia, pneumococcal meningitis, phagocytosis, neuroinflammation

Introduction: Bacterial meningitis is an inflammation of the meninges, predominantly caused by *Streptococcus pneumoniae* (pneumococcus). Microglial cells are the immune sentinels of the brain and are central players in the pathophysiology and resolution of meningitis. In a murine experimental meningitis model, we observed a low-level chronic pneumococcal infection of the brain for up to 10 days, implying that bacteria are not readily cleared by microglia and other macrophages, but may survive within intracellular niches. To further investigate the pneumococcal-microglia interplay we set up a series of *in vitro* assays.

Methodology: Bioluminescent signals of pneumococci in the brain of mice were imaged with the IVIS Spectrum Imaging System at the time of sacrifice after 10 days of systemic pneumococcal infection. Brain homogenates were used for quantification of CFU and cryosections were prepared for analysis by high-resolution microscopy. BV2 microglial cells were infected with *S. pneumoniae* and uptake and intracellular survival of bacteria was monitored in a modified gentamycin gentamicin assay. Changes in microglial morphology in the presence of pneumococci were investigated by live-cell imaging, and the role of pneumococcal capsule for uptake and intracellular survival of the bacteria within microglia was assessed by high-resolution microscopy using Lysotracker.

Results: An asymptomatic presence of low numbers of bacteria was detected in some of the mice in the bacteremia-derived meningitis model. *In vitro*, microglia obtained an activated morphology in the presence of TIGR4 pneumococci within 30 minutes from exposure. In addition, pneumococcal strains TIGR4 and D39, and clinical isolates of serotype 6B are internalized by microglia and remain viable intracellularly for at least 6 hours post infection. Furthermore, in accordance with previous findings, the pneumococcal capsule confers resistance to intracellular killing in our model.

Conclusion: *Streptococcus pneumoniae* can survive over time within microglia after uptake/invasion *in vitro* and possibly *in vivo*. Whether the internalization is an active process by the cells or due to bacterial invasion needs to be elucidated. Unraveling the mechanism of the pneumococci-microglia interaction may help advance therapeutic strategies in the near future.

Funding source: Åke Wiberg Foundation, Jeanssons Foundation, Petrus and Augusta Hedlund Foundation, KI Research Foundation, StratNeuro

#DT7 Brain sequelae caused by bacterial meningitis: interactions between pneumococci and neurons

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Keywords: Neurons, *Streptococcus pneumoniae*, Bacterial adhesion and invasion, Type 1 pili, Neuronal cell death

Introduction: Bacterial meningitis is an inflammation of the meninges, caused by a bacterial infection of the brain. Even though mortality is not extremely high varying from 10-30% depending on geographical region, around 50% of survivors suffer from permanent brain damages often linked to neuronal cell damage caused by the bacterial infection of the brain. *Streptococcus pneumoniae* is the main etiological cause of bacterial meningitis worldwide, and it is known to enter the brain mainly through the bloodstream. It was previously shown that the pneumococcal major toxin pneumolysin can induce neuronal cell death; however, it remains unknown whether *S. pneumoniae* can directly interact with neurons. Furthermore, the pneumococcal pilus-I is reported as a major virulence factor in bacterial meningitis pathogenesis. In this study, we investigated the capacity of S. pneumoniae to actively adhere and invade neurons, and to understand whether pilus-I is involved in this process.

Methods: Differentiated neurons from human neuroblastoma cells (SH-SY5Y) are used as *in vitro* model, immunofluorescence staining and western blotting were used for validation of differentiation. Infection assays were performed to assess the capacity of pneumococci to adhere to and invade neurons; such assays followed with count of CFU and immunofluorescent microscopy. Two laboratory bacterial strains, serotype 4 TIGR4 wild type and its isogenic mutant lacking the pilus-I genetic islet TIGR4ΔrrgA-srtD, and two clinical isolates of two different serotypes 11A (non-piliated) and 15A (pilated) were also used in infection assays.

Results: Our results have shown that *S. pneumoniae* can interact with neurons through active adhesion and invasion. *S. pneumoniae* with pilus-I has significant increased level of adherence and invasion in neurons. Interestingly, *S. pneumoniae* inside neurons co-localized with microtubule associated protein 2 (MAP2), suggesting that MAP2 could be a potential receptor for the intracellular transport of *S. pneumoniae* in neurons. Preliminary data also has shown that the plasma membrane neuronal protein DBN1 co-localized with piliated *S. pneumoniae* on the neuronal cell membrane, while no co-localization was observed between DBN1 and non-piliated pneumococci, which suggests that interaction between pilus-I and DBN1 could mediate the initial interaction between pneumococci and neurons.

Funding source: The strategic research area Neuroscience (StratNeuro), KI Research Foundation grants, Jeansson Foundation, Åke Wiberg Foundation, Petrus and Augusta Hedlund Foundation

#DT8 Prevalence of cervical lymphadenopathy in acute CNS infections – Testing the Glymphatics in humans

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Keywords: Cervical lymphadenopathy, Prevalence, Acute CNS infections, Glymphatics, Biopsy

Introduction: Central nervous system (CNS) infections are important cause of morbidity and mortality worldwide. Current diagnostic methods used in acute CNS infections are limited by its pauci-microbial nature in cerebrospinal fluid(CSF). Recently discovered Glymphatics has been shown to play an important role in the movement of CSF along with the substance present in it to cervical lymph nodes in animal models. We had planned to study the prevalence of cervical lymphadenopathy in acute CNS infections and assess the diagnostic yield of cervical lymph node biopsy in the definitive diagnosis of acute CNS bacterial infections. This may indirectly prove the presence of glymphatics in humans for the first time.

Methodology: A prospective crossectional study was performed in 105 patients with acute CNS infections where they were clinically and radiologically (ultrasound) screened for cervical lymphadenopathy. Biopsy (surgical/FNAC) was carried in cases wherever it was feasible following informed consent. The biopsy sample was sent for histopathology, aerobic and MGIT culture. The results were compared with CSF reports (smear and culture) and the clinician's diagnosis.

Results: 105 patients with acute CNS infections were enrolled for the study with Tuberculous meningitis being the most common (33%) cause of acute CNS infections followed by pyogenic (31%), viral (12%), aseptic (11%), fungal (3%) and others (10%). 30 cases out of 105(28.57%) enrolled acute CNS patients had cervical lymphadenopathy with no significant difference in prevalence of cervical lymphadenopathy among different types of CNS infections (chi-square - 1.2, p-value – 0.94). Cervical lymphadenopathy was bilateral and their distribution across different levels was found to be statistically significant (p-value <0.001) with Level II being the most common (23.4%).
Out of the 30 patients with cervical lymphadenopathy, only 6 patients had met the criteria for biopsy. Out of these 6 cases, 2 cases were TB meningitis where histopathology report of the cervical lymph node biopsy sample showed granulomatous inflammation which was subsequently correlated with positive MGIT culture in CSF in both the cases.

Conclusion: This is the first study to report the prevalence of cervical lymphadenopathy in adults with acute CNS infections which was found to be significantly higher (28.6%) than what has been previously described in normal adults(<1%). Cervical lymphadenopathy could provide for additional diagnostic aid in rapid and accurate diagnosis of acute CNS infections and also its higher prevalence in acute CNS infections has provided evidence for presence of glymphatics in humans for the first time.

Funding source: Fluid Research Grant - Institutional funding from Christian Medical College, Vellore, India.

#DT9 Clinical characteristics of patients with acute meningitis after lumbar epidural nerve block

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Keywords: Meningitis, epidural anesthesia, nerve block, steroids, spinal puncture

Backgrounds: Lumbar epidural nerve block (ENB) is widely used for the treatment of lumbar radicular pain caused by the inflamed spinal nerves. Various complications like post-dural puncture headache, transient paraparesis, and hypotension may occur. Meningitis, which is an acute inflammation of the meninges covering the central nervous system, has been rarely reported after receiving a lumbar root injection. The purpose of this study was to assess the clinical characteristics of acute meningitis after lumbar ENB.

Subjects and Methods: 113 patients who had treated with acute bacterial meningitis during a 5-year period between August 2014 and July 2019 were retrospectively evaluated. Only patients with a history of lumbar ENB just before the development of meningitis were enrolled for this study. ABM was diagnosed according to the EFNS guideline for ABM through cerebrospinal fluid (CSF) analysis. Medical data including epidemiologic features, clinical findings, laboratory findings, and radiologic findings.

Results: Six patients with acute meningitis just after lumbar ENB were enrolled. The median time interval from lumbar ENB to onset of meningitis was 2.5 hours (range, 1-4 hours), and median time interval from symptom onset to arrival to emergency room was 12.5 hours (range, 2-40 hours). All enrolled patients presented with headache and high fever, but altered mentality, seizure, focal neurologic sign were not seen, which were completely subsided just after treating with intravenous corticosteroids and antibiotics including cephalosporin and vancomycin. All patients were hospitalized in 14 days for antibiotics treatment. Laboratory findings revealed leukocytosis (range, 12,000-20,900/mm^3) with no significant elevation of CRP. Leukocytosis has been slightly decreased, whereas CRP has been more increased just after the treatment. CSF analysis revealed pleocytosis (range, 5,425-8,614/mm^3), an elevated proteins (range, 264.9-620 mg/dL), the decreased ratio of CSF glucose to serum glucose (range, 0.02-0.43), high titers of CSF lactate (range, 5.84-13.2), but no bacteria was cultured in CSF. Diffuse leptomenigeal-or pachymeningeal enhancement and diffuse sulcal hyperintensity on T2-weighted images were common. Pneumocephalus was identified in two patients.

Conclusion: Acute menigitis may occur in patients who received lumbar ENB, especially within only several hours after the treatment of lumbar root injection, which have been dramatically improved within 24 hours after the treatment. No prominent evidence of the constitutional infection, which suggests that acute meningitis after lumbar ENB may be chemicals-induced meningitis rather than bacterial meningitis. Further study will be needed for verifying the pathomechanism in acute meningitis after lumbar ENB.

Funding source: Chonnam National University Hospital

#DT10: Evaluating the use of dried blood and CSF spots as a means of storing and transporting clinical material for molecular diagnosis of invasive meningococcal disease

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Keywords: Meningococcal, Epidemic, Diagnosis, PCR, Transport

Introduction: N, meningitidis has the propensity to cause devastating invasive disease outbreaks in sub-Saharan Africa. During these outbreaks, a prompt and efficient public health response is dependent on comprehensive case ascertainment. Real-time PCR can provide rapid laboratory confirmation, however, it requires clinical samples to be stored at low temperatures during transportation in order to maintain DNA stability. The infrastructure and facilities required to allow cold chain transport are not always present in parts of the African meningitis belt and so case ascertainment can be less than optimal.

This pilot study aimed to evaluate the use of filter paper to dry blood and cerebrospinal fluid (CSF) for storage and transportation at ambient temperatures, thereby eliminating the need for cold-chain.

Methods: Whole blood and CSF from healthy donors was spiked with heat killed meningococcal suspensions at six concentrations (equivalent to 101 to 106 CFU/mL). For each sample/concentration, 50 µL of spiked sample was inoculated on to the filter paper. Three different filter papers (Whatman® protein saver, PerkinElmer 226 and Flinders Technology Associates (FTA)) were evaluated.

Dried spots were stored with a desiccant overnight at ambient temperature (18 °C-25 °C) before DNA extraction. Meningococcal real-time PCR was performed using Taqman® assays targeting the ctrA gene and the genogroup-determining siaD gene.

To assess, medium-term storage stability, re-extraction and repeat PCR testing was performed from selected dried spots after approximately one month of storage at ambient temperature.

Results: Meningococcal DNA was detected and genogrouped from blood and CSF inoculated on all three filter papers stored overnight. The limit of detection from the spiked CSF or blood was ~103 CFU/mL. Of the three filter papers tested, Whatman® protein saver and PerkinElmer 226 allowed for the most sensitive detection.

After one month storage on filter paper at ambient temperature, real-time Ct values for selected samples were analogous to the initial detection (at 24 hours). This suggests the DNA is stable at least up to one month at ambient temperature.

Conclusions: Storage and detection of meningococcal DNA was possible from spiked blood and CSF samples down to an equivalent meningococcal concentration of ~103 CFU/mL following overnight ambient storage. This approach has the potential to allow transport of clinical samples to laboratories at ambient temperature, facilitating laboratory confirmation

in resource limited settings. The next step is to validate this approach using archived clinical specimens

Funding source: NIHR Unit on Mucosal Pathogens Research (MPRU)

#DT11 GWAS identifies a long non-coding RNA single nucleotide polymorphism which is associated with susceptibility to severe meningococcal disease

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Keywords: meningococcal disease, genetic susceptibility, Genome wide association studies (GWAS), prognosis, single nucleotide polymorphism (SNP)

Introduction: Invasive meningococcal disease, most commonly presenting as meningitis or septicaemia, results in significant mortality and morbidity. In the UK, 755 cases were reported between 2017-2018 with a mortality rate of 6.9% (52/755) (1). While approximately 10% of the population carry the causative bacterium, *Neisseria meningitidis*, only a small proportion develop the clinical disease (2). Recent advances in genomics have supported the influence of host genetic variation on disease susceptibility (3).

Objective: To understand the impact of host genetic variations on susceptibility to severe meningococcal infection.

Methods: Ten separate GWAS analyses were performed on a discovery cohort of 1236 meningococcal cases from the UK, Spain, Austria and Netherlands (4), looking at intermediate blood markers and severe outcomes (mechanical ventilation, amputation, skin graft, death).

Results were validated on a cohort of 1959 suspected bacterial cases (all causes including meningococcal infections) (5).

Results: The strongest association in the discovery cohort was a locus on chromosome 22 in a long-non coding RNA with 8 single nucleotide polymorphisms (SNPs) reaching genome-wide significance for association with white cell count ($p<5x10-8$). The allele associated with lower

levels of WCC was also associated with lower levels of platelets (p=0.0025), base excess (p=0.025), CRP (p=0.0089) and higher levels of: GMSPS (p=0.0075), INR (p=0.0053), APTT (p=0.041); the directions of effect on all blood markers are indicative of more severe outcomes. The allele was also associated with increased risk of mechanic ventilation (p=0.0015) and death (p=0.05).

In the validation cohort, the risk allele was associated with higher levels of APTT in meningococcal patients (p=0.0045) and all patients with definite bacterial infection (p=0.017) and increased risk of mechanic ventilation in all patients (p=0.105).

Conclusions: A long non-coding RNA locus on chromosome 22 may confer increased susceptibility to severe meningococcal disease. This risk may extend to other bacterial infections. Exploring the biological role of this SNP will allow better understanding of the disease, patient risk stratification and tailored management.

Funding source: none

#DT12 Risk factors predicting the development of neurological complication in acute bacterial meningitis

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Keywords: Meningitis, spinal puncture, cerebrospinal fluid, lactate, prognosis

Backgrounds: Bacterial meningitis (BM) is acute inflammation of the meninges covering the central nervous system, which is caused by several different bacteria. Acute BM can lead to serious neurological complication, permanent disability, or death. Therefore, it is important to predict the patient's outcome including neurologic complication in the early stage of acute BM. The aim of this study was to evaluate the risk factors affecting the development of neurologic complication.

Methods: Adult patients who have been treated with acute BM were screened retrospectively during a 7-year period between July 2012 and June 2019. Only patients who fulfilled with the diagnostic guideline for acute BM proposed by EFNS scientific task, but partially-treated BM or BM secondary to bacteremia or septicemia was excluded. The enrolled patients were divided into 2 groups according to the presence of neurologic complication; Group 1 (patients with neurologic complication) and Group 2 (patients without neurologic complication). Neurologic complications consisted of impaired mental state, seizure, cranial nerve palsies, sensorineural hearing loss, weakness and gait disturbance, urinary difficulty, shock, and death following neurologic problem.

Results: 47 patients with acute BM were enrolled for this study. 27 (56.3%) were men, and the mean age at symptom onset was 60.1 ± 15.1 years (range, 16-91 years). There were 28 (58.3%) patients in Group 1 and 20 (41.7%) in Group 2. The mean value (87.1%) of the percentage of neutrophils in cerebrospinal fluid (CSF) of Group 1 was significantly higher compared to that (71.8%) in Group 2 (P = 0.001), and the decreased ratio of glucose in CSF to serum was significantly different (P = 0.02, 0.17 vs. 0.31, in Group 1 and 2, retrospectively). The mean values of protein and lactate in CSF of Group 1 were significantly higher compared to those in Group 2 (P = 0.007, and P = 0.003, respectively). There was no significant difference between the two groups in age at onset, gender, the absolute neutrophil counts in CSF, and systemic inflammatory markers including leukocytosis, C-reactive protein, and procalcitonin in blood. On the multivariate analysis, the lactate and percentage of neutrophils in CSF were the independent risk factors affecting the occurrence of neurologic complication (OR, 1.228; 95% CI, 1.024 to 1.473; P = 0.026 and OR, 1.138; 95% CI, 1.004 to 1.291 P = 0.044, respectively).

Conclusion: Neurologic complication may be not uncommon in patients with acute BM. CSF analysis performed in the early state of the disease can be helpful in evaluation of the risk of neurologic complication. Especially, the lactate and percentage of neutrophils in CSF before the treatment may be strongly related to the occurrence of neurologic complication.

Funding source: none

#DT13 Streptococcus pneumoniae prioritises genes involved in the avoidance of opsonophagocytotic killing in the CSF of adults with pneumococcal meningitis:

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Keywords: Transcriptome, Streptococcus pneumoniae, virulence, genes, pathogenesis

Positively influencing the outcome of the host-pathogen interaction in pneumococcal meningitis is likely to improve clinical outcome from pneumococcal meningitis (PM). However, the clinical contribution of *S.pneumoniae* on outcome is poorly understood *in-vivo*.

Objectives: We describe the first report on the *S.pneumoniae* transcriptome in CSF during PM, validated against an *in-vitro* transcriptomic model. We investigated the role of highly expressed, poorly annotated genes from the transcriptome in a human CSF neutrophil-killing model of meningitis

Methods: CSF from adults with PM was collected prior to antibiotics and stored at -80ºC in PAXgene®. Total RNA was isolated and sequenced after ribodepletion on the Illumina Nextseq platform. Transcripts were mapped against multiple *S.pneumoniae* genomes, normalised and quantified. The clinical transcriptome was analysed against infection-relevant conditions in the *in-vitro* D39 transcription model PneumoExpress. Gene-deleted mutant bacteria were generated from highly expressed, poorly annotated virulence genes. Effects on growth and neutrophil-mediated killing in a human CSF model of meningitis were tested between wild-type and mutant bacteria.

Results: CSF transcriptomes were available for 11 Adults with PM (median age 32 years, 60% male, 70% HIV-1 co-infected, 10/11 non-survivors, median bacterial load $1.6x10^7$ copies/ml CSF (IQR $4.1x10^6$ – $7.0x10^7$), predominant serotypes 1/23F/12F). Mapping was optimal against Serotype 1 strains (gamPN10373, P1031), 23F (D141, D122, D219), 3 (A66) and 19A (Hu15, Hu17). The top quartile of expressed genes by transcript copies/million reads was dominated by genes annotated in avoidance of opsonophagocytic killing and meningitis pathogenesis (including BgA, PsaA, PspC, CiaRH, NanA, ply, pepO, Pbp1A, CbpA) and genes with unknown function. Highly upregulated genes were co-correlated into clusters and tested against D39 expression in *in-vitro* conditions using pneumoexpress. The closest association was in the host-pathogen interaction model between *S. penumoniae* D39 and A349 epithelial cells.

We investigated further the role of highly upregulated genes with no known function in meningitis pathogenesis. We created gene deleted mutants of betagalactosidase (BgaA) and the operon SP_1800-5, and phenotyped the role of these genes in human CSF models of meningitis. Data on differential growth in human CSF and neutrophil-mediated killing of these gene-deleted mutants will be presented.

Conclusions: The pathogen transcriptome in PM represents unique insights into interactions with the host. *S.pneumoniae* prioritises expression of genes that avoid oposonophagocytic killing and resist oxidative stress during meningitis. The transcriptome revealed activity of genes with no known function in meningitis currently under investigation. The role of these genes in pathogenesis may reveal new adjunctive targets for intervention to reduce mortality from pneumococcal meningitis.

Funding source: Wellcome Trust, Academy of Medical Sciences, UCL Institutional Strategic Fund, Robin Weiss Fund.

#DT14 Over-expression of Elongation Factor Tu of Streptococcus pneumoniae in CSF is associated with non-survival from pneumococcal meningitis

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Keywords: Mortality, proteomics, Streptococcus pneumoniae, HIV

Background: Mortality from bacterial meningitis, predominately caused by *Streptococcus pneumoniae*, is persistently high in Low and Middle Income Countries in sub-Saharan Africa with high HIV prevalence. Underlying mechanisms of such high mortality are poorly understood.

Objective: We examined the host and pathogen proteome in adults with proven pneumococcal meningitis (PM), testing if differentially expressed proteins in CSF correlated with outcome.

Materials/methods: CSF proteomes were analysed by quantitative Mass-Spectrometry. Spectra were identified using the Swissprot human and TIGR4 pneumococcal protein databases. Proteins with Uniprot identification were quantitated and analysed against clinical outcome. Proteins were ranked against normal CSF proteomes to identify unique proteins in PM. Proteins of interest were synthesized in E.coli and tested in models of opsonophagocytic killing.

Results: CSF proteomes were available for 57 Adults with PM (median age 32 years, 60% male, 70% HIV-1 co-infected, mortality 63%). 360 individual human and 23 pneumococcal proteins were identified in the CSF. Of the human protein hits, 30% were not expressed in normal CSF and were primarily related to neutrophil activity. No human protein was associated with outcome. However, expression of the essential bacterial protein *S. pneumoniae* Elongation Factor Tu (Tuf) was significantly increased in CSF of non-survivors (False Discovery Rate (q) <0.001). Expression of Tuf was *co*-correlated against expression of Neutrophil defensin (r 0.4 p p<0.002), but not against complement proteins C3 or Factor H. Data on the role of Tuf in neutrophil-mediated killing in a model of meningitis will be presented.

Conclusions: Expression of Tuf in CSF is implicated in poor clinical outcomes from pneumococcal meningitis and may be involved in avoidance of neutrophil-mediated killing.

Funding source: Wellcome Trust, Academy of Medical Sciences, UCL ISSF award, Robin Weiss Fund

#DT15 National Audit of Meningitis Management (NAMM): a National Infections Trainees Collaborative for Audit and Research (NITCAR) audit of adherence to the 2016 UK joint specialist societies' guideline on the diagnosis and management of acute meningitis in adults

Fiona McGill, Jayne Ellis, David Harvey, Sylviane Defres, Tom Solomon, Arjun Chandna, Eloisa Maclachlan, Robert Heyderman on behalf of the NAMM investigators

Background: Bacterial meningitis has significant mortality but frontline doctors will see it infrequently. Therefore, UK guidance on meningitis in adults, with auditable standards, was revised in 2016. We undertook a national audit to assess adherence to the guidelines.

Methods: Patients with community acquired meningitis were identified through coding or laboratory data. Audit standards, including immediate management, diagnostics and treatment, were evaluated by notes review.

Results: Notes from 1472 patients with meningitis were reviewed – 309/1472 (21%) had bacterial aetiology, 615/1472 (42%) viral, 548/1472 (37%) unidentified aetiology. Only 50% of patients had blood cultures taken within one hour of admission and just 2% had a lumbar puncture (LP) within the first hour. 27% received antibiotics within one hour. Most patients received ceftriaxone or cefotaxime but only 37% of over-60s received empirical anti-listeria antibiotics. 26% of patients who had antibiotics were given adjunctive steroids. Half had CSF microscopy within two hours of LP. Less than a third had pneumococcal and/or meningococcal PCR on cerebrospinal fluid. Only 44% had an HIV test. 62% had unnecessary neuroimaging before LP. Overall mortality was 3% - 16% in pneumococcal disease and 8% in meningococcal meningitis. There was a trend toward improved survival in patients with pneumococcal meningitis who received dexamethasone [85/96 (88%)] compared to those who did not [57/73 (78%)] (p=0.066).

Conclusions: Adherence to the meningitis guidelines is inadequate, potentially compromising patient safety. Improvements in guideline dissemination, novel educational resources and clinician and patient engagement are required if we are to increase guideline adherence and improve outcome.

#DT16 HIV-infected individuals with cryptococcal meningitis have impaired monocyte function

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Keywords: Phagocytic activity superoxide burst zymosan

Background: Cryptococcal meningitis (CM) is a leading cause of death in HIV-infected adults in Malawi, even in the era of expanded free access to antiretroviral therapy (ART). Previous studies have reported that some HIV-infected individuals are able to clear the infection completely whilst others relapse after successful antifungal therapy and others do not clear the infection at all. There is limited understanding the role the immune system plays in CM infection. This study focuses on the role of host immunity in the clearance of cryptococci by probing the relationship between whole blood phagocyte immune function and outcomes of CM.

Methodology: This study is nested within the AMBITION trial currently underway at Queen Elizabeth Central Hospital in Blantyre. 27 HIV-infected participants of Median age 35(31-66) years, with first episode of CM were recruited upon consent. Participants had a median CD4 count of 36.5 cells/ml (9-427). Participants were randomized into two treatment arms; control arm which receives standard dose for CM and single arm which receives a single dose of liposomal amphotericin B together with 14 days of fluconazole and flucytosine. The function of neutrophils and monocytes in peripheral blood samples collected on day 1, 7 and 14 following recruitment were assessed using a flow cytometry-based whole blood phagocyte assay that uses zymosan particles tagged with fluorescent reporters which provide a readout of phagocytic uptake and superoxide burst activity.

To quantify oxidative activity, we calculated median fluorescence intensity of the positive superoxide burst population minus the median fluorescence intensity of superoxide burst activity of the negative population. The difference was divided by 2 times the robust standard deviation of the negative superoxide population.

Results: Preliminary results show that irrespective of the day of sample collection, neutrophils are not impaired in their ability to phagocytose zymosan particles with optimal oxidative burst occurring at 30mins (day 1, median of 77; day 7, median 79, p=0.9773). Monocytes, appear to have impaired superoxide burst activity on day 1 which recovers by day 7 (median 10mins = 29 vs 141, p=0.0051; median 30mins = 43 vs 226, p=0.0025; median 60mins = 44 vs 355, p=0.0167 ; median 90mins= 38 vs 367, p=0.0025).

Conclusion and interpretation: The preliminary data suggest that HIV-infected individuals with CM have impaired monocyte function. Furthermore, Treatment of CM with antifungal therapy is associated with recovery of monocyte function.

Funding source: London School of Hygiene Tropical Medicine (LSHTM)

#DT17 Determine the frequency of positive cerebrospinal fluid cultures (CSF)

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Keywords: Acute bacterial meningitis, cerebrospinal fluid, antibiotic sensitivity, neck stiffness, altered consciousness

Introduction: Bacterial meningitis is characterized by sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary), headache and one of the following signs: neck stiffness, altered consciousness or other meningeal sign or petecheal/purpural rash.1 Incidence of bacterial meningitis is higher in developing countries. Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type b (Hib) cause meningitis beyond the neonatal period.

Objectives: Determine the frequency of positive cerebrospinal fluid cultures (CSF)

Study design: Cross sectional study.

Duration with dates: Six months

Sampling Technique: Non probability purposive sampling

Subjects and Methods: After consent from parents, 150 children from 1 month to 14 years of age (in six months period) fulfilling clinical case definition of acute bacterial meningitis were included in the study. Lumbar puncture was done by standard protocol and frequency of positive CSF cultures studied.

Results: The study population consisted of 150 children with suspected acute bacterial meningitis from 1 month to 14 years of age. Mean age of children was 17.6+20 months. Majority of children 83 (55.3%) were below one year of age. There was male predominance. Twenty eight (18.7%) CSF cultures were positive. Out of total 28 positive cultures, 19 (67.9%) were positive for S.pneumoniae, followed by E.Coli 5 (17.9%), H.Influenzae 2 (7.1%), and S.aureus 2 (7.1%). All isolates of S. pneumoniae were sensitive to vancomycin and meropenem. Seventeen (90%) isolates of S. pneumoniae were sensitive to ceftriaxone and 13 (68%) to chloramphenicol, while only 1 (5%) isolate was sensitive to penicillin G. Eighteen (95%) isolates of S. pneumoniae were resistant to penicillin G, 6(32%) to chloramphenicol while all isolates were resistant to ampicillin. All isolates of H. influenzae were sensitive to ceftriaxone, vancomycin and meropenem while all of them were resistant to penicillin G, chloramphenicol and ampicillin. All isolates of E. coli were sensitive to vancomycin and meropenem and 2(40%) sensitive to ceftriaxone while all were resistant to penicillin G, chloramphenicol and ampicillin. All isolates of S. aureus were sensitive to vancomycin and meropenem while resistant to penicillin G, chloramphenicol and ampicillin.

Conclusion: S. pneumoniae was most common organism in children from 1 month to 14 years causing acute bacterial meningitis. High resistance against penicillin and ampicillin was observed.

Funding source: none

Disease surveillance

#D1 Pneumo Pathogenwatch: a one-stop platform for pneumococcal genomic data from analysis to visualisation

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Keywords: Streptococcus pneumoniae, web application, *in silico* typing, open data, Global Pneumococcal Sequencing project

Delivery of the right analysis for making public health decisions relies on developing species-specific analytics and presenting them appropriately to a public health audience. Here, in a collaboration between Genomics of Pneumonia and Meningitis team and the Centre for Genomic Pathogen Surveillance within the Wellcome Sanger Institute, we have tailored the web application Pathogenwatch (https://pathogen.watch) to offer *in silico* detection and characterisation of whole-genome sequence (WGS) data from *Streptococcus pneumoniae*.

Pathogenwatch's core features include:

- Quality metrics
- Species prediction
- Multi-locus sequence type (MLST) by BLAST against PubMLST databases
- Antimicrobial resistance using PAARSNP against an in-house resistance database

Users simply drag-and-drop raw sequence data or assemblies generated from WGS into the browser and manage the outputs through personal accounts. Uploaded data are kept private by default and metadata can be integrated without upload.

The addition of Streptococcus pneumoniae-specific features:

- Global Pneumococcal Sequencing Cluster (GPSC) assignment to an isolate using PopPUNK
- *in silico* prediction of serotype using SeroBA

has been made possible through the combined work of scientists and software engineers in both teams.

In addition, the application contains >20,000 pneumococcal genomes from the Global Pneumococcal Sequencing project and previously published studies, providing the most comprehensive curated database of pneumococcal genomes and allied epidemiological context. Users can visualise the geographical distribution of the whole database or on a selected subset of genomes by GPSC, sequence type or serotype. This web application offers

a wealth of genomic data and easy-to-use functions to a wide range of end users, from trained bioinformaticians to clinical microbiologist.

Live demonstrations during the poster session will demonstrate the speed and simplicity to researchers who may wish to use this web application.

Funding source: Bill and Melinda Gates Foundation, Wellcome Sanger Institute, The development of Pathogenwatch is funded by The Centre for Genomic Pathogen Surveillance

#D2 Epidemiology and surveillance of meningococcal disease in England

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Keywords: Epidemiology, Surveillance, Meningococcal disease, England

Introduction: To describe the epidemiology of IMD in England,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.

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 characterisation and, since October 2007, *porA* sequencing. MICs of penicillin, cefotaxime, rifampicin and ciprofloxacin are determined. Since July 2010 all case isolates have undergone whole genome sequencing (WGS)*. Clinical samples are submitted by hospital laboratories for non-culture detection and capsular group confirmation by PCR.

Results: Laboratory confirmed cases rose from the mid-1990s to peak at 2,595 (in 1999/00) then fell to 636 in 2013/14 since increasing 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 in England but 42 were confirmed in 2015/16 and 64 in 2017/18.

There has been an overall 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 programme has resulted in reduced disease in targeted cohorts[1].

Serogroup Y accounted for 12% (88 cases) of IMD in 2017/18, and total serogroup Y cases have been relatively stable since peaking at 103 cases in 2015/16. 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 confirmed as cc11 by WGS[2]. The observed outbreak stimulated the introduction of the ACWY conjugate vaccine programme for UK teenagers which replaced the previous MenC dose in teenagers.

Conclusion: The continued accurate surveillance and characterisation of meningococcal cases is essential to monitor the recent UK vaccine interventions and schedule modifications.

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

Funding source: UK Government

#D3: Whole genome sequencing for health protection action

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Keywords: Meningococci, surveillance, WGS

Background: Whole genome sequencing (WGS) is rapidly becoming a key component of microbial typing and outbreak tracking in public health. The highly reproducible fine discrimination offered to determine relatedness and clustering is a key advantage. However, there remain potential limitations, such as the requirement for isolates and receiving results within the time frame for health protection action. Moreover, the evidence base for what degree of genomic relatedness should trigger such action is not yet fully established.

Study objective: In Scotland, we retrospectively analysed data, from 2009-2018, to evaluate the potential impact WGS may have had for health protection purposes, had it been available real-time. This was achieved by retrospectively examining core genome MLST (cgMLST) profiles derived from WGS data for clusters that had previously been identified epidemiologically, and conversely, analysing cgMLST data to ascertain whether potentially linked cases may previously have been overlooked through traditional methods.

Results: Epidemiological analysis identified 10 clusters in a variety of settings. Of these, for five, WGS could offer no further insight, as isolates were not available, or available for only one case. Four clusters were independently detected using WGS data, and one putative epidemiological cluster was dismissed using WGS data, having a difference of more than 900 alleles. In contrast, WGS detected an additional eight novel putative clusters, and an additional case for one of the existent epidemiologically defined clusters. These putative clusters are undergoing further analysis to determine the likelihood of them being genuinely linked cases. A preliminary distance threshold of ≤ 30 alleles has been deemed appropriate to initiate such further investigation.

Conclusion: WGS data has shown great potential in aiding public health intelligence. However, this can only be utilised when the appropriate primary samples are available. Furthermore, the thresholds at which clustering investigation is triggered, for public health purposes, and linked cases confirmed needs further definition; a challenge with a organism displaying inherent marked differences in strain variability. This analysis therefore significantly contributes to the limited evidence base, particularly the proposed analytical threshold.

Funding source: NHS Scotland

#D4: Linking genomic, clinical and epidemiological data from meningococcal disease in Scotland

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Keywords: Meningococci, WGS, Sequelae, Genomics

Background: Linking clinical and whole genome sequencing (WGS) data promises insight into features associated with particular meningococcal strains. WGS data for all isolates in Scotland (2009-2016) were linked to individual patient data, including epidemiological, hospitalisation, prescribing, microbiological and death.

Study objective: To investigate patterns of disease linked with core genome MLST (cgMLST) and whole genome MLST (wgMLST) in terms of association with: clinical presentation, severity and outcome; underlying clinical risk factors; sequelae.

Results: WGS – Based on 337 isolates, clonal complex (cc) distribution followed known epidemiology, with increases in W and Y, plus a 2016 C increase.

Genomic analysis – A diverse population was revealed with cc. Detailed Bexsero® Antigen Sequence Typing (BAST) analysis enabled potential genomic coverage to either MenB vaccine to be determined.

Linkage of clinical datasets - The combined clinical dataset comprised 780 cases, of which 46% had WGS samples. Cases >65 years had increased risk of clinical complications, particularly sepsis, pneumonia, bone and kidney complications. Serogroups C, W and Y were associated with increased risk of clinical complications and death. There was an increased risk of pneumonia with serogroup Y, skin complications with serogroup C, and kidney complications with serogroups C, W and Y. Cc11 and 23 were associated with increased risk of complications. Sequelae differed by age, with those >65 years at increased risk of renal failure, amputation/bone and skin sequelae. Skin sequelae increased in those aged 1-4 years. For prescribing, pre-hospitalisation, antibiotics were increased, while post-hospitalisation, there was increased non-steroidals, arthritis and psychotropic drugs.

Linkage of clinical datasets to genomic data – An increased risk for ≥2+ complications was significantly associated with family 2 fHbp alleles or PorA VR2: 10-1, PorA VR2:2 or PorA VR2:9 expression, predominantly belonging to cc11 and cc269. Pneumonia was significantly associated with cg 120 (cc23, serogroup Y), while bone complications were significantly associated with Nm-cgc_200 120 or 65.

Statistical analysis – a hospital-based case-control study showed cases more likely to have previous cancer or diabetes diagnosis and more likely to have ≥1 previous diagnoses. Complication risks were compared between cases and controls and stratification employed to show risk by age-group.

Conclusion: Results will inform many future areas of work. These include:

- WGS analysis, which has now been incorporated into routine surveillance in Scotland,

- awareness of particular clinical complications and sequelae in certain age groups, particularly older ages

- further bioinformatic research to investigate genomic association

Funding source: Meningitis Research Foundation

#D5 Global epidemiology of serogroup Y invasive meningococcal disease: a literature review

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Keywords: Invasive meningococcal disease, surveillance, serogroup Y, incidence, vaccination

Aims: Invasive meningococcal disease (IMD) is associated with substantial morbidity and mortality worldwide and five serogroups (A, B, C, W, Y) are responsible for about 96% of IMD cases. Serogroup Y has recently increased in many European countries. We conducted a systematic literature review to assess the burden of serogroup Y IMD (IMD-Y) worldwide since 2010.

Methods: Through Embase and Medline, published studies between January 1 2010 and April 23 2019 and publicly available national and international surveillance reports for the years 2010 - 2018 were screened. The main outcomes were the incidence of IMD-Y and proportion of serogroup Y among all IMD cases. The results were described by geography and age groups.

Results: Of a total of 4001 articles, 557 articles were selected for full review of which 105 were included in our analysis including Europe (28), Australia (21), North America (20), Africa (15), Asia (12) and Latin America (9). Eighty-three national surveillance reports from 32 countries were also included. Serogroup Y was not specifically part of serogroups determined in early 2010 studies in Africa and Asia. The proportion (%) of serogroup Y among all IMD varied largely by region of the world. In Europe recent emergence of IMD-Y cases was observed in Norway, Sweden, Finland, France, Belgium, Netherlands and Australia over the last 5 years (2013-2017). Serogroup Y now represents 12% of all IMD in all ages with the highest proportion in Finland (56%), Norway (44%) and Sweden (31%) in 2017. Of all IMD-Y, the most affected age groups were those ≥65 years (41% in Europe; >40% in Finland, Germany, Netherlands, Sweden) and 15-24 years old (21% in Europe; >20% in Finland, Germany, Italy, Belgium and Spain) in 2017. Large decreases of IMD-Y cases were observed in the United States.

Conclusions: Recent increases in IMD-Y cases in young adults and older age groups warrants close monitoring. Significant benefits of MenACWY vaccine were observed in the United States with cases decreasing to <20 cases per year in the last 5 years. MenACWY vaccine recently replaced MenC vaccine in the UK, in Spain as an adolescent program and in the Netherlands and Australia as toddler and adolescent programs. IMD-Y emergence may necessitate a revision of meningococcal immunization policies.

Funding source: Pfizer Inc. Collegeville, United States

#D6 Incidence, complications and mortality of invasive meningococcal disease (IMD) in Europe: results from a systematic literature review

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Keywords: Invasive meningococcal disease, incidence, complications, mortality, morbidity

Background: Although rare and mostly vaccine-preventable, invasive meningococcal disease (IMD) continues to be a public health concern due to its severe morbidity with substantial short- and long-term consequences, and relatively high case fatality rate (CFR). Six serogroups (A, B, C, W, X, Y) of *Neisseria meningitidis* are responsible for almost all IMD cases. Serogroup epidemiology 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.

Aim: The aim of the review was to determine IMD clinical burden in EU-27.

Methods: A systematic review of PubMed, EMBASE and Cochrane Library databases was conducted (publication from 2000 to January 2018). Here we report the results of incidence, mortality, acute events and complications/sequelae for EU countries, for all age groups and serogroups.

Results: The highest incidence of IMD was reported in infants < 1 year old (median of 36/100 000).
Out of 182 included papers on IMD in EU-27 countries, 74 papers presented data on acute events and 37 on complications/sequelae, covering the period from 1974 to 2017. IMD main acute events reported were meningococcal meningitis (range: 3.6-89.2% of the cases, highest mean for serogroup B); meningococcal septicaemia (range: 0.0-100.0%, highest mean for serogroup C); and meningitis + meningococcemia (range: 0.0-64.5%, highest mean for serogroup Y). Neurological complications were more frequent with serogroup B, including hearing loss (range: 0.0-40.0%); seizure (range: 2.0-13.0%); motor deficit (range: 0.0-12.9%); and visual disturbance (range: 0.4-9.2%). The physical complications were more frequent with serogroup C, including skin scarring (range: 0.0-87.3%); amputation (range: 0.0-40.0%); renal dysfunction (range: 0.0-22.2%). Moreover our results showed a variation of sequelae depending on serogroup, the highest mean was observed for serogroup Y (range: 12.0-53.8%). Among vaccine preventable IMD, serogroup C, W and Y reported the highest mortality rate, with a CFR respectively 14.6%, 12.4% and 11.2%. Although B is the most prevalent serogroup in Europe, CFR was below 8%. For all IMD cases, the highest mortality rate was observed in adults and older adults (9.8% from 25-65 years and 28.4% above 65 years old).

Conclusion: The review highlights the high morbidity of IMD with variation according to serogroup and age groups. 18% of IMD survivors are affected by a broad range of sequelae which can impact their quality of life. Recent studies showed an increased incidence and spread of W & Y hypervirulent serogroups. The unpredictability and fatality of infection

suggest that immunization for disease prevention and accurate surveillance of the circulating serogroups can control the burden of IMD with adapted vaccination policies.

Funding source: Sanofi Pasteur

#D7 Genomic surveillance of invasive meningococcal disease in the Czech Republic, 2015-2017

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Keywords: whole genome sequencing; genomic surveillance; invasive meningococcal disease; Neisseria meningitidis

Introduction: The study presents the results of the genomic surveillance of invasive meningococcal disease (IMD) in the Czech Republic for the period of 2015–2017.

Material and Methods: The study set includes all available IMD isolates recovered in the Czech Republic and referred to the National Reference Laboratory for Meningococcal Infections in 2015-2017, a total of 89 *Neisseria meningitidis* isolates – from 2015 (n = 20), 2016 (n = 27), and from 2017 (n = 42). The isolates were assigned to serogroups by conventional serological methods (Pastorex Meningitidis Bio-RAD, antisera *N. meningitidis* ITEST, Bio-RAD). The next step was the isolation of DNA, using the QIAamp DNA MiniKit. All isolates were studied by whole genome sequencing (WGS), which was conducted by the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, using the Illumina MiSeq platform. WGS data was subsequently processed and optimised, using the Velvet *de novo* Assembler software. Genomes were then analysed and compared using the BIGSdb Genome Comparator tool using the core genome cgMLST scheme v1.0 for *N. meningitidis* (1605 loci). Distance matrices were generated automatically and phylogenetic networks constructed and edited using the SplitsTree4 software and the Inkscape tool.

Results: Serogroup B was the most common, followed by serogroups C, W, and Y. Altogether 17 clonal complexes were identified, the most common of which was hypervirulent complex cc11, followed by complexes cc32, cc41/44, cc269, and cc865. Over the three study years, hypervirulent cc11 (MenC) showed an upward trend. The WGS method showed two clearly differentiated clusters of *N. meningitidis* C: P1.5,2:F3-3:ST-11 (cc11). The first cluster is represented by nine isolates, all of which are from 2017. The second cluster consisted of five isolates from 2016 and eight isolates from 2017. Their genetic discordance is illustrated by the changing *nadA* allele and subsequently by the variance in BAST type. Clonal complex cc269 (MenB) also increased over the time frame. WGS identified the presence of MenB vaccine antigen genes in all B and non-B isolates of *N. meningitidis*. Altogether 49 different Bexsero antigen sequence types (BAST) were identified and 10 combinations of these have not been previously described in the PubMLST database.

Conclusions: The genomic surveillance of IMD in the Czech Republic provides data needed to update immunisation guidelines for this disease. WGS showed a higher discrimination power and provided more accurate data on molecular characteristics and genetic relationships among invasive *N. meningitidis* isolates.

Funding source: none

#D8 Clinical manifestation of invasive pneumococcal diseases in children – 2018, Czech Republic

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Keywords: Streptococcus pneumoniae, clinical manifestation, serotype

The surveillance of invasive pneumococcal disease (IPD) was implemented in the Czech Republic in 2007. A sensitivity of the surveillance has improved continuously, as confirmed by capture-recapture analysis. Pneumococcal conjugate vaccine (PCV) is available in the Czech Republic since 2005 ((PCV7). PCV was imlemented into the National Immunisation Program in 2010 (PCV10 and PCV13 equally). In the age group 0-4 years, we experienced pneumonia, sepsis and meningitis.

Objectives: The surveillance database is bringing together the data from the National Reference Laboratory (NRL) for Streptococcal Infections and ISIN data.

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 2018, 481 cases of invasive pneumococcal disease (IPD) were entered into the surveillance database merging the data of the NRL for Streptococcal Infections and ISIN.*

Funding source: Supported by Ministry of Health of the Czech Republic, grant nr.17-29256A.

#D9 Invasive bacterial diseases in young infants in rural Gambia: a population based surveillance study

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Keywords: Invasive bacterial diseases, young infants, population-based surveillance, Gambia, Rural

Background: Invasive bacterial diseases (IBD) cause significant morbidity and mortality in young infants globally. There are limited population-based data on the burden of IBD in sub-Saharan Africa.

Aims: To determine the incidence, aetiology and outcome of IBD in young infants in rural Gambia.

Methods: We conducted standardized, population-based surveillance for IBD among infants aged <91 days, residing within the Basse and Fuladu West Health and Demographic Surveillance Systems, in rural Gambia between March 2011 and December 2017. Children admitted to health facilities within the study areas had conventional microbiological investigations. All admitted children were eligible for blood culture. The primary endpoint was IBD defined as isolation of pathogenic bacteria from blood, cerebrospinal fluid, lung or pleural aspirate.

Results: During the study period, 3794 infants aged <91 days were admitted. 3605(95.0%) had at least one invasive sample collected for culture (3588 blood; 133 CSF; 16 lung aspirates and 2 pleural fluids). Samples from 428(11.9%) patients yielded contaminants. 254 (8.0%) episodes of culture-confirmed invasive bacterial diseases were detected (bacteraemia 234; meningitis 14; pneumonia 6)
The incidence of IBD in infants aged <91 days was 25/1000 person-years (95%CI 22 – 28). In infants aged 30 to <91 days, incidence of IBD was 12/1000 person-years (95%CI 9 – 15). In neonates, the incidence of IBD was 50/1000 person-years (95%CI 43 – 58) or 3.3/1,000 live births (95%CI 2.8 – 3.8). The incidence rate ratio of IBD in infants aged <30 days relative to infants aged 30 to <91 days was 4.26 (95% CI 3.25-5.63).
The most common bacteria causing IBD were *Staphylococcus aureus* (40%), *Escherichia coli* (15%), *Streptococcus pneumoniae* (9%) and *Klebsiella pneumoniae* (5%).The case-fatality ratios of IBD in infants aged <91 days; 30 to <91 days and neonates were 26%(95%CI 21-32); 19%(95%CI 11-29) and 29%(95%CI 23-37) respectively.

Conclusion: IBD is common in young infants in rural Gambia with high case-fatality. Maternal or neonatal prevention strategies are needed to prevent IBD in young infants.

Funding source: Bill and Melinda Gates Foundation

#D10: Gonorrhoea: The State of Surveillance Globally and Observed Burden of Infection

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Keywords: Neisseria gonorrhoeae, epidemiology, surveillance, prevalence

Background: In 2016, 87 million cases of gonorrhoea were estimated among adults worldwide and globally, incidence is increasing. Gonorrhoea is frequently asymptomatic and, if left untreated, it causes pelvic inflammatory disease, ectopic pregnancy and infertility, epididymitis in men, and can facilitate human immunodeficiency virus (HIV) transmission. Accurate estimation of the burden of infection remains challenging due to substantial under diagnosis and underreporting. In this review, we evaluate the prevalence of urogenital, rectal and pharyngeal infection in the general population and in population subgroups at increased risk, including men-who-have-sex-with-men (MSM) and sex workers, and describe the state of gonorrhoea surveillance at national level in 104 countries globally.

Methods: We conducted a systematic search of the literature, according to PRISMA guidelines, for papers published from 22 August 2008 to 11 April 2019. The primary outcome of interest (prevalence of gonorrhoea) was the proportion of positive tests per number tested at the study level. Studies were included according to pre-specified inclusion criteria. Estimates were adjusted for laboratory test performance and geographic location. The systematic search was supplemented with a grey literature online search of websites, data repositories and surveillance reports of national, regional and international or public health and /or governmental agencies to provide contextual information about the surveillance systems in each country or region.

Results: Data are reported from 235/2042 empirical studies reviewed and 12 data repositories, including routine (inter)national and surveillance reports. Overall, prevalence or surveillance data from 104 countries are presented. In the general population (both men and women), prevalence was highest in Oceania and countries in Southern and Sub-Saharan Africa. Among MSM, more than 70% of reported prevalence of urethral and/or rectal and/or pharyngeal infection ranged from 1%-10%, with highest rates reported for rectal infections. Among sex workers, prevalence estimates across all countries were approximately 10x higher than the general population.

Conclusion: Prevalence studies highlight the magnitude of the infection burden, particularly in MSM and sex workers globally, but there is a lack of standardized gonorrhoea monitoring, reporting and surveillance is weak or absent in many countries. At local, national and regional level, serial prevalence monitoring at intervals, including assessment and reporting of a minimum set of epidemiological variables on the infection, should be considered to optimize evaluations of the burden of disease and maximize the utility of the data collected to inform STI control programs.

Funding source: GlaxoSmithKline Biologicals SA

#D11 Systematic review and meta-analyses of Group B Streptococcus serotypes worldwide distribution, sequence types and virulence to inform vaccine development

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Keywords: Group B Streptococcus, vaccine, serotypes, whole genome sequencing, proteins

Objective: More than 21 million women are estimated to carry Group B streptococcus (GBS), resulting in invasive infant disease, but also consequences for pregnant women, stillbirths and preterm births. We aimed to synthesise data on circulating GBS serotypes/strains worldwide characterised by their capsular polysaccharide or multi-locus sequence types (MLST), in order to inform vaccine development.

Methods: We conducted systematic literature reviews, and did meta-analyses to obtain pooled estimates of the proportions of GBS serotypes (1) colonising mothers and causing (2) invasive disease in pregnant women, (3) stillbirths, (4) infants, and (5) older adults (over 60 years), considering variation by region and over time (before 2000 compared to 2018). Information about antibiotic resistance was abstracted and descriptively reported.

Results: Serotype III was the most common serotype (33% of all isolates), serotypes Ia, Ib, II, III, IV and V collectively account for more than 93% of all isolates. Serotypes differ by age group affected, particularly between early and late onset infant invasive disease, with ST17 to be most highly associated with infant invasive disease, and the overall proportion of ST17 was 24.96% (95%CI: 20.1-30.0). Resistance to any first line antibiotic treatment ranged from 0% to 10%, while resistance to at least one of the second line antibiotics ranged from 0% to 95%.

Discussion: Despite some regional variation, currently the most common serotypes worldwide (Ia, Ib, II-V) would be included in a hexavalent vaccine, covering up to 98% of GBS isolates. Surveillance of GBS disease-causing serotypes and sequence types in all regions of the world is fundamental to ensure an effective implementation.

Funding source: The Bill & Melinda Gates Foundation, Seattle, WA (OPP1180644)

#D12: Meningococcal Disease (MCD) in England from 2014 to 2019: A Five-Year Healthcare Resource Use Study using an Administrative Electronic Dataset

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Keywords: Meningococcus, Data Science, Real World Data, Healthcare Resource Use, Disease Surveillance

Neisseria meningitidis are gram-negative bacteria that cause serious infections which can rapidly progress, leading to permanent disability and even death. Six of the 13 strains of meningococcus (A, B, C, W, X, and Y) are the cause of the majority of infections. Young children, teenagers and young adults are most at risk of meningococcal disease (MCD). Vaccination programmes have been effective in reducing cases over time.

This descriptive study assessed the health care resource burden of MCD in England's secondary care setting using Hospital Episode Statistics (HES), an administrative dataset covering all healthcare interactions in secondary care.

The analysis included non-elective admissions of patients diagnosed with MCD through ICD-10 coding (A39) in any diagnosis position from 1 April 2014 to 31 March 2019, covering five full financial years (FYs). Patients with ante-/peri-/post-natal activity were excluded. Data extraction was performed through DB Visualizer Pro 10.0.10 and validation was performed by two independent analysts.

The study included 4,021 patients with a slight male predominance (51.3%), covering 684,154 patient-days of follow-up, with a mean age of 29.2 years (median 17 years).

There was a decrease in the number of patients who were admitted for meningococcal disease from 974 in FY2014-2015, to 590 in FY2018-2019.

Two peaks of incidence were noted overall at ages 5-10 years and 18-21 years. There was a larger peak number of cases at ages 0-2 years in FY2014-2015 which disappeared from FY2015 onwards, with the two peaks at 5-10 and 18-21 years stabilizing until the last FY in the study.

There were 5,503 non-elective admissions, decreasing from 1,332 (FY2014-2015) to 1,118 (FY2018-2019). Mean length of stay increased from 6.85 days to 9.02 days, possibly signalling increased severity of these cases. The 28-day readmission rates have remained the same (0.19 per patient), although this decreased in absolute numbers (185 to 112). The total cost of non-elective admissions for meningococcal disease was £13,846,223 throughout the 5-year period (Mean: £4,006 per patient). There were a total of 220 inpatient mortalities, with the annual rate increasing from 4.00% to 6.61%. 4,553 A&E visits were recorded, costing £504,992 over the 5-year period.

The results of this analysis show that MCD poses a significant burden to the NHS. This study focused on the acute phase of the disease, further analysis is needed to explore the cost-burden associated with long-term sequelae. Strengthening prevention through optimisation of vaccination programs may assist in reducing overall burden.

Funding source: Sanofi Pasteur, Health iQ Ltd

#D13 The relationships between respiratory viral infections and meningococcal carriage in healthy adolescents

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Keywords: Meningococcus, carriage, rhinovirus, virus, density

We explored the associations between respiratory viral infection and presence and density of meningococcus using the opportunity of serial throat swabs obtained from a subset of Bristol recruits to the UKMenCar4 study in 2014-2015.

Of 1813 students recruited to UKMenCar4 who had throat swabs taken, 917, including all those willing whose initial swab was meningococcus PCR+ were enrolled for up to 5 further swabs taken over the winter at monthly intervals into STGG broth and frozen until analysis. Nucleic acid extracts were subjected to quantitative PCR analysis for meningococcus(porA) and a respiratory virus panel (rhinovirus (RhV), influenza (flu) A H1 and H3 and B, parainfluenza viruses 1,2 and 3 (PF), respiratory syncytial virus (RSV), adenovirus, human metapneumovirus and enterovirus). Data were analysed using logistic regression, including exact and mixed effects models as appropriate to take clustering and meningococcal carriage in a previous sample into account.

433/5448 samples tested positive for at least one virus (323 RhV, 46 flu, 37 RSV, 15 PF, 11 AdV) but most individual viral species were too rare for analysis. Although 276/917(30%) students who had multiple samples had a virus detected at least once, only 46(5%) had more than one positive test and only RhV was detected at more than one visit in the same student (n=22). In contrast multiple *porA* carriage-positive visits were seen in 67 (7.3%) of these 917 students; the number of students who had 2, 3, 4 and 5 carriage-positive visits was 34, 20, 9 and 4, respectively. The co-incident detection of RhV corresponded to an approximately 3(95%CI 1.05–9.0) fold increase in density of meningococcus ($p<0.043$) but no association between presence of RhV or any virus in the previous sample and meningococcal density in the following sample was found. Little evidence was found to suggest that detection of a virus in the previous or the same sample was associated with an increased likelihood of detection of meningococcus. An association was observed for RSV in the initial samples (OR 6.33 $p=0.02$) but numbers were small and confidence intervals wide.

Investigating the relationships between viral infections and bacterial colonisation in healthy adults is challenging because the former are relatively unusual. This study provides evidence that intercurrent RhV infection may be associated with increases in meningococcal density which could result in increased onward transmission. In contrast, evidence that viral infection may cause increased acquisition and so higher carriage rates was not found. However absence of evidence relating to other respiratory viruses than RhV in this study may reflect the relatively small number of samples in which they were detected.

Funding source: Meningitis Research Foundation, NIHR-Health Protection Research Unit in Evaluation of Interventions, University of Bristol, Wellcome Trust.

#D14 Invasive Meningococcal Disease Epidemiology in the Eastern Mediterranean and North African Region

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Keywords: Invasive meningococcal disease, epidemiology and Surveillance, Carriage, Serogroup distribution, Middle-East and North Africa

Objective: People living in the Eastern Mediterranean and North African (EMNA) Region are at risk of invasive meningococcal disease (IMD) partly due to the Hajj mass gathering and proximity to the meningitis belt. We conducted a systematic review to describe the epidemiology and burden of IMD in the EMNA region.

Method: MEDLINE and EMBASE were searched for publications from January 2000 to December 2018 covering Eurasia, Middle East, and North Africa. Articles were selected by screening the titles and abstracts, followed by a full-text screening. A grey literature search was conducted to complete the peer-reviewed literature. Relevant data from the included articles were summarized using standard data-extraction forms. Data on carriage, incidence, and mortality were extracted and stratified by age groups (children only, adults only, and children and adults) and risk groups (military, students, pilgrims, and household contacts)

Results: Out of 1,038 unique records, 83 articles were included of which 71 studies were conducted in the EMNA region. Meningococcal carriage was reported in 4 countries. From 2000 to 2018, the carriage rate among the risk groups ranged from 0.0% to 27.4% in pilgrims, 0.6% to 12.3% in students, 0.1% to 32.9% in military recruits, and was 25.6% in household contacts. Among the general population, the carriage rate ranged from 0.0% to 11.0%. Incidence rates were reported in 5 countries in the Middle-East and only in Egypt in North Africa. Data were scarce and varying. Heterogeneous serogroup distribution of IMD was observed in 9 countries. Serogroups W and B dominated in the last decade in the Middle-East followed by serogroup A. In North Africa, serogroups A and B dominated followed by serogroup C. Mortality and complication rates were high in children to up to 60% with heterogeneous data by country and period. The overall quality of the included studies appears to be low with significant heterogeneity in the methodology and reporting.

Conclusion: High risk groups remain a significant reservoir of meningococcal carriage. The incidence of IMD in the EMNA region is not well defined yet. Data are heterogeneous and may not reflect the true disease burden and serogroup distribution across the EMNA region. Improving national surveillance systems and laboratory capacity as well as increasing awareness for the systematic collection of suspected meningitis and septicaemia are crucial to understand IMD epidemiology and design health policies to reduce its burden

Funding source: This systematic review is funded by Sanofi Pasteur

Support and care for people affected by meningitis

#S1 Believe & Achieve – supporting young people after meningitis and meningococcal disease

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Keywords: Meningitis, support, wellbeing, skills, adolescence

Background: Meningitis Now's extensive experience of supporting people, together with more specific research activity, provided valuable insight into the impact meningitis can have on teenagers and young people. In addition to the physical impact of the disease, young people can experience anxiety and isolation that affect their education, employment and social lives [1-3]. Evaluation of existing services, such as Family Days for younger children and their parents/carers, also identified a lack of continuing support for this age group. Believe & Achieve, an individualised programme of support and activities for young people aged 14 – 25 years affected by meningitis, was developed to meet this need.

Development of Believe & Achieve

The framework for Believe & Achieve was developed in consultation with young people affected by meningitis and professionals from other relevant organisations. Staff working on the programme are trained in mentoring, impact measurement and evaluation.

The project outcomes are:

1. Young people will gain new skills and opportunities to better equip them for education, employment and a successful future
2. Young people will become more emotionally resilient and will face the future with confidence and optimism
3. Young people will create a dynamic community of support, inspiring each other to lead more healthy, active and fulfilled lives

The Outcomes Star™ [4], a family of evidence-based tools for measuring and supporting change, is used to help young people identify their own needs and priorities in life, education and work.

Believe & Achieve launched in March 2019.

The first 18 months

100 young people have accessed the programme through events, activities, one to one support or online information.

Skills workshops (82 attendees) have included:

- Coping with change and dealing with stress
- Cooking and budgeting
- Health and fitness
- Social media

Coaching and mentoring have resulted in improved communication skills and ability to interact with others.

Most young people accessing counselling reported improved coping strategies and emotional resilience, but half requested more sessions.

Meeting others and undertaking challenging activities together at a residential weekend (11 attendees) improved confidence and inspired young people to face new challenges and support each other.

Plans for the future

Evaluation of the first year has identified the overall benefit of the programme, with young people continuing to guide its development and improvement. Peer mentoring will be expanded and the need for ongoing emotional wellbeing support will be addressed.

Funding source: National Lottery (Community Fund), BBC Children in Need, St James' Place, The Gannochy Trust

#S2 Late onset Group B Streptococcal (LOGBS) infection: insights from affected families:

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[1]Group B Strep Support

Keywords: Late-onset, Group B Streptococcus (GBS), Sepsis, Meningitis, Survey

Objectives: GBS is recognised as the UK's most common cause of life-threatening infection in newborn babies, and the main cause of meningitis in babies <90 days. Research has rarely focused on the family experience of LOGBS infection at the time of the baby's illness and subsequently. We use survey data to explore the health, social and financial issues faced by affected families, with a focus on meningitis and sepsis.

Methods: An online survey (n=535) of parents and carers of babies affected by LOGBS infection was commissioned by charity Group B Strep Support. Participants were asked questions about their awareness of GBS status in pregnancy and about whether IV antibiotics were administered in labour. They were asked about the clinical course of their baby's LOGBS infection, and about the longer-term health, social and financial consequences of their baby's illness.

Results: 55% of babies made a full recovery from LOGBS infection, 32% recovered with long-term sequelae and 13% died. The most common clinical presentations of confirmed LOGBS infection were sepsis (47%), meningitis (39%) and pneumonia (6%).

Hospital stays were significant, with over 50% of babies requiring a stay of 3 weeks or longer. Parents reported practical difficulties associated with the hospital stay, including caring for other children at home, obtaining food and drink for themselves, finding parking and finding accommodation, plus financial difficulties including taking time off work and paying for parking.

The impact of LOGBS infection continued long after the initial illness. Family dynamics were changed, with 29% of parents with other children reporting that siblings experienced difficulty as a result of the baby's LOGBS infection. 39% of parents reported financial problems associated with their child's LOGBS infection; 70% of parents reported issues with their own or their family's mental health and 67% with reported reduced enjoyment of subsequent pregnancies as a result of their baby's LOGBS infection.

Conclusions: These data give a unique insight into what families may be experiencing during and after LOGBS infection, including in subsequent pregnancies. These data allow health professionals to reflect on the care, support and information these families may need, and suggest that long term issues remain for many families, impacting mental health and family dynamics, even where the baby has made a full recovery from LOGBS infection.

Funding source: Group B Strep Support

#S3 The Dutch 20|30 Postmeningitis study: a cross-sectional follow-up study of ex-meningitis patients between 20 and 30 years of age on long- term outcome

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Keywords: childhood bacterial meningitis, sequelae, quality of life, adolescents, functioning

This study aimed to provide more insight into long-term effects of childhood bacterial meningitis. The most common severe to moderate sequelae of bacterial meningitis are sensorineural hearing loss, neuromotor disabilities and mental retardation. Subtle sequelae that might occur are mainly academic and/or behavioural disabilities. Considering subtle sequelae, it is largely unknown whether these sequelae persist in adolescence and adulthood. Better understanding of long-term effects and early identification of adverse outcome after bacterial meningitis can be of importance to be able to provide a tailored intervention for each patient, if necessary.

Adolescents and young adults who encountered childhood bacterial meningitis (N = 947) were invited to determine executive and behavioural functioning, health- related quality of life, subjective hearing, mood and sleeping disorders, academic performance, and economic self-sufficiency cross-sectionally by using internet-based questionnaires.

The present study is a follow-up study of a study initiated in the Netherlands in 1999 to determine the incidence and course of adverse consequences after childhood bacterial meningitis in patients who encountered bacterial meningitis between January 1990 and December 1995 (first cohort). And patients who survived bacterial meningitis between January 1997 and December 2001 (second cohort). For this study patients from both cohorts were invited to participate.

During the present study 534 patients registered online to complete the questionnaires of which 488 registrations were useful. 45,2% (221) of this group were male. Currently, the young adults of the first cohort (N=321) have a median age of 28 years (IQR 27.0-30.0) and time since infection is approximately 24 years. For the young adults (N=167) from the second cohort time since infection is approximately 19 years and the median age is 22 years (IQR 21.0-24.0).

Preliminary results show that subtle sequelae are present and do persist over time. Especially physical health which was measured as part of quality of life was reduced in survivors of childhood bacterial meningitis compared to general population norms. The incidence of sensorineural hearing loss was 8,6% (42 from 488). However, the remaining survivors also show reduced self-perceived hearing abilities.

In conclusion apart from severe impairment after childhood bacterial meningitis, subtle sequelae persist in adolescence and therefore can impact quality of life.

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