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Prevention and epidemic control

#P1 A Phase 3 Trial of Safety, Tolerability and Immunogenicity of V114, 15-Valent Pneumococcal Conjugate Vaccine, Compared with 13-Valent Pneumococcal Conjugate Vaccine in Adults 50 Years of Age and Older (PNEU-AGE)

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Keywords: Pneumococcal conjugate vaccine adults immunogenicity

Background The incidence of pneumococcal disease (PD) has declined since the introduction of pneumococcal conjugate vaccines (PCVs). However, unmet medical need remains for vaccines with broader serotype coverage. V114 is an investigational 15-valent PCV containing the 13 serotypes in licensed 13-valent pneumococcal conjugate vaccine (PCV13) plus serotypes 22F and 33F. Serotypes 22F and 33F contribute significantly to PD burden. This phase 3 study evaluated the safety, tolerability, and immunogenicity of V114 in adults compared with PCV13.

Methods Adults ≥ 50 years of age in generally good health and/or with stable chronic medical conditions were randomised 1:1 to receive a single dose of V114 (n=604) or PCV13 (n=601). Randomisation was stratified by age (50–64 years, 65–74 years and ≥ 75 years). Safety was evaluated as the proportion of participants with adverse events (AEs). Pneumococcal serotype-specific opsonophagocytic activity (OPA) and IgG were measured prior to and 30 days after vaccination (Day 30). Primary objectives included demonstration of noninferiority of immune responses at Day 30 for the 13 shared serotypes between V114 and PCV13 and superiority of V114 to PCV13 for the two unique serotypes, 22F and 33F. Superiority of V114 to PCV13 for shared ST3 was assessed as a secondary objective.

Results The most common AEs across both groups were the solicited AEs of injection-site pain, fatigue, and myalgia. V114 met noninferiority criteria compared to PCV13 for the 13 shared serotypes as measured by serotype-specific OPA geometric mean titers (GMTs) at Day 30. V114 met superiority criteria compared to PCV13 for serotypes 3, 22F, and 33F as measured by OPA GMTs at Day 30 as well as based on the proportions of participants with a ≥ 4 -fold rise in OPA from prevaccination to Day 30.

Conclusions In healthy adults ≥ 50 years of age, V114 has a safety profile comparable to PCV13 and elicits an immune response that is noninferior to PCV13 for the shared serotypes, and superior to PCV13 for serotypes 3, 22F, and 33F. This pivotal study is in support of licensure and use of V114 for the prevention of PD in adults.

Funding source This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

#P2 Phase 3 trial to evaluate safety, tolerability, and immunogenicity of V114 followed by 23-valent pneumococcal polysaccharide vaccine 6 months later in at-risk adults (PNEU-DAY)

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Keywords: Pneumococcal conjugate vaccine adults immunogenicity

Background: Risk factors for pneumococcal disease (PD) in immunocompetent individuals include comorbidities (e.g., chronic lung, liver or heart disease and diabetes mellitus), behavioural habits (e.g. smoking) or living in a community/environment with increased risk of PD transmission. Pneumococcal vaccination of adults is recommended with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) alone or sequentially with a pneumococcal conjugate vaccine (PCV). V114, an investigational 15-valent PCV, contains all 13 serotypes in PCV13 plus two epidemiologically important serotypes, 22F and 33F. This descriptive phase 3 study evaluated safety, tolerability and immunogenicity of V114 and PCV13 administered on Day 1, and PPSV23 6 months later, in immunocompetent adults aged 18–49 years with or without risk factors for PD.

Methods: Eligible adults (n=1515), including a cohort of Native Americans (n=593), were randomised 3:1 to V114 (n=1135) or PCV13 (n=380), followed 6 months later by PPSV23. Randomisation was stratified by type/number of risk factors and site of enrolment. Solicited adverse events (AEs) were collected after each vaccination. Serotype-specific opsonophagocytic activity (OPA) was measured 30 days after each vaccination.

Results: Most participants (54.7%) had one risk factor; 25.2% had no risk factors; 20.1% had ≥ 2 risk factors. The most frequent individual risk factors were smoking (14.6%), chronic lung disease (14.3%) and diabetes mellitus (13.8%). The most common solicited AEs following V114 or PCV13 as well as PPSV23 were injection-site pain and fatigue, and the proportion of participants with AEs were comparable in both groups. V114 and PCV13 were immunogenic based on OPA geometric mean titres (GMTs) 30 days post-vaccination for all serotypes contained in each respective vaccine. OPA GMTs to the two unique serotypes in V114 were robust in the V114 group. PPSV23 was immunogenic for all 15 serotypes contained in V114 in both vaccination groups, including 22F and 33F.

Conclusions: V114 administered alone or sequentially with PPSV23 is well tolerated and immunogenic for all 15 serotypes, including those not contained in PCV13, in immunocompetent adults aged 18–49 years with or without risk factors for PD. This study is in support of licensure and use of V114 for the prevention of PD in adults.

Funding source: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

#P3 Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of V114 in Healthy Infants, Children, and Adolescents (PNEU-PLAN)

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Keywords: Pneumococcal conjugate vaccine infants immunogenicity

Background: Despite widespread use of pneumococcal conjugate vaccines (PCVs) in children, morbidity and mortality caused by pneumococcal disease (PD) remain high, in part due to the emergence of disease caused by non-vaccine serotypes (STs). In addition, many children do not receive the recommended number of PCVs on schedule and, therefore, are at risk for PD. V114 is an investigational 15-valent PCV that contains two epidemiologically important STs, 22F and 33F, in addition to the 13 STs present in the licensed 13-valent PCV (PCV13). This Phase 3 descriptive study evaluated the safety and immunogenicity of V114 and PCV13 when given as catch-up vaccination in children who are pneumococcal vaccine-naïve or previously immunised with lower valency PCVs.

Methods: Solicited adverse events (AEs) were collected for 14 days after each vaccination. Serious adverse events (SAEs) were collected throughout study participation. Immunogenicity was evaluated by anti-pneumococcal polysaccharide ST-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days post-last vaccination.

Results: 606 healthy children, aged 7 months through 17 years, were randomised (double-blind) to receive V114 (n=303) or PCV13 (n=303) via age-appropriate catch-up vaccination schedules. V114 had an acceptable safety profile and was well tolerated. Similar proportions of children aged 7–11 months and 2–17 years reported AEs in the V114 and PCV13 groups. A larger proportion of children aged 12–23 months reported AEs in the V114 group (79%) than the PCV13 group (59%). The proportion of children who reported SAEs was comparable among vaccination groups (V114 and PCV13, respectively, 7–11 months: 10.9%, 7.8%; 12–23 months: 6.5%, 6.3%; 2–17 years: 2.3%, 2.3%). No SAEs were reported to be vaccine-related, and no deaths occurred. At 30 days after the last PCV dose, ST-specific IgG GMCs were comparable for the 13 shared STs and were higher in the V114 group for 22F and 33F.

Conclusions: Catch-up vaccination with V114 in healthy children aged 7 months through 17 years had an acceptable safety profile, was well tolerated, and provided comparable immune responses to the 13 serotypes shared with PCV13, and higher immune responses to serotypes 22F and 33F.

Funding source: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

#P4 A Phase 3, Multicenter, Randomised, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION)

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Keywords: Pneumococcal conjugate vaccine infants immunogenicity

Background Pneumococcal diseases (PD) caused by *Streptococcus pneumoniae* are a major health concern globally. In children, currently licensed pneumococcal conjugate vaccines (PCVs) provide protection against PD from vaccine serotypes, but other non-vaccine serotypes have emerged and contribute to most residual disease. V114 is a 15-valent investigational PCV containing serotypes 22F and 33F in addition to the 13 serotypes shared by Prevnar 13™ (PCV13). This phase 3 study evaluated safety and immunogenicity of mixed PCV13/V114 regimens when changing from PCV13 to V114 at doses 2, 3, or 4.

Methods In this double-blind trial, 900 infants were randomised in equal ratios to five treatment groups using a 3+1 immunisation schedule (3-dose infant primary series followed by one toddler dose). Groups 2, 3, and 4 started with PCV13 and switched to V114 at doses 4, 3, and 2, respectively. Groups 1 and 5 received four doses of PCV13 and V114, respectively. Immunoglobulin G (IgG) responses to the 15 pneumococcal serotypes in V114 were measured at 30 days post-dose 3, prior to dose 4, and 30 days post-dose 4 (PD4). Primary immunogenicity analysis was based on 13 shared serotype responses at PD4. Safety was evaluated as the proportion of participants with adverse events (AEs).

Results At 30 days PD4, IgG geometric mean concentrations (GMCs) for the 13 shared serotypes were generally comparable between V114/PCV13 mixed regimens (Groups 2-4) and participants that received the 4-dose PCV13 regimen (Group 1). Additionally, IgG GMCs for the 13 shared serotypes were generally comparable for participants that received the 4-dose V114 regimen (Group 5) and participants that received the 4-dose PCV13 regimen (Group 1). Infants given at least one dose of V114 mounted immune responses to two unique serotypes in V114 (22F and 33F). Frequency of injection-site and systemic AEs among study participants were generally comparable across all study groups.

Conclusions V114 was well tolerated with a generally comparable safety profile to PCV13. For the 13 shared serotypes, both mixed-dose and 4-dose regimens of V114 induced generally comparable antibody responses to a PCV13 4-dose regimen. Study results support interchangeability of V114 with PCV13 in infants.

Funding source: This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

#P5: Evolution of the routine childhood meningococcal immunisation schedule in the UK and Ireland and its impact on the clinical burden of invasive meningococcal disease

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Keywords: IMD, meningococcal immunisation, childhood, schedule

Background Invasive meningococcal disease (IMD) is the leading infectious cause of death in early childhood in the UK and Ireland. Control of IMD is a public health priority, with vaccination the mainstay of IMD prevention. Disease monitoring and surveillance guide the evolution of meningococcal vaccination schedules in response to the changing epidemiology and protect those most at risk.

Objectives and methods We reviewed publicly available national health surveillance data for the UK and Ireland to understand the evolution of the routine childhood meningococcal immunisation schedules and evaluate their impact on IMD.

Results:

MenC vaccination: High uptake of infant MenC vaccine, introduced from 1999 in response to rising MenC-IMD incidence, led to >90% reductions in cases within 5 years. Subsequently, MenC schedules have evolved to maintain optimum protection, with an adolescent booster MenC dose introduced in 2013 to provide herd protection by reducing nasopharyngeal carriage. The incidence of MenC-IMD remains low, but there has been a slight rise in cases over the last few years.

MenACWY vaccination: From 2015, the adolescent MenC vaccine was replaced with quadrivalent MenACWY vaccine in response to a rising incidence of MenW-IMD since 2009, with highest carriage rates in adolescents. In England, it has been estimated that the adolescent MenACWY vaccine has indirectly prevented between 114 and 899 MenW cases in children <5-years-old during the first four years after its implementation.

MenB vaccination: Since introduction of MenC vaccine in 1999, MenB has been the most common serotype in the UK and Ireland, accounting for almost 90% of IMD cases in 2008. Introduction of a MenB vaccine for infants from 2015 led to a decline in MenB disease, and during the epidemiological year 2018/2019, MenB accounted for <60% of total IMD.

Overall, IMD cases have continued to decline since the introduction of the vaccination schedules. During 2019/2020, there were 491 confirmed cases and 30 deaths from IMD in England (compared with 2,595 cases and 159 deaths in 1999/2000), and overall incidence remains stable in England at 1/100,000 since 2011/2012. Meningococcal vaccine uptake is generally high but remains below 95% across many areas of the UK and Ireland.

Conclusion Routine childhood vaccination against IMD in the UK and Ireland has led to significant reductions in clinical burden. High vaccine uptake and continued disease surveillance are crucial to ensure optimum protection and prevention of IMD and enable modification of the schedule should new meningococcal strains emerge.

Funding source: Sanofi Pasteur

#P6 The Evolution of the UK School-Age Vaccination Programme

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Keywords: School-age, vaccination, prevention, schedule, evolution

Routine vaccination remains the single most effective way to protect against infectious diseases,¹ promote social good and protect the vulnerable through herd protection². Herein we provide an overview of the history of the UK school-age vaccination, examples of how the schedule has changed in this cohort and how the programme could adopt the learnings from COVID mass vaccination campaigns in future iterations.

The school environment allows for large numbers of young people to be vaccinated effectively in a relatively short period of time and has the capacity to reach out to those who would otherwise remain unvaccinated or partially vaccinated in the community³.

Table 1 illustrates examples of the introduction and removal of some early vaccinations in school-age cohorts within the UK vaccination programme⁴:

Vaccine	Introduction	Removal	Notes
Bacille Calmette-Guérin	1953	2005	Replaced with targeted service for babies and high-risk
Live Oral Polio Vaccine (OPV)	1964	2004	Last case of naturally occurring Polio in UK in 1984, Europe declared Polio free in 2002 ⁵ .
Adolescent Diphtheria and Tetanus boosters	1994	2004	This was replaced by inactivated Td/IPV in 2004, replacing the DT + OPV given separately.
MMR	1988	-	2008 saw nationwide catch-up programs for individuals < 18 yrs of age yet to have two doses
HPV	2008 (girls)	-	Extended to boys in 2019
MenC	2013	2015	Replacement with MenACWY
Nasal flu	2013	-	2021: fully extended to all children in school from reception age through year 11

Table 1 Examples of the introduction and removal of some early vaccinations in the school-age cohorts

The successes of COVID mass vaccination could be applied to the school-age vaccination programme: COVID mass vaccination adopted a multi-faceted approach from the outset; involving local Clinical Commissioning Groups, primary care managers, doctors, nurses, pharmacists, retired professionals and volunteers all working together to provide an efficient and timely service⁶. Community hubs e.g. sports grounds were used to increase accessibility⁷. School aged vaccinations could benefit similarly from an improved joint directive defining the responsibility for service provision between the school immunisations teams, GP's and the education Service to ensure young people receive their vaccinations. The value of mass vaccination clinics for borough wide school catch-ups should also not be discounted.

Post-pandemic vaccine awareness is at an all-time peak. This opportunity should be utilised to increase understanding and address (mis)information spread particularly through social media. Health professionals must be able to constructively respond to vaccine myths and provide relevant education to support and encourage vaccination⁸.

Funding source: Sanofi Pasteur

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#P7 Recent advances in meningococcal B disease prevention: real world evidence from 4CMENB vaccination

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Keywords: # 4CMenB ; # effectiveness ; # vaccine ; # meningitis; # meningococcus serogroup B

BACKGROUND AND OBJECTIVES: The 4-component meningococcal serogroup B (MenB) vaccine (4CMenB) was licensed in 2013 based on immunogenicity and safety data. Considerable real-world data describing its impact, effectiveness and safety have only recently accumulated following 4CMenB program introduction.

METHODS: Available evidence on vaccine impact (VI), effectiveness (VE) and safety of 4CMenB in routine use were reviewed.

LEARNING POINTS DISCUSSION: Estimates of VE are available from 5 countries obtained during funded routine use in the United Kingdom (UK) and Italy; a healthcare setting in Portugal; a prospective observational study in South Australia; and outbreak control in Saguenay-Lac-Saint-Jean, Canada. VE of at least 3 doses of 4CMenB administered to infants ranged from 59.1% to 93.6%, and estimates were usually higher than predicted strain coverage rates using the Meningococcal Antigen Typing System (MATS). VE in children and adolescents (including 2 months to 20-year-olds in Quebec), was 100% in the first 2-3 years after vaccination. Effectiveness was sustained for 4 years in Quebec and for 2 years after the booster dose in young children vaccinated in infancy in the UK.

The impact of 4CMenB on MenB invasive disease was demonstrated in infants in the UK, Italy, and Spain, and in children/adolescents/young adults in prolonged outbreaks in Saguenay-Lac-Saint-Jean and South Australia. VI on university/college outbreaks cannot be measured due to the small number of cases. However, the absence of breakthrough cases after vaccine implementation is suggestive of VI. The safety profile of 4CMenB administered in real-world settings appears to reflect that established in pre-licensure clinical trials. No safety concerns have been raised in post-marketing surveillance.

CONCLUSIONS: The substantial body of data demonstrating 4CMenB effectiveness and impact in real-world settings supports its use in IMD prevention.

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#P8 Identification of *Neisseria meningitidis* specific patient derived antibodies using reverse vaccinology 2.0

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Keywords: Vaccines, monoclonal antibodies, complement deposition

Our study aimed to clone *N. meningitidis* specific antibodies from patients recovering from meningococcal disease and assess their ability to bind to and kill *N. meningitidis*. By identifying the targets of these antibodies on the bacteria, we could identify potential vaccine antigens. Ideal vaccine candidates will be highly conserved, surface-exposed proteins which induce serum bactericidal antibodies against *N. meningitidis*.

Blood was taken from patients and their peripheral blood mononuclear cells (PBMCs) were isolated. Plasmablasts were single cell sorted from patient PBMCs using FACS, and IgG antibodies were cloned. Currently we have cloned 35 anti-meningococcal human monoclonal antibodies (hmAbs) from six patients that display binding to one or more meningococcal strains. Antibody binding was confirmed using ELISA and flow cytometry against a panel of 20 meningococcal strains. Some hmAbs bind to a conserved target, with hmAb P09-2F2 binding to 14 out of the 20 strains tested. A selection of hmAbs were tested in functional assays including serum bactericidal antibody assay (SBA) and complement deposition assay (CDA). To date three hmAbs have shown killing in SBA, the correlate of protection for licensing meningococcal vaccines, whilst nine have been shown to recruit C3c and/or C5b-9 of the human complement system in a CDA.

The target antigen size of five antibodies has been identified using western blot and do not correlate to the size of the vaccine antigens present in Bexsero. Immunoprecipitation followed by mass spectrometry analysis has five potential targets for two antibodies, and future work will focus on confirming the identity of these target antigens.

The results show that reverse vaccinology 2.0 can be used to successfully clone meningococcal specific hmAbs from patient blood samples. These hmAbs bind to a variety of meningococcal strains, suggesting conservation of antigen/epitope structure. Functional assays have shown killing of meningococci and/or recruitment of components of the complement cascade by our hmAbs. Once the cognate antigens have been identified, they can be characterized and assessed as vaccine candidates.

Funding source: BBSRC studentship BB/R505742/1

#P9: Meningococcal serogroup C (MenC) immune response of a novel tetanus toxoid conjugate quadrivalent meningococcal vaccine (MenACYW-TT) compared to a quadrivalent (MCV4-TT) or monovalent (MenC-TT) meningococcal vaccine in healthy meningococcal vaccine-naïve toddlers

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Keywords: Meningococcal TT conjugate vaccines, immunogenicity, serogroup C, superiority, toddlers

Background: MenACYW-TT (MenQuadfi®) is a recently-licensed quadrivalent meningococcal conjugate vaccine for use in individuals 12 months and older in the EU and some other countries. Safety and immunogenicity (meningococcal serogroup C immune response only) of MenACYW-TT compared to that of a quadrivalent (MCV4-TT [Nimenrix®]) or adjuvanted monovalent meningococcal vaccine (MenC-TT [NeisVac-C®]) were evaluated in healthy meningococcal vaccine-naïve toddlers aged 12-23 months.

Materials: In this modified double-blind Phase-3 study (NCT03890367) conducted in Denmark, Germany, and Finland, 701 toddlers received one dose of either MenACYW-TT, MCV4-TT or MenC-TT vaccine. Serum bactericidal assays with human (hSBA) and baby rabbit (rSBA) complement were used to measure anti-meningococcal serogroup C antibodies at baseline and 30 days post-vaccination. A sequential statistical testing approach was used for primary and secondary objectives. As a primary objective, we evaluated the non-inferiority of MenC seroprotection rates and GMTs induced by MenACYW-TT versus MCV4-TT (hSBA) and MenC-TT (rSBA). If non-inferiority was demonstrated, we evaluated the superiority of MenC immune response induced by MenACYW-TT versus MCV4-TT (hSBA GMTs and seroprotection rates) and MenC-TT (rSBA GMTs). As a secondary objective, we evaluated the non-inferiority of MenC seroprotection rates and GMTs induced by MenACYW-TT versus MCV4-TT (rSBA) and MenC-TT (hSBA). If non-inferiority was demonstrated, we evaluated the superiority of GMTs compared to MCV4-TT and MenC-TT. The safety of all vaccines within 30 days post-vaccination was described.

Results: We demonstrated the non-inferiority and superiority of MenACYW-TT versus MCV4-TT (MenC hSBA GMTs, ratio of 16.3 [12.7; 21.0]) and versus MenC-TT (MenC rSBA GMTs, ratio of 1.32 [1.06; 1.64]). We also demonstrated the non-inferiority and superiority of MenACYW-TT versus MCV4-TT (MenC hSBA seroprotection rates, difference of 10.43% [5.68; 16.20]) and the non-inferiority of MenACYW-TT versus MenC-TT (MenC rSBA seroprotection rates, difference of 0.0% [-2.30; 2.28]). Furthermore, we demonstrated the non-inferiority and superiority of MenC immune responses of MenACYW-TT versus MCV4-TT (rSBA GMTs, ratio of 6.80 [5.04; 9.18]) and versus MenC-TT (hSBA GMTs, ratio of 2.27 [1.82; 2.84]), and the non-inferiority versus MCV4-TT (rSBA seroprotection rates, difference of 5.24 [1.83; 9.85] and versus MenC-TT (MenC hSBA seroprotection rates, difference of -0.00 [-2.71; 2.67]). The safety profiles of a single dose of MenACYW-TT, MCV4-TT and MenC-TT were comparable.

Conclusions: The trial met all primary and secondary objectives. MenACYW-TT induced non-inferior/superior serogroup C immune responses versus MCV4-TT and MenC-TT based on seroprotection rates or GMTs,

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when administered as a single-dose to meningococcal vaccine-naïve toddlers. No safety concern was observed.

Funding source: Sanofi Pasteur

#P10 Modeling meningococcal A conjugate vaccine coverage in the meningitis belt from 2010 to 2019

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Keywords: MenAfriVac, meningococcal serogroup A, meningitis belt, meningococcal vaccine, vaccine coverage

Background: MenAfriVac, a meningococcal A conjugate vaccine (MACV), has been deployed for mass vaccination campaigns in the meningitis belt since 2010. As of the end of 2019, twenty-four of the twenty-six countries in the belt have conducted mass immunization campaigns, with ten introducing MACV into their national routine immunization schedules. The WHO has previously published post-campaign coverage data in select meningitis belt countries. However, no study currently exists comprehensively estimating MACV coverage in the meningitis belt across age, country, and time.

Objective: This study synthesizes WHO-published campaign coverage data with routine immunization data to produce estimates of MACV coverage in all meningitis belt countries from 2010 to 2019.

Methods: Coverage of MACV was estimated in two stages. In the first stage, routine immunization coverage was modeled using Spatiotemporal Gaussian Process Regression. A second stage of modeling incorporated information on past mass campaigns, catchup campaigns, and modeled routine immunization using a cohorting model. For each country, each age cohort from age 1 to 29 years was tracked over time, from the initiation of MenAfriVac in 2010 through 2019. The result is a time series of immunization coverage that incorporates mass campaign data, catchup campaign data, and routine immunization estimates.

Results: Total immunity amongst children aged 1 to 4 years in 2019, considering campaigns and routine immunization, was estimated to be highest in Burkina Faso with 83.5% (95% uncertainty interval (UI) 80.9-85.9) coverage, followed by Mali with 73.8% (95% UI 70.5-77.0). High coverage in both of these countries was driven by an initial successful mass immunization campaign, followed by a catchup campaign, followed by introduction of routine immunization into the infant schedule. Total immunity amongst children and adolescents ages 1 to 29 was also estimated to be highest in Burkina Faso with 93.6% (95% UI 92.6-94.5) coverage and Mali with 93.6% (95% UI 90.7-95.7). Due to the influence of older mass vaccination campaigns, coverage proportions skewed higher in this group than the 1-4 group, with eleven countries having immunization coverage more than 60% in the 1-29 age group, compared to five countries in the 1-4 age group.

Conclusions: Continued control of MenA is essential to the WHO's goal of "defeating meningitis by 2030". These estimates help to highlight where gaps in immunization remain, and emphasize the need for rapid introduction of routine immunization into those at-risk countries where early campaigns are currently the only source of population immunity.

#P11 Immunogenicity of a Single 4CMenB Vaccine Booster in Adolescents 11 Years After Childhood Immunisation

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Keywords: Group B meningococcus, vaccine, 4CMenB, adolescent, booster

Objective: The group B meningococcal vaccine 4CMenB is licensed for use in a two-dose schedule for adolescents. While clinical development in adolescents involved vaccine-naïve individuals, in the future adolescents in the UK will have had three doses of 4CMenB in early childhood. We hypothesized that, despite waning immunity since infancy, this priming may provide sufficient B-cell memory so that serological evidence of protection of teenagers might be evident after a single booster dose.

Method: Forty children over 11 years of age who took part in previous trials involving the administration of 3-5 doses of 4CMenB at infant/preschool age in 2006, and 32 naïve age-matched controls were recruited in an open-labelled trial. Previously immunised participants received one booster dose of 4CMenB. Naïve (previously unvaccinated) participants were randomised to receive two doses of 4CMenB either at 0 and 28 days, or 0 and 365 days. Blood samples were collected prior to vaccination, and at 1, 6 and 12 months. Serum bactericidal antibody (SBA) assays using human complement were performed against three reference strains, and memory B cell ELISPOT against four antigens.

Results: No safety concerns were raised after administration of fourth, fifth or sixth doses of 4CMenB in adolescence. Prior to vaccination, seroprotective SBA responses were detected in 25% of participants previously vaccinated in infancy, and 70% of those who received a further boost at 3 years of age against one of the three indicator strains (5/99, indicating NadA-specific responses), while persistence against the other two strains 44/76-SL and NZ98/254 was poor (5 and 12% respectively). Previous vaccination was associated with higher SBA responses to a single booster vaccine at 11 years of age when compared with a single dose in naïve age-matched controls, especially to strain 5/99 in those who had previously received a booster vaccine at three years of age ($p_{adj}=5 \times 10^{-5}$ one month post vaccination). The SBA titers induced by a single dose in the latter group were similar to the responses elicited by two doses in vaccine-naïve adolescents 6 and 12 months later.

Conclusion: Persistence of antibody responses into the second decade of life following early childhood vaccination is poor. These are the first data showing the potential of a single dose booster vaccine in the second decade of life to provide enhanced immunity in adolescents against capsular group B meningococcal disease and support further evaluation of single dose adolescent boosting.

Funding source: Meningitis Research Foundation (MRF, meningitis.org), award £1702, and by the NIHR Oxford Biomedical Research Center (BRC) Vaccine theme

#P12 Human B cell Responses to Dominant and Sub-dominant Antigens induced by a Meningococcal Outer Membrane Vesicle Vaccine in a Phase I trial

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Objective: *Neisseria meningitidis* outer membrane vesicle (OMV) vaccines are safe and provide strain-specific protection against invasive meningococcal disease (IMD), primarily by inducing serum bactericidal antibodies against the immunodominant outer membrane protein (OMP), the porin PorA. To design broader coverage vaccines, knowledge of the immunogenicity of all the antigens contained in OMVs is needed.

Methods: In a Phase I clinical trial an investigational meningococcal OMV vaccine, MenPF1, made from a meningococcus genetically modified to constitutively express the iron-regulated FetA protein, induced bactericidal responses to both the PorA and the FetA antigen. Material from this trial was used to analyse the kinetics of, and relationships between, B-cell responses against PorA and FetA, including: (i) plasma cell production; (ii) memory B-cell responses; and (iii) functional antibody responses.

Results: Following MenPF1 vaccination, PorA-specific IgG-secreting plasma cell responses were detected in up to 77% (20/26) of participants, and FetA-specific responses in up to 36% (8/22). Memory B cell responses to the vaccine were low or absent and mainly detected in participants who had evidence of pre-existing immunity ($p=0.0069$, ANOVA with an arbitrary value assigned to non-detectable responses). Similarly, FetA-specific antibody titers and bactericidal activity increased in participants with pre-existing immunity.

Conclusions: The results are consistent with the hypothesis that immune responses are elicited to minor antigens during asymptomatic *Neisseria* carriage, which can be boosted by OMV vaccines.

Funding source: This work was supported by a translational award from the Wellcome Trust, Innovation Schemes (Development of a PorA/FetA meningococcal vaccine to Prof. AJ Pollard, Ref 082102/Z/07/A and 091634/Z/10/Z), and by the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom, Vaccine theme.

#P13 A Novel Vaccine against Capsular Group B Meningococcal Disease Based on an Adenoviral Vector: Preclinical Development, Evaluation and Optimization for Clinical Development

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Keywords: Group B meningococcus, vaccine, adenovirus, viral vector, outer membrane proteins

Background: Adenoviral vectors are used in vaccines against SARS-CoV-2 and development of new vaccines against cancer, viruses and parasitic diseases. However, the case for their use in bacterial vaccines is less clear. The expression of a bacterial protein in a eukaryotic cell may impact on the antigen's localization, induce glycosylation or affect protein conformation. Nevertheless, the potential of the viral vector platform to induce T Helper type 1 and high antibody responses in humans makes the use of this approach attractive in efforts to combat the disease and disability caused by bacteria. Here, the potential of an adenoviral vector as a delivery platform for capsular group B meningococcal (MenB) antigens was investigated.

Methods: A replication-deficient adenovirus vector was engineered to express different versions of the MenB antigens Neisserial Adhesin A (NadA) and factor H binding protein (fHbp), including judicious mutations abrogating the binding to human factor H (fH) for the latter. The resulting vaccine candidates were evaluated for antigen expression, binding to human factor H, immunogenicity including human complement-serum bactericidal activity in wild-type and human fH transgenic mouse models.

Results: Immunization with the adenovirus-based candidate vaccines generated high antigen-specific antibody responses in mice after a single dose. Candidate vaccines expressing an fHbp variant induced functional serum bactericidal responses, with titers superior or equal to those induced by two doses of protein-based licensed comparators. Moreover, a judicious mutation that prevented the binding of the antigen to human complement fH was introduced and induced further enhancement of the bactericidal response in a transgenic mouse model.

Conclusions: We show here that an outer membrane protein from a Gram-negative bacterium can be incorporated into a viral-vector platform for novel vaccine development. The resulting MenB vaccine candidate has progressed to clinical development (phase I/IIb).

Funding source: This work was supported by a project grant from Action Medical Research (SP4594), MeningitisNow, Medical Research Council Confidence in Concept award (Oxford), Oxford Innovation Fund (9534), Medical Research Council DPFS (MRM0076931), and by the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom, Vaccine theme.

#P14 Mechanism for Efficient Dissemination of Tn916-Like Integrative and Conjugative Elements in Pneumococcal Nasopharyngeal Biofilms

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Keywords: integrative and conjugative elements, multi-drug resistance, biofilm bioreactor, transformation, homologous recombination

Multi-drug resistance in *Streptococcus pneumoniae* (Spn) has been attributed to the exchange of integrative and conjugative elements (ICEs). Tn916-like ICEs, Tn2009 (23.5 kb) and Tn2010 (26.3 kb), carry the *mefE/mel* genes on the Macrolide Efflux Genetic Assembly (Mega) element and/or the *ermB* gene, conferring macrolide resistance. Additionally, both ICEs contain a *tetM* gene, conferring tetracycline resistance. In other bacteria, prototype Tn916 (18.0 kb) conjugates from donor to recipient by circular intermediate (CI) production and genome integration via site-specific recombination. However, the mechanism for Tn916-like ICE transfer in Spn has not been elucidated. In a nasopharyngeal biofilm bioreactor system, Tn2009 or Tn2010 dissemination from donors GA16833 or GA47281 to recipient D39 was observed at recombination frequencies (rF) of 10⁻⁴. However, in vitro transformation with added CSP did not support Tn2009 nor Tn2010 uptake by planktonic D39 cells (tF < 10⁻⁸-10⁻⁷). Correspondingly, non-CSP-supplemented early competence gene expression of *comD* and *comE* in recipient D39 was 120-fold greater in nasopharyngeal biofilms compared to in vitro transformation conditions. Dual-strain biofilms do not support Tn2009 CI production (CI:chromosome ratio 10⁻⁷-10⁻⁵) nor conjugative gene expression. Deletion of the critical conjugative gene, *ftsK*, from Tn2009 does not affect ICE transfer from GA16833 to D39 in the nasopharyngeal biofilm (rF 10⁻⁴), while DNaseI addition (rF < 10⁻⁷) and deletions of the early competence gene, *comE*, or transformation apparatus genes, *comEA* and *comEC*, in the D39 recipient lead to significantly lower rFs (< 10⁻⁸-10⁻⁷). Recombinant whole genome sequencing reveals that Tn2009 and Tn2010 were incorporated on distinctly sized donor DNA fragments simultaneously with other distant donor genome fragments. Thus, Spn Tn916-like ICEs disseminate in dual-strain, nasopharyngeal biofilms via competence and transformation and integrate into a genome by homologous recombination

Funding source: NIH R21 AI144571-01

#P15 Changes in the epidemiology of invasive meningococcal diseases during the COVID-19 pandemic in Germany

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Keywords: COVID-19, Surveillance, Infection Control, Transmission, Epidemiology

Since the COVID-19 pandemic had hit Germany since March 2020, nation-wide containment measures including social distancing were implemented consequently. This may have also influenced infectious diseases other than COVID-19. Neisseria meningitidis (Nm) is transmitted by respiratory droplets and can cause invasive infections and it has already been shown earlier that Nm carriage is associated with the number of social contacts. In this study, prevalence data of invasive Nm infections for twelve months under containment measures in Germany were compared to the preceding year's period to analyse changes in the epidemiology. The data extend a recent analysis covering the months until June 2020 (Brueggemann et al., Lancet Digit Health 2021;3(6)).

Besides notification according to the German infection protection act (IfSG), diagnostic laboratories send invasive Nm isolates on a voluntary basis to the NRZMHi. Submissions were analysed for 01.04.2019 to 31.03.2020 (pre-pandemic period, pre-PP) and 01.04.2020 to 31.03.2021 (pandemic period, PP). Coverage was assessed by comparing the NRZMHi cases with the number of notified cases (SurvStat@RKI).

Invasive Nm was detected in 210 cases in pre-PP. The number dropped to 45 cases in PP, which equals a decrease by 79%. Nm invasive infection incidence for pre-PP and PP according to IfSG notifications was 0.30/100,000 and 0.07/100,000, respectively. The coverage of cases analysed at the NRZMHi was 84% for the pre-PP, and 83% for the PP.

The reduced submission to the NRZMHi correlated with pandemic response measures. Whereas submissions were comparable to the previous year in the first months of 2020, they decreased significantly after March 2020. Declined notification rates have been reported by the RKI for many infectious diseases in 2020. Only tick-borne encephalitis notification rates have increased.

Infection protection measures against COVID-19 seem to have a significant impact on both, invasive Hi and Nm infections. Since invasive bacterial infections such as meningitis and sepsis are life threatening events and the coverage for Nm and Hi did not change significantly, a bias by unnotified cases seems unlikely. In light of these dynamics infection surveillance and epidemiologic analysis are important to monitor further developments as the pandemic is ongoing.

It will be important to carefully monitor the development after restrictions have been lifted, since the effects of reduced transmission on natural immunity of the population are unknown.

Funding source: Robert Koch Institut, Berlin, Germany

#P16 University Students Attitudes to COVID-19 and Meningococcal Vaccine Uptake

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Vaccine uptake by university students is currently a major issue. The critical concern is to prevent spread of COVID-19 infections as students resume normal face-to-face studies. However, there is also the potential that the end of lockdown and return of normal activities will lead to the return of meningococcal disease among students. We aimed to investigate student knowledge of COVID-19 and meningococcal vaccines and to examine potential barriers to vaccine uptake.

Method. Anonymise online questionnaire to all University of Leicester undergraduates in early June 2021. Questionnaire contained 29 questions encompassing attitudes to and knowledge of COVID-19, MenACWY and MMR vaccines. Responses were analysed using univariate and multivariate statistical tests.

Results. Data was obtained from 827 students. Respondents were young, ethnically diverse and from a wide catchment area. Key findings were that 26% of students did not know their vaccine status for the MenACWY vaccine and 4% had not had this vaccine (comparator values for the MMR vaccine were 11% and 3%) while 93% of students were willing to take up a COVID-19 vaccine. On campus MenACWY/MMR vaccine campaigns were favoured by 57% of UK students and 69% of UK-based international students. Many students (20%) were unaware that the MenACWY and MMR vaccines were free.

Conclusions. A key recommendation from our study is for provision of vaccine status information for all vaccines on digital platforms, such as the NHSapp. Increasing student awareness of their MenACWY vaccine status is likely to increase uptake of this vaccine. Additionally we recommend widespread implementation of on campus vaccine campaigns in order to maximise delivery to students in general and to international students in particular.

Funding Source: ESRC

#P17 *Neisseria lactamica* induces anti-*Neisseria meningitidis* B cell responses

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Keywords: *Neisseria lactamica*, *Neisseria meningitidis*, B cell, cross-reactive, controlled human infection

Background: Colonisation with *Neisseria lactamica* (Nlac) prevents *Neisseria meningitidis* (Nmen) colonisation and disease. If the mechanism underlying this effect was elucidated it could be exploited to develop novel strategies to protect against Nmen-associated disease. We theorised that an adaptive cross-reactive immune mechanism, independent of SBA, may be implicated in this protection and performed a Nlac controlled human infection experiment to test this hypothesis.

Methods: 31 participants were randomised to receive intra-nasal inoculation with 10⁵ colony-forming units (CFU) of Nlac or sham control. Nlac and Nmen colonisation status was assessed at baseline and at 7-, 14- and 28-days post-inoculation. Nlac- and Nmen-specific IgA- and IgG-secreting plasma cell (BPLAS) and IgG memory B cell (BMEM) frequencies were quantified in blood at baseline and post-inoculation time points using enzyme-linked immunospot assays. Associations between Nlac nasopharyngeal colonisation density and B cell responses prior to and following inoculation were also assessed.

Results: Colonisation with Nlac (n = 17) induced Nlac-specific IgA- and IgG-secreting BPLAS, and IgG BMEM (all P < 0.0001) post-colonisation. Interestingly, there was also induction of Nmen-specific IgA- and IgG-secreting BPLAS (P = 0.0044 and P = 0.0156), and IgG BMEM (P = 0.0161). Nlac- or Nmen-specific BPLAS/BMEM responses were not induced in control subjects (n = 10). Nlac colonisation density in nasal wash inversely correlated with baseline Nmen-specific but not Nlac-specific IgG BMEM frequencies at 14 days (rs = -0.664, P = 0.0016) and 28 days (-0.562, P = 0.0319) post-inoculation. Nlac colonisation density was significantly lower amongst participants with both detectable baseline Nlac- and Nmen-specific IgG BMEM responses as compared to those participants without Nmen-specific responses (median 136.5 CFU ml⁻¹ [range 0-1472] vs. 5910 CFU ml⁻¹ [range 3233-18197], P = 0.0057). The reduced Nlac colonisation densities observed amongst participants with detectable Nlac- and Nmen-specific IgG BMEM at baseline coincided with significantly higher IgA- and IgG-secreting BPLAS responses with specificity to Nlac (P = 0.0121 and P = 0.0485) and Nmen (P = 0.0199 and P = 0.0108) in this group.

Discussion: Our findings confirm that colonisation with Nlac induces Nmen cross-reactive B cell responses. That detectable anti-Nlac and anti-Nmen IgG BMEM responses at baseline were associated with higher BPLAS responses and lower Nlac colonisation densities suggests that these responses may be implicated in controlling colonisation density. We would expect that the protection against Nmen afforded by Nlac colonisation would only be observed in cases where anti-Nmen responses were generated. **Funding source:** Wellcome Trust Research Training Fellowship (203581/Z/16/Z)

#P18 Natural Immunity in the African Meningitis Belt to *Neisseria meningitidis* serogroup X: A Seroprevalence Study

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Keywords: SBA, MenX, Vaccine, Immunity, Seroprevalence

Invasive meningococcal disease (IMD) affects approximately 1.2 million people worldwide annually. Prevention of IMD is provided through conjugate vaccines; however, no licensed vaccine is currently available to protect against meningococcal serogroup X associated infection. This study aimed to provide seroprevalence data to assess natural immunity to serogroup X within the African sub-Saharan meningitis belt using a serum bactericidal antibody (SBA) assay. This assay will also be used to evaluate the immunogenicity of a pentavalent conjugate vaccine containing serogroup X, NmCV-5 (Serum Institute India), prior to its introduction into the meningitis belt.

A seroprevalence study was conducted to assess natural immunity and identify the SBA baseline to *N. meningitidis* serogroup X from 377 serum samples gathered in March 2012 from Niger, West Africa, within the meningitis belt.

The age-specific prevalence of SBA to serogroup X was measured. Data were analysed to identify the percentage of individuals with protective SBA titres (≥ 8) to serogroup X prior to the introduction of the NmCV-5 vaccine.

(c) Seroprevalence data show that natural immunity to *N. meningitidis* serogroup X were present in 52.3% of study participants. The highest protective SBA titres (≥ 8) to serogroup X were seen in age group 5-14 years-old (73.9%) and lowest in ages <1 year old (0%).

(d) Seroprevalence data support the need for implementation of the NmCV-5 vaccine into the sub-Saharan meningitis belt. Following the introduction of NmCV-5, a secondary seroprevalence study should be completed to determine the impact of the vaccine within the meningitis belt.

Funding source: Public Health England

#P19 Identification and study of Neisseria surface protein A (NspA) mutants with low affinity for factor H as vaccine candidates against pathogenic Neisseria

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Keywords: Vaccines, NspA, outer membrane vesicles, Neisseria meningitis, Factor H

Introduction: Neisserial surface protein A (NspA) is a highly conserved outer membrane protein present in both *Neisseria meningitidis* and *N. gonorrhoeae*. It is a small beta-barrel protein that binds to human complement Factor H (hFH). It is known to elicit protective antibodies against *N. meningitidis* in mice. However, a vaccine composed of an unfolded, recombinant NspA failed to induce protective serum bactericidal antibodies against meningococci in humans. Previous vaccination studies from our group in wild-type and Factor H transgenic mice attributed the poor immunogenicity of NspA and the impaired serum bactericidal antibody responses against *Neisseria* to its binding to its ligand, hFH. Hence in our current study, we aim to develop a NspA vaccine with decreased affinity for hFH that might have the potential to elicit protective antibody responses against *Neisseria*. Studies have also shown that the resistance of *N. meningitidis* clinical isolates to anti-Factor H binding protein (FHbp) bactericidal activity is enhanced by the binding of hFH to PorB3 and NspA. Since FHbp, a component of currently licensed vaccines, has limitations in strain coverage against meningococcal strains with no or low expression of FHbp, inclusion of NspA could result in better strain coverage and enhancement of protective antibody responses.

Methods: Based on the known crystal structure of NspA, we introduced mutations in the amino acid residues in the surface exposed loops of the protein. We then tested *E. coli* strains expressing NspA mutants on their surface, for their ability to bind hFH by whole bacterial cell ELISA. We also tested the binding of two monoclonal antibodies (MAbs), AL-12 and 14C7, to the NspA mutants. We then purified outer membranes vesicles (OMVs) from *E. coli* expressing mutant NspA proteins with low affinity for hFH. We conducted immunization experiments in CD-1 wild-type and transgenic hFH mice with the purified *E. coli* OMVs. We collected sera from the immunized mice and analysed them for their protective antibody responses.

Results: We identified several NspA mutants with low binding of hFH. Interestingly, we found that these NspA mutants with low hFH binding also had decreased ability to bind the MAbs AL-12 and 14C7, known to bind external loops 2 and 3 of NspA, which indicates that the hFH binding site overlaps with the MAb epitopes. Anti-NspA antibody titres of sera from WT CD-1 mice were significantly lower among groups immunized with mutant NspA, whereas in the presence of circulating hFH, the antibody titres of sera from transgenic FH mice were not significantly different between the groups. We are in the process of analysing the sera for protective antibody responses.

Funding source: NIH

#P20: A Pentavalent Meningococcal Vaccine: Review of the Rationale for Development

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Keywords: Meningococcal disease, MenABCWY vaccine, epidemiology, children, adolescents

Objective: Invasive meningococcal disease (IMD) is a severe, often life-threatening disease caused by *Neisseria meningitidis*. The incidence of IMD varies with age, with infants and adolescents/young adults at greatest risk. Currently, there are no approved meningococcal vaccines that cover the 5 most common disease-causing serogroups: A, B, C, W, and Y. Here we review the burden of disease and current recommendations for vaccination in Europe, development of a pentavalent MenABCWY vaccine, and the potential impact of such a vaccine.

Methods: A literature review was conducted to identify relevant information from peer-reviewed publications, government and manufacturer resources.

Results: In 2017, the overall incidence rate of IMD in Europe was 0.6 per 100,000. The incidence rate was highest in infants and young children at 8.2 per 100,000 in children under one year of age, and 2.5 per 100,000 in children 1-4 years of age. A second peak was observed in adolescents and young adults 15-24 years of age, with a rate of 1.0 per 100,000. The highest percentage of cases were caused by serogroup B (51%), followed by serogroup W (17%), serogroup C (16%), and serogroup Y (12%), with a recent rise in the incidence of serogroup W clonal complex 11 observed in several European countries. There are currently 3 licensed quadrivalent conjugate vaccines against serogroups A, C, W, and Y and 2 licensed serogroup B vaccines in Europe. Vaccine recommendations vary widely by country and age group; many include a quadrivalent (MenACWY) vaccine as well as a MenB vaccine. MenACWY vaccines are generally administered as a single primary dose for toddlers, adolescents, and young adults. MenB vaccines as a 3-dose primary series in infants/children and a 2- or 3-dose series in adolescents. A pentavalent MenABCWY vaccine is being evaluated in healthy infants 2 and 6 months of age and individuals ≥ 10 –<26 years of age. Widespread use of MenABCWY could offer broad protection against meningococcal disease with a single vaccine and simplify number of injections as well as the interpretation of vaccine schedules for providers.

Conclusions: Although IMD remains rare throughout Europe, the constantly evolving epidemiology and rise of hypervirulent clones present a significant challenge. High quality surveillance and vaccination is key to successfully reducing the burden of disease. Updating current recommendations to include MenABCWY, a vaccine covering all 5 serogroups, provides a comprehensive approach to preventing meningococcal disease in terms of both vaccine characteristics and implementation of any recommendations.

Funding source: Funded by Pfizer Inc

#P21: Real-world impact and effectiveness of MENACWY-TT

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Keywords: Effectiveness, impact, invasive meningococcal disease, MenACWY-TT, national immunization program

Objective: The meningococcal ACWY polysaccharide conjugate vaccine using tetanus toxoid as a carrier protein (MenACWY-TT) is licensed to prevent disease caused by meningococcal serogroups A, C, W, and Y in individuals aged ≥ 6 weeks. Following licensure in 2012, MenACWY-TT has been incorporated into many national immunization programs (NIPs). We provide an overview of the recent impact and real-world effectiveness of MenACWY-TT from several countries.

Methods: Meningococcal disease epidemiology, vaccine impact, and effectiveness data were collected from countries that introduced single-dose MenACWY-TT into their NIPs. The Netherlands used MenACWY-TT exclusively following its introduction in 2018 for vaccination of toddlers (age 14 months) and adolescents (age 14–18 years; catch-up campaign for birth cohorts 2001–2005). Data were also available from Australia, Chile and England, where MenACWY-TT was recently used exclusively or predominantly in the NIP, despite other MenACWY vaccines being previously used. Australia introduced MenACWY-TT in 2017–2018 for vaccination of adolescents (age 15–19 years); Chile introduced MenACWY-TT in 2014 for toddlers (age 1–4 years) and catch-up vaccination following a mass MenACWY vaccination campaign for children (aged 9 months through 4 years; 10/2012–12/2013); and England introduced a MenACWY NIP in 2015 for adolescents (13/14 years of age)/catch-up vaccination (age 14–18 years up to 25 years). The following time periods were analyzed: the Netherlands, 2017/2018 vs 2019/2020; Australia, 2017 vs 2019; Chile, 2014–2019; and England 2015/2016 vs 2018/2019. Due to low case numbers, vaccine impact for MenA was not determined.

Results: MenACWY-TT vaccine effectiveness (VE) of 92% was reported against MenW disease after vaccination of toddlers in the Netherlands (VE data in adolescents were not available as no MenW cases were observed in vaccinated individuals). The toddler program in conjunction with the adolescent program resulted in a decrease of 85% (95% confidence interval [CI]: 32, 97) in MenCWY incidence in vaccine-eligible age groups. Decreases in the number of MenCWY cases were similarly reported in vaccine-eligible age groups in Australia, Chile, and England (83%, 80% [MenW], and 78%, respectively). In nonvaccine-eligible age groups in the Netherlands, a 50% (95% CI: 28, 65) decrease in MenCWY incidence was also observed, indicating potential indirect (herd) protection. Similar decreases were observed when all ages were considered in Australia, Chile and England.

Conclusions: Recent data from multiple countries have confirmed the effectiveness of MenACWY-TT, providing direct protection in toddler and adolescent age groups, and indirect protection imparted through adolescent vaccination programs.

Funding source: Funded by Pfizer Inc

#P22 Understanding the breadth of coverage afforded by meningococcal vaccines

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Keywords: Breadth of coverage; correlates of protection; MenB-fHbp; serogroup B meningococcal vaccines; serology

The link between the serological evaluation, serology results and protection afforded by meningococcal capsular vaccines is generally well established, accepted and understood. A singular test strain may be employed in the serum bactericidal antibody (SBA) assay and resultant data interpreted as applying to all circulating strains with the same capsule irrespective of any sub-capsular diversity. Vaccines for the prevention of serogroup B (MenB) disease rely on sub-capsular components and determination of their breadth of coverage (BoC) against diverse circulating MenB strains requires more careful consideration.

Determining the BoC of sub-capsular vaccines is significantly more complicated, as circulating MenB strains are diverse and vary in the following ways that may impact a vaccine's ability to provide protection: (1) absence of the gene used as the vaccine antigen; (2) if the gene is present, low or no expression; and (3) if the gene is present and sufficiently expressed, sequence diversity can impact on the ability of vaccine-induced antibody to cross-react and provide protection.

The SBA assay is the accepted correlate of protection for meningococcal vaccines. Due to MenB strain diversity, however, the choice of target strain(s) directly influences how much information is provided on BoC in addition to the assay strain itself. Furthermore, BoC relies on the cross-reactivity of induced antibody to sub-capsular sequence variants (where expressed), and consequently there are differences between individuals' responses.

Two main strategies have been employed for the serological evaluation of sub-capsular vaccines. The first employs the use of a single MenB strain for a given vaccine antigen and has frequently incorporated a strain with high expression of a vaccine homologous or closely matched variant; this process alone provides limited BoC information. The second approach, which was used in the evaluation of MenB-fHbp, incorporated multiple MenB strains randomly chosen with low-medium expression of vaccine heterologous variants representative of known antigenic diversity. SBA data from these strains has confirmed the BoC of MenB-fHbp.

The diversity of circulating MenB strains necessitates an understanding of BoC to assess sub-capsular vaccines' utility. The comprehensive approach taken to assess MenB-fHbp using the accepted correlate of protection demonstrates the vaccine's broad BoC.

Funding source: Funded by Pfizer Inc

#P23 Breadth of the human immune response to MENB-FHBP Vaccine (Trumenba): Genotypic and phenotypic characterization of MenB strains that are susceptible in the hSBA

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Keywords: Breadth of coverage; MenB-fHbp; serogroup B meningococcal vaccines; serology

Objective: The MenB-fHb vaccine (Trumenba®; bivalent rLP2086), a vaccine for the prevention of *Neisseria meningitidis* serogroup B (MenB) disease, consists of two protein antigens, variants of meningococcal factor H binding protein (fHBP). fHBP exists as two subfamilies, A and B. Within each subfamily several hundred unique fHBP variants have been identified. Despite this sequence diversity, a vaccine containing one protein from each subfamily was demonstrated to induce broad coverage across MenB strains that represent the diversity of fHBP variants. Licensure was based on the ability of the vaccine to elicit antibodies that initiate complement-mediated killing of invasive MenB strains that express fHBP variants different from the vaccine antigens in serum bactericidal assays using human complement (hSBA). To further explore the breadth of coverage conferred by Trumenba, we describe the genotype and phenotype of additional MenB strains that are susceptible in the hSBA.

Methods: MenB invasive strains (n=109) were selected to confirm Trumenba breadth of coverage. The fHBP variant type, signal peptide class and 5'-flanking sequences were determined from whole genome sequence. Bacterial surface expression of fHBP was determined using the flow cytometric MEningococcal Antigen SURface Expression (MEASURE) assay. Exploratory hSBAs were performed using pre- and post-vaccination sera (subject-matched) from young adults. A strain was considered susceptible to Trumenba immune sera if a 4-fold rise in the hSBA titer was achieved between the pre- and post-vaccination serum samples.

Results: Eighty-seven of the 109 strains were susceptible to Trumenba immune serum in hSBAs. This included strains expressing fHBP variants A02, A28, A42, A63, A76, B05, B07, B08, B13, B52 and B107, in addition to variants that had been reported previously. Sequence of the fHBP signal peptide was not predictive of hSBA susceptibility. The majority of strains that could not be killed had fHBP expression levels that were below the level considered sufficient to initiate bactericidal killing in an hSBA.

Conclusion: The hSBA is recognized as the surrogate of efficacy for meningococcal vaccines. To illustrate the breadth of immune coverage conferred by Trumenba, we show that MenB strains expressing more than two dozen sequence-diverse fHBP variants heterologous to the vaccine antigens can be killed in hSBAs.

Funding source: Funded by Pfizer Inc.

Diagnosis and Treatment

#DT1 Fluconazole plus flucytosine vs. fluconazole alone for cryptococcal antigen-positive patients identified through screening: A phase III randomised controlled trial

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Keywords: Cryptococcal disease, clinical trial, advanced HIV, Sub-saharan Africa, Cryptococcal antigen (CrAg) screening

Cryptococcal meningitis (CM) is the commonest form of adult meningitis in much of Sub-Saharan Africa (SSA), accounting for 15%-20% of all AIDS-related deaths. Targeting cryptococcal disease in its early stages, prior to the development of meningitis, could reduce this persistently high mortality.

Screening patients with low CD4 counts using a simple point-of-care test to detect cryptococcal antigen (CrAg) and treatment of CrAg-positive patients in advance of severe disease represents a practical and cost-effective approach to reducing mortality, with such screening programs now recommended in many SSA countries. However, recent data has shown that current pre-emptive treatment with fluconazole alone may be suboptimal with a significant number of patients going on to develop meningitis and die. Testing of more effective antifungal regimens is thus urgently required. In the phase III ACTA trial, a combined treatment of fluconazole and flucytosine was shown to be safe and effective in those with symptomatic meningitis, with mortality halved compared to historic cohorts treated with fluconazole alone.

The EFFECT trial is a phase III, multi-centre, pragmatic open-label, randomised controlled trial embedded in existing screening programs in South Africa and Tanzania. HIV-infected adults (>18 years old) identified through routine laboratory screening at participating centres as CrAg-positive in blood and who are also cerebrospinal fluid CrAg-negative or who decline a lumbar puncture will be recruited into the study following informed consent. Participants will be randomised, 1:1, to receive either fluconazole alone (1200 mg/day, control arm, current recommended treatment) OR a combined regimen of fluconazole (1200 mg/day) plus flucytosine (25 mg/kg qds, intervention arm) for 2 weeks. Fluconazole (800 mg daily) will be given to all participants for a further 8 weeks and fluconazole 200 mg/d thereafter as per national guidelines.

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Participants will be seen in clinic on day 1 and 14 and contacted on days 3 and 9 by telephone for adherence counselling and at 1, 2.5 (10 weeks), 4 and 6 months to determine survival status. The primary end point of all-cause mortality at 6-months will be compared between the two groups. A total of 600 participants will be recruited over a 2.5-year period, beginning at the end of 2021. The trial will also assess progression to cryptococcal meningitis, tolerability and safety, and cost effectiveness.

A safe and potent oral treatment regimen, which could be administered to outpatients, could have a major impact on survival, and driving down AIDS-related mortality.

Funding source: Joint Global Health Trials (JGHT) - Wellcome, Medical Research Council (UK), UK Department for International Development (DFID) and the National Institute for Health Research (NIHR)

#DT2 Transcriptome analysis of CSF from meningitis patients identifies a novel *Streptococcus pneumoniae* operon that is essential for establishing brain infection

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Keywords: *Streptococcus pneumoniae*, meningitis, gene expression, pathogenesis, mortality

Background: Pneumococcal meningitis (PM) is a highly lethal infectious disease, survivors are at risk of significant disability. To investigate the pathogenesis of PM, we have characterised the in-vitro and in-vivo characteristics of highly upregulated bacterial genes with no known function during human PM.

Methods: RNA from CSF from 11 patients with proven PM was isolated, sequenced and analysed. Pneumococcal transcripts were quantitated, ranked and analysed against the D39 transcription model PneumoExpress. For selected highly expressed genes, function was predicted using HMMR. Serotype 1 (ST5316) deletion mutants were constructed for selected genes and their virulence phenotypes characterised in a non-haematogenous murine and a zebrafish larvae hindbrain meningitis models.

Results: Transcripts mapped optimally against a serotype 1 strain (gamPN10373, P1031). Highly expressed genes included multiple known virulence determinants and many genes with unknown function. Using PneumoExpress, highly expressed genes aligned closely with pneumococcal responses to A549 epithelial cells. Two abundantly expressed genes in CSF were *bgaA* and *sp_1800-5* (unknown function). Predictive modeling using HMMR suggested *Sp_1801-5* are cell wall proteins involved in alkaline shock responses.

Subsequent gene deletion mutants transmigrated an in-vitro multicellular blood-brain barrier, transcriptional responses in human CSF suggest these genes are part of the bacterial survival response in CSF, *BgaA* may additionally be expressed in response to opsonophagocytosis in CSF.

In a trans-nasal (non-haematogenous) murine meningitis model, both mutants colonized the nasopharynx and olfactory bulb to a similar extent as the wild-type strain, but neither mutant successfully established infection in brain tissue. In the hind-brain infection zebrafish model, embryos infected with *-/-BgaA* mutant had an improved survival compared to those infected with WT. Patients infected with *S. pneumoniae* strains containing *BgaA* have lower CSF leukocyte counts and worse clinical outcomes.

Conclusions: Using transcriptional analysis of human meningitis we have defined the *S. pneumoniae* genes likely to be important for disease development, and identified previously undescribed virulence determinants involved in PM pathogenesis. **Funding source:** Wellcome Trust, Francis Crick Institute, Academy of Medical Sciences, UCL institutional strategic fund

#DT3 Non-invasive cerebrospinal fluid leukocyte counter to screen and monitor infant meningitis.

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Keywords: Leukocytes, concentration, meningitis, non-invasive, screening

Our group has developed an ultrasound-based device to non-invasively count white blood cells in the cerebrospinal fluid (CSF) located directly below the infant's fontanelle, as an alternative to laboratory analysis of CSF obtained through a lumbar puncture. A clinical proof of concept study is being conducted in Mozambique to evaluate cell counting accuracy as well as efficacy of this approach for the screening of meningitis—a life threatening infection which is difficult to diagnose in low-resource settings.

The device combines three different and essential technologies necessary for good sensitivity to very low diagnostic cell concentrations and complete measurement automatization: 1) high frequency ultrasound allowing single cell resolution suspended in serous fluids 2) in-house developed bio-compatible PVA-based materials optimising transfer and reception, i.e. coupling, of the ultrasound signal to/from the fontanelle tissue; and 3) AI-based models enabling fluid segmentation, cell pattern detection and counting. At the current validation stage, the user simply places the device probe on the anterior fontanelle. Signal configuration changes, ultrasound focus positioning on the CSF space, and data storage are performed remotely by technical assistants. The entire process takes about 5 minutes but ultimately, when automatised, should last in the order of seconds.

This study is being coordinated by the Barcelona Institute of Global Health (ISGlobal) and implemented at Maputo Central Hospital, Mozambique. The target population are patients <24 months of age with an indication for lumbar puncture based on suspicion of meningitis, and an open fontanelle. The sample size is of 86 patients, 36 of which are projected to be positive for meningitis. To date, twelve patients have been recruited, nine of which were negative, two were diagnosed with meningoencephalitis, and one with meningitis. The user and the technician providing remote support are blind to cytologic and culture results at the time of data acquisition with the device.

While more data need to be collected to provide confident cell counting and screening capabilities results, the technology detects patterns only observable in positive patients that highly resemble in-vitro data and that can be associated either to individual or a group of cells. Preliminary in-vitro results in highly-realistic fontanelle models at concentration ranges between 0-1,200 cells/ μ L showed accuracy errors about 30% close to diagnostic thresholds, i.e. 20 cells/ μ L, and of less than 15% for higher concentrations.

Conclusion: Our non-invasive screening meningitis device is providing promising results that will need to be substantiated in larger multi-centric studies.

Funding source: Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Ministry of Health of Spain (FIS PI16/00738)

#DT4 The Host Transcriptome in Neisseria Septic Shock in Infants, a Force in Precision Cellular Dysfunction Detection?

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Keywords: Host Transcriptome Neisseria Septic Shock

Introduction: Early diagnosis in acute sepsis saves lives. Further, tracking the sepsis process aids clinical management. Hence biomarkers, such as CRP and Pro-calcitonin are useful. More recently, interleukins such as IL-6, IL-27 {Wang, 2021 #2535} have also found clinical utility for sepsis tracking. However, such biomarkers generate arbitrary values for trend analysis. Tracking transcriptomic changes and relating these to the bedside, could provide enhanced clinical information to follow physiological processes. Thereby clinical correlation analysis of the meningococcal septic shock transcriptome in infants with meningococcal disease, was undertaken.

Method: Gene-expression data was parsed through Qlucore Ohms explorer QOE software. Temporal Paediatric datasets included a MSS1, Meningococcal Group B Sepsis study from the United Kingdom (29 samples) and MSS2, from Holland (41 samples). Primary Component analysis and Gene Set Expression Analysis (GSEA) were the principal tools used to illustrate dynamic transcriptomic changes.

Results: PCA plot was generated using qlucore bioinformatics anova multi-group analysis, demonstrating a temporal transcriptomic pattern for MSS1 and MSS2. Using the Hallmark gene-set, GSEA showed significant inflammation associated gene sets for both datasets as well as gene-sets related to electrolytes and clotting. For MSS1, GSEA t-Test comparison of the non-surviving patient against four surviving patients showed differential gene down-regulation for apoptosis (WP_APOPTOSIS, normalised expression score -1.60, $p = 0.02$ and $q = 0.15$), for ICAM3, TNF and Cytokine gene expression. Box plots suggested similarities between MSS1 and MSS2 for MMP9, TIMP1, NFKB1 gene expression and allowed survival analysis showing down-regulation of ICAM3 gene-expression in the deceased patient.

Discussion: This MSS study illustrates temporal aspect of the transcriptome over an acute period of Meningococcal shock in infants. Changes in ICAM-3 signalling suggested apoptotic effects and showed the potential for the transcriptome to be used for survival analysis. The exploitability of the transcriptome for theranostics requires further investigation.

Funding source: Self-funded

#DT5 Replication in perivascular meningeal macrophages precedes meningitis in mice

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Keywords: Pneumococcus, perivascular macrophages, pathogenesis, pyroptosis

Hematogenous spread of pneumococci through the blood brain barrier (BBB) is one of the routes of spread to the meninges. Mouse models have shown that endothelial attachment precedes passage through the BBB (Iovino et al., J Exp Med. 2017). To study the successive steps in the pathogenesis of infection, we utilised a murine model exploiting cefazolin administration 12 hours after challenge which reliably prevents sepsis (Tsao et al., FEMS Immunology and Medical Microbiology 2002). Confocal microscopy analysis of the brain samples document that following the invasion of perivascular endothelial cells (CD31+), pneumococci transfer to perivascular macrophages (CD169+CD206+) 24 to 36 hours after challenge. During this time the pneumococci appear to replicate within these macrophages resulting in an increase in pneumococcal numbers and the subsequent release of pneumococci into the CSF initiating meningitis and pleocytosis at 60 to 72 hours after challenge. Furthermore, inhibition by antibodies and the caspase-1 inhibitor VX765 prevent meningitis. Clusters of pneumococci can also be detected in human periarteriolar macrophages in autopsy samples following meningitis. These data add a further step to the pathogenesis of hematogenous meningitis and underline the central role of tissue macrophages in invasive infection.

Funding source: BBSRC

#DT6 Use of high throughput phenotyping and genome wide association studies to identify genetic determinants of meningococcal disease traits

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Keywords: *Neisseria meningitidis*, high-throughput phenotyping, GWAS, phase variation, disease potential

Despite ongoing vaccination programmes, *Neisseria meningitidis* is a major cause of septicaemia and meningitis. In 2017-18, MenW and MenY isolates caused 38% of all UK invasive meningococcal disease cases. Genome sequence data is generated for all meningococcal disease isolates and deposited in the MRF Meningococcal Genome Library. Using this resource, we aim to determine how genetic variation contributes to differences in clinically important bacterial phenotypes. We have adapted assays, mimicking carriage and disease behaviours, for high-throughput phenotypic testing of MenW cc11 and MenY cc23 isolates. We have determined the extent of phenotypic variation for 162 MenW cc11 disease and carriage isolates in three assays (growth rate, biofilm formation and adhesion to a human cell line). This data was utilised for Genome Wide Association Studies (GWAS) enabling linkage of specific genomic variants, or variant combinations, with phenotypic variation. Genomic data includes whole genome sequences and repeat-mediated phase variation states.

Our preliminary data from high-throughput phenotypic assays showed significant variations within clusters of isolates (e.g., carriage and disease) and evidence of distinctive adhesion abilities or biofilm formation. For each phenotypic assay, isolates were separated into two groups (e.g., high versus low) encompassing non-overlapping percentile ranges from normally distributed data. Binary groups were utilised as inputs for the GWAS. Our approach is based on unitigs and implementation of a whole genome elastic net model in Pyseer. A maximum likelihood clonal frame tree model was employed to account for recombination and for calculation of pairwise phylogenetic distances. Our preliminary results pinpoint a range of genetic variants and gene pathways that are potentially linked to each phenotype and provide a basis for further confirmatory experimental assessments. This genetic variation may reflect physiological divergence due to selection of minor genetic modifications between highly phylogenetically related strains.

The availability of large data sets of complete genome sequences with accompanying phenotypic metadata promises to revolutionise the identification of disease-associated phenotypes and may lead to an enhanced ability to predict disease potential.

Funding source: Medical Research Council UK

#DT7 *In silico* evaluation of current PCR diagnostic targets for the molecular detection of bacterial meningitis

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Keywords: bacteria, meningitis, diagnosis, evaluation, PCR

Improvements in diagnostic methods have been identified as an essential pillar of the WHO road map to defeating meningitis worldwide by 2030. Indeed, timely diagnosis of the causes of bacterial meningitis is vital for adequate care management. *Neisseria meningitidis* (Nm), *Haemophilus influenzae* (Hi), *Streptococcus agalactiae* (GBS) and *Streptococcus pneumoniae* (Sp) are the most common causes of bacterial meningitis and currently the most reliable diagnostic methods employ nucleic acid-based approaches such as PCR. Several genetic targets have been described for detection of these pathogens; however, their sensitivity and specificity vary and can be affected by the evolving genomic diversity of these bacteria. This study aimed to evaluate *in silico* PCR genetic targets published for the detection of Nm, GBS and Hi.

A total of 35063, 2126 and 10720 genome sequences were analysed for Nm, Hi and GBS, respectively, on the pathogen specific PubMLST databases. *In silico* analysis was performed using two tools available on the Bigsdb software hosted on PubMLST: i) **Gene Presence** which allows the identification of a sequence of interest in a list of genomes sequences using a BLAST algorithm and ii) ***in silico* PCR**, with the option of no mismatch, which allows to predict the binding of PCR primers in a list of genome sequences. Sensitivity and specificity of the primers were assessed for all gene targets identified using whole genome sequence identification as the gold standard.

Target genes evaluated were present in at least 88.1% (Nm), 32.9% (Hi) and 97.9% (GBS) of genomes analysed. Sensitivity and specificity were variable, and the best results for Nm were obtained for *sodC* with a sensitivity of 99.5% and specificity of 99.4%. Similarly, *fucK* was the best option tested for Hi with 96.3% and 94.7%. Finally *sip* gave the best results for GBS with 99.9% and 100%.

Our results show that the accuracy of assays was variable with the best target genes identified as *sodC*, *fucK* and *sip* for Nm, Hi and GBS, respectively. However, the specificity and sensitivity of *fucK* for Hi is relatively low compared to the other pathogens and more work is needed to identify a better target. As new interventions are going to be deployed, such as novel vaccines, it is important to regularly monitor the accuracy of these assays. Databases such as PubMLST, with semi-automatic curation and annotation of genomes and genomic analysis tools can be instrumental to this endeavour.

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#DT8 Serogroup analysis of Meningococcal strains causing Septic Meningococcal Arthritis in England and Wales: A retrospective study

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Background: *Neisseria meningitidis*, a coloniser of the nasopharynx, is the cause of invasive meningococcal disease (IMD) and associated with increased morbidity and mortality. Systemic meningococcal infection may present as septicaemia or meningitis or both, with life-threatening sequelae such as myocarditis, endocarditis, pericarditis, pneumonia, and septic meningococcal arthritis, as well as long-term effects like amputation, hearing loss and seizures. Septic meningococcal arthritis (SMA), a rare sequela of IMD, has been found to manifest as primary, secondary, or tertiary meningococcal arthritis. Meningococcal arthritis can present as mono or polyarthritis with the knee being the joint involved in most cases.

Objective: This study describes cases of septic arthritis in England and Wales from samples received at the Meningococcal Reference Unit, Manchester over a ten-year period, and the use of culture and PCR techniques in the laboratory diagnosis of meningococcal arthritis.

Methods: Synovial fluid samples sent to the Meningococcal Reference Unit (MRU) in Manchester were confirmed for the presence of *N. meningitidis* either directly by *ctrA* PCR test and/or following a positive culture result. In many cases, corresponding blood samples were also tested. Septic meningococcal arthritis was defined as the detection of *N. meningitidis* in a joint fluid following a bacterial culture or PCR test. *N. meningitidis* strains were further characterised based on their capsular polysaccharides into MenB, MenC, MenW, MenY and MenE serogroups.

Results: In all 276 samples with requests for the detection of *N. meningitidis* were selected for this study, of which 160 were joint or synovial fluid (representing approximately 58% of cases). *N. meningitidis* strains were detected by culture, PCR or both methods from 108, 37 and 15 joint fluid samples respectively. More than half (56.9%) of the joint fluid samples were knee joint fluid ($n = 91$), followed by hip (36.7%), ankle (8.1%), wrist (5.6%), elbow (5%) and shoulder (3.1%). Preliminary results show that MenW was the most frequent (41.25%) serogroup followed by B (26.25%), Y (20.63%), C (11.25%), and E (0.63%).

Conclusions: This study confirms knee joint, as previously published elsewhere, as the joint predominantly involved in SMA, with MenW as the predominant serogroup (representing 41.25%). Due to the rarity of SMA, most published studies are based on a few case reports. This study includes a large number of SMA cases. Further analysis of existing data will be needed to discuss the epidemiological implications of serogroups and their clonal complexes with respect to sample sites, age groups, and gender.

Funding source: Not specified

Surveillance

#S1 Impact of the COVID-19 pandemic on meningococcal vaccine coverage and disease incidence

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Keywords: Vaccination, COVID-19, impact, VCRs, incidence

Objective and Methods: Social distancing and other health measures implemented from March 2020 to slow the spread of COVID-19 may also impact other potentially life-threatening diseases such as invasive meningococcal disease (IMD). To understand the impact of COVID-19 restrictions on IMD incidence and coverage of routine meningococcal vaccines, we reviewed publically available health surveillance data for the UK.

Results: The UK COVER (Cover of vaccination evaluated rapidly) quarterly statistics for Jan–Mar 2021, which includes vaccinations scheduled following implementation of COVID-19 restrictions, shows a decrease in coverage of the MenB 16-week vaccine dose and Hib/MenC 12/13-month vaccine dose compared with the previous quarter (Table 1) [1].

	MenB dose 2	MenB booster	Hib/MenC
Oct-Dec 2020	92.4%	90.0%	90.9%
Jan-Mar 2021	92.3% (-0.1%)	89.2% (-0.8%)	89.9% (-1.0%)

The early impact of COVID-19 has been assessed in England using the three infant Hexavalent (DTaP/IPV/Hib/HepB) vaccine doses and the 12–13 month measles, mumps, rubella vaccine (MMR1) vaccine dose as proxies for routine primary immunisations scheduled <1 year of age and those scheduled ≥1 year of age, respectively, through monthly extractions of coverage data from Immform for all children who reach 6 months or 18 months of age in that calendar month. Up to April 2021, the data show a decrease in Hexavalent and MMR vaccine coverage every month since April 2020, compared with 2019 (April data summarised in Table 2) [2].

	Hexavalent	MMR1
April 2019	88.8%	87.8%
April 2020	84.2% (-4.6%)	87.6% (-0.1%)
April 2021	87.9% (-0.9%)	86.7% (-1.1%)

UK coverage of the adolescent, school-administered MenACWY vaccine was significantly lower during the 2019/2020 academic year compared with 2018/2019 [3–6]. The impact of MenACWY catch-up programmes introduced later in the 2019/2020 academic year will not become evident until these cohorts are re-evaluated in 2020/2021.

	MenACWY
2018/2019	87.3%
2019/2020	60.3% (-27.0%)

In England, 461 confirmed cases of IMD were reported during the 2019/2020 epidemiological year, a 12% decrease from the 526 cases reported in 2018/2019 [7]. During Oct-Dec 2020, there were 19 confirmed cases of IMD, a 90% decrease from 184 confirmed cases in the equivalent 2019 period [8].

Conclusion: The incidence of IMD cases has significantly declined during the COVID-19 pandemic, most likely due to measures implemented to prevent its spread. However, meningococcal vaccine coverage has

also decreased, potentially leaving many vulnerable once COVID-19 restrictions ease. It is vital that routine immunisations continue to be offered/rescheduled and catch-up plans implemented to prevent outbreaks of IMD in the future.

Funding source: Sanofi Pasteur

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#S2 Variations and inequalities in coverage of routine vaccinations against invasive meningococcal disease in the UK and Ireland

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Keywords: VCRs, variations, inequalities, vaccinations, IMD

Background: High vaccine uptake is crucial to the success of meningococcal vaccination programmes in the UK and Ireland, with $\geq 95\%$ vaccine coverage as the national targets.

Objectives/methods: We reviewed publicly available vaccine coverage data for the UK and Ireland to understand variation in uptake of routine meningococcal vaccines.

Results: Annual national vaccine coverage rates (VCRs) for routine meningococcal vaccines vary across the UK and Ireland and are generally $< 95\%$ (Table 1).

Within each nation, VCRs vary by region. In England in 2019/2020, Hib/MenC and MenB VCRs ranged from 80.6% (London) to 96.1% (South West), with only 2 out of 9 regions achieving $\geq 95\%$. In England, there is large variability in MenACWY VCRs across Local Authorities, with no area achieving $\geq 95\%$, further impacted by school closures through the COVID-19 pandemic. In England, VCRs for the GP-based catch-up cohorts in older adolescents and young adults remain low at $\sim 40\%$.

Socioeconomic inequalities in VCRs have been observed in the UK. In Wales, during 2017/2018 and 2018/2019, socioeconomic inequities in routine immunisation uptake in 2–5-year-olds widened. The proportion of children who were up-to-date with immunisations was higher in the least deprived vs most deprived areas. In Scotland; in 2018/2019, by the end of school year S4, 80.7% of pupils had received the MenACWY vaccine in most deprived vs 92.5% in least deprived areas.

Conclusion: Across the UK and Ireland, VCRs remain below national targets in many regions, and socioeconomic inequalities in coverage exist, with unvaccinated children remaining vulnerable to IMD. Understanding local drivers for low uptake and sharing best practice initiatives may help underachieving areas improve coverage.

Table 1. VCR for Hib/MenC and MenB vaccines in the UK (2019/2020) and Ireland (2018); and school-administered MenACWY vaccine in the UK (2019/2020) and GP-based catch-up programme in England (to end August 2019)

	VCR (%)								
	Hib/MenC		MenB		MenACWY				
	24 months	5 years	12 months	24 months	England and Wales Year 10, Scotland Year S4, Northern Ireland Year 12	England and Wales Year 9, Scotland Year S3, Northern Ireland Year 10	GP Cohort 1 (born 01.09.96 –31.08.97)	GP Cohort 2 (born 01.09.97 –31.08.98)	GP Cohort 3 (born 01.09.98 –31.08.99)
UK	91.0	92.9	92.9	89.4	86.8	60.3	–	–	–
England	90.5	92.5	92.5	88.7	87.0	58.3	38.7	36.7	40.8
Wales	94.1	94.9	95.5	93.8	86.0	75.0	–	–	–
Northern Ireland	92.2	95.5	94.5	92.0	82.1	64.5	–	–	–
Scotland	94.3	95.9	95.8	93.6	86.8	71.6	–	–	–

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Ireland	88	–	92	90	–	–	–	–	–
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Red=<95% target Green=>95% target

Funding source: Sanofi Pasteur

#S3: Changes in Pneumococcal Meningitis Incidence Following Introduction of PCV10 and PCV13: Results from the Global PSERENADE Project

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Keywords: Pneumococcal meningitis, PCV impact, global, incidence

Invasive pneumococcal disease has been reduced in countries that introduced pneumococcal conjugate vaccines (PCVs) in childhood national immunization programs. Because PCV impact may differ by syndrome, we assessed the change in pneumococcal meningitis incidence globally after PCV10/PCV13 introduction for children <5 years (<5y) and adults ≥65 years (≥65y), by PCV product.

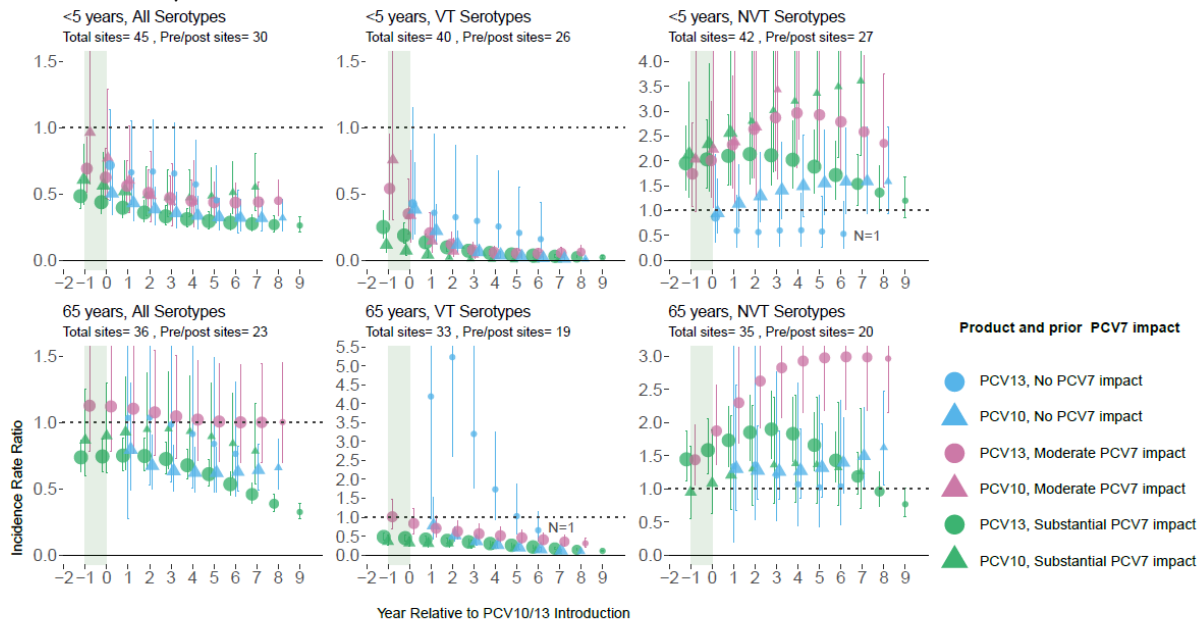
Meningitis cases with pneumococcus detected in cerebrospinal fluid and population denominators were obtained directly from surveillance sites. Meningitis incidence rate ratios (IRRs) were estimated by age group for each site by comparing pre-PCV incidence to each year post-PCV10/13 using Bayesian multi-level, mixed effects Poisson regression, accounting for trends in pre-PCV period. All-site weighted average IRRs were estimated using linear mixed-effects regression. Results were stratified by product (PCV10/PCV13) and prior PCV7 impact (none, moderate, or substantial). Analyses were performed for meningitis due to all serotypes (all-ST), vaccine-types (VT) (serotypes in product in use), and non-vaccine types (NVT).

Analyses included 20,728 cases (<5y: PCV13=10,588, PCV10=2849; ≥65y: PCV13=6293, PCV10=998) from 44 surveillance sites (13 PCV10, 33 PCV13; 2 sites contributed data to both) in 33 countries, primarily high-income (80%). Five years after PCV10/PCV13 introduction, all-ST pneumococcal meningitis in <5y declined 52-71% across product and PCV7 impact strata, but impact was heterogenous for ≥65y, ranging from no significant impact to a 39% decline (Figure). Impact against PCV10 types for PCV10 sites, and PCV13 types (including ST3, 6A,19A) for PCV13 sites was generally high across all strata for <5y (PCV10=98-100%, PCV13=79-96%), but lower for ≥65y (PCV10=80-82%, PCV13=54%-75%, except one stratum with no significant impact which had a single high HIV-prevalence site with concurrent non-vaccine interventions, including ART). NVTs increased across all strata for <5y (PCV10=1.5-3.4 fold, PCV13=1.9-2.9 fold), except one stratum that declined, but were heterogenous for ≥65y, ranging from no significant change to 2.7-fold increase (PCV10=1.3-1.4 fold, PCV13=1.0-3.0 fold).

Five years after PCV10/PCV13 introduction, all-ST pneumococcal meningitis in <5y significantly declined, driven by substantial declines in VTs and partially offset by increases in NVTs. Impact among ≥65y was heterogeneous, with overall net declines in some settings and return to baseline in others. Changes in post-PCV meningitis were similar to those of all IPD for <5y (data not shown). Data were limited from the meningitis belt, low-income, and high-burden settings.

Figure. All-site weighted average incidence rate ratios

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Size of point estimates (circles/ triangles) are proportional to the number of sites with both pre- and post-PCV data.

Total sites = any incidence data; pre/post = has both pre and post PCV10/PCV13 incidence data.

Year 0 = year PCV10/13 introduced; year -1 = last year of PCV7 use prior to switch to PCV10/13.

Funding source: The PSERENADE project is funded by the Bill and Melinda Gates Foundation as part of The World Health Organization Pneumococcal Vaccines Technical Coordination Project, grant number INV-010429/OPP1189065.

#S4 Regulation of Laterally Transferred *ispD* Gene in Meningococcal Urethral Clade US_NmUC

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Keywords: *Neisseria meningitidis*, *Neisseria gonorrhoeae*, Gene transfer, Terpenoid, Urethritis

The exclusively human pathogen *Neisseria meningitidis* (Nm) is estimated to cause over a million cases of meningococcal disease annually, resulting in 135,000 deaths. Nm typically colonizes the nasopharynx, but since 2013 cases of meningococcal urethritis have increased; these urethritis cases were originally presumed to be caused by the urogenital pathogen *Neisseria gonorrhoeae* (Ng). This emerging group of urethral Nm has been designated the US Nm urethritis clade, US_NmUC. Whole genome sequencing of over 200 US_NmUC isolates revealed that the Nm ancestor underwent recombination with Ng, resulting in the integration of a 3.3 kb segment of gonococcal DNA into the meningococcal genome; the 3.3 kb segment contains 5 genes that are part of a larger 9-gene operon. Preliminary data showed that one of the recombinated gonococcal alleles, the terpenoid precursor synthesis pathway gene *ispD*, has a 50-fold higher expression in US_NmUC isolates compared to non-US_NmUC meningococci, while the genes flanking *ispD* do not have altered expression. To determine if the increased expression of *ispD* in US_NmUC was the result of newly created promoters, LacZ reporters spanning the beginning of the operon to the 5' region of *ispD* were used to measure promoter activities by a β -galactosidase assay. Translational reporters of clade and non-clade Nm upstream sequences of *ispD* showed comparable activity, suggesting that the difference in *ispD* expression was not a result of increased transcription in US_NmUC isolates. *IspD* has been shown to be essential in several gram-negative bacteria including *E. coli* and *Salmonella enterica*. Viable *ispD* deletion mutants were only successfully generated in a strain with *ispD* complemented at a distinct genomic location, indicating that *ispD* was essential in the clade. The biological consequence of integrating the gonococcal *ispD* into US_NmUC remains under investigation.

Funding source: NIH/NIAID R01AI127863 R21AI128313

#S5 Etiologies of community acquired bacterial meningitis and antibiotic resistance patterns in Africa over the last 30 years: A Systematic Review

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Keywords: bacterial meningitis, antimicrobial resistance, community acquired bacterial meningitis, Africa

ABSTRACT: Community Acquired Bacterial Meningitis (CABM) is a leading cause of morbidity and mortality in Africa, affecting over 2.8 million people globally annually. The African continent bears the largest burden of CABM with six out of the ten countries having the highest incidence and mortality. This systematic review set out to determine the leading causes of CABM in Africa, the distribution of etiologies across regions, and the extent of antimicrobial resistance of identified microbial agents.

Methodology: The databases PubMed and Embase were queried with key search words “bacterial meningitis in Africa”, “community acquired bacterial meningitis” or “meningitis in Africa” published between 1990 and 2019. Using the PRISMA guidelines for systematic reviews, the search retrieved 112,972 articles. We included studies reporting primary patient data with confirmed CABM.

Results: Sixty-four studies were analyzed which were conducted in 23 African countries between 1990 and 2019. Cumulatively, we analyzed 118,716 suspected cases of CABM, with confirmed CABM in 34,593 (29%) cases. Streptococcal pneumoniae (Spn) was found to be the most prevalent cause of disease at 12.4% (CI 11.1%-13.6%), Neisseria meningitidis (Nm) at 8.1% (CI 7.1%-9.2%) and Hemophilus influenza (Hib) at 4.0% (CI 3.6%-4.3%). The etiologies varied by region, with Nm being most prevalent in West and South Africa regions and Spn in the rest of the continent. Salmonella prevalence was 0.35% (0.22%-0.47%) representing 16% of the total cases in East Africa but less than 1% in other regions. Of the 64 studies reviewed, 29 (45%) reported on antimicrobial resistance. Resistance was found to be highest in ampicillin 2.7% (CI 2.1%-3.3%) and gentamycin 2.75%(2.09-3.40)

Conclusions: We found gross paucity of data on CABM in Africa despite bearing the highest burden of disease. Spn and Nm are still the leading causes of disease, and etiology varied markedly with region. Antimicrobial resistance of ampicillin and gentamycin are widespread despite being the commonest drugs used in the treatment of CABM in Africa.

Funding source: Kiran Thakur is supported by the National Institute of Health, NINDS K23 NS105935-01 and NIH/NICHD 1R01HD074944-01A1

#S6: K1 Escherichia coli Have the Capacity to Colonise and Adult Mouse Brain at 48h Post Infection by Utilising a Cellular Component Inside the Host

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Keywords: K1 E.coli; meningitis; neonates; infection; ExPEC

Extraintestinal pathogenic Escherichia coli (ExPEC) are a common cause of septicaemia and one of the leading causes of neonatal meningitis. Within this group, K1 capsule type E. coli are the most associated with meningeal infection in neonates. In our meningitis mouse model, previously used in pneumococcal meningitis studies, cefazolin treated adult CD1 mice were used to research the pathogenic steps in K1 E. coli meningitis. Following double treatment with cefazolin at 12 and 24h post infection with a K1 E. coli strain IHE 3034, groups of mice (n=5) were sacrificed at predetermined time points. Blood samples from the groups indicate decreasing bacteraemia for the first 48h, with negative blood counts at day 3. Spleen – a major blood filtering organ – is E. coli positive for the entire time course, with a decreasing bacterial load pattern as seen in the blood. –In contrast to blood and spleen, brain counts show an increase in CFUs, which remain elevated during the 72h infection. Control mice become septic by 24h, therefore cannot be monitored for the whole three days as all animals would succumb to the infection without treatment. Confocal microscopy shows E. coli associated with CD31+ perivascular endothelial cells at 24h. Very few bacterial clusters or foci can be seen at the 24h time point, with most bacteria seen as single cells, suggesting an invasion event on day one post infection. At 48h major E. coli foci can be observed around the meningeal perimeter, however, no association to CD31+ cells can be seen. At 60h majority of bacterial signal is within or near CD169+ perivascular macrophages. From these observations, it is likely the K1 E. coli hijack multiple cellular components, potentially in a sequential way, before spreading into the CSF and causing invasive disease.

Funding source: BBSRC-iCASE

#S7: Comparing MATS, gMATS and MenDeVAR for estimating 4CMenB vaccine strain coverage among English invasive serogroup B meningococcal isolates

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Keywords:

- Meningococcal Antigen Typing System
- MATS
- Meningococcal Derived Vaccine Antigen Reactivity
- MenDeVAR
- 4CMenB coverage

Background: The meningococcal serogroup B (MenB) vaccine, 4CMenB, incorporates PorA, fHbp, NHBA and NadA. The Meningococcal Antigen Typing Scheme (MATS) assesses 4CMenB strain coverage based on expression or genotypic assignment of PorA P1.4, and/or sufficient expression of sufficiently cross-reactive fHbp, NHBA or NadA. Genetic (g)MATS and the Meningococcal Deduced Vaccine Antigen Reactivity (MenDeVAR) Index provide genotypic alternatives to MATS. We compared 4CMenB coverage of English MenB isolates according to MATS, gMATS and MenDeVAR.

Methods: MATS, gMATS and MenDeVAR analyses were applied to English invasive MenB isolates with complete MATS data from 2014/15 to 2017/18 (n=775/792).

Results: MATS predicted coverage for 100% of isolates (72% covered, 28% not covered). gMATS gave a relatively high level of prediction vs MenDeVAR (76.6% vs 63.1%). gMATS was also a closer match to MATS in terms of isolates covered (73.9% vs 53.8%) and not covered (26.1% vs 9.3%).

Discussion: When assessing 4CMenB coverage of a national collection of invasive meningococcal isolates, gMATS performed better than current version of MenDeVAR in terms of % prediction and closeness to MATS outcomes.

Publication of available MATS data, default consideration of fHbp variant 2 and 3 peptides as not covered, and a less stringent threshold for MenDeVAR would serve to eliminate the majority of discrepancies.

Funding source: GSK

#S8 Assessing 4CMenB strain coverage of invasive meningococcal strains in an English and Welsh vaccine-eligible cohort using non-culture draft genome sequences

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Keywords: Meningococcal, MenB, Bexsero, PCR, Surveillance

Introduction and Aim: Approximately one half of the invasive meningococcal disease cases in England and Wales are confirmed solely using PCR on clinical samples in the absence of a viable *N. meningitidis* isolate. Such 'non-culture' samples contain limited amounts of residual meningococcal DNA and so only a certain proportion of samples have sufficient bacterial DNA concentrations to allow whole genome sequence analysis (WGS). WGS is a useful tool for identifying the complete repertoire of 4CMenB antigen sequences among meningococcal strains. The genetic sequences can be used to predict strain coverage of 4CMenB using the Genetic Meningococcal Antigen Typing System (gMATS) scheme. Here we describe WGS of a substantial proportion of non-culture strains among vaccine-eligible cohorts (0-5 years olds) in England and Wales and the corresponding gMATS coverage predictions.

Methods: Illumina sequencing was performed following RNA-bait enrichment using the Agilent SureSelect system and sequences were screened for human reads before assembly. Draft genomes were indexed and annotated within PubMLST.org/*Neisseria*. The isolate-derived antigenic data for corresponding vaccine-eligible culture cases were extracted from the Meningococcal Genome Library (MGL) on PubMLST.org/*Neisseria*. 4CMenB coverage for the non-culture and culture cases was predicted using the published gMATS scheme. A small proportion of non-culture genomes yielded incomplete antigen profiles. These were considered 'unpredictable' in the absence of a covered antigenic variant.

Results: Between 1st September 2015 and 31st August 2018, 327 non-culture cases occurred among the vaccine eligible cohort. A clinical sample suitable for WGS was submitted for 100 (30.6%) of these cases. After sequencing, a total of 84 samples yielded complete 4CMenB antigen profiles (fHbp, NHBA and PorA). Two of three antigens were characterised from a further nine samples and the remaining seven samples yielded only one antigen sequence. The gMATS coverage prediction among the genome sequenced subset of non-culture cases was 70% (70/100). This compares to gMATS coverage estimate of 70.7% (195/276) among the culture cases in the same cohort and study period. Among all genome sequenced culture and non-culture cases (n=376/603, 62.4% of total IMD cases) the gMATS coverage was 70.5%.

Conclusions: These results indicate that culture status has no substantial impact on gMATS strain coverage predictions. Whole genome sequencing of non-culture samples is a useful tool for assessing coverage of individual strains (especially for outbreak/cluster management), however, in England and Wales, isolates alone provide a representative dataset on which to base overall strain coverage predictions.

Funding source: Whole genome sequencing of non-culture cases was funded by GlaxoSmithKline (GSK)

#S9: Rapid Transmission of a Hyper-Virulent Meningococcal Clone Due to High Effective Contact Numbers and Super Spreaders

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Keywords: *Neisseria meningitidis*, meningococcus, meningitis, asymptomatic carriage, transmission, mathematical model

Rapid transmission, a critical contributory factor in outbreaks of invasive meningococcal disease, requires naïve populations of sufficient size and intermingling. We examined genomic variability and transmission dynamics in a student population subject to an 11-fold increase in carriage of a hypervirulent *Neisseria meningitidis* serogroup W ST-11 clone. Phylogenetic clusters, mutation and recombination rates were derived by bioinformatic analyses of whole-genome sequencing data. Transmission dynamics were determined by combining observed carriage rates, cluster sizes and distributions with simple SIS models. Between 9 and 15 genetically-distinct clusters were detected and associated with seven residential halls. Clusters had low mutation accumulation rates and infrequent recombination events. Modeling indicated that effective contacts decreased from 10 to 2 per day between the start and mid-point of the university term. Transmission rates fluctuated between 1 and 4% while the $R(t)$ for carriage decreased from an initial rate of 47 to 1. Decreases in transmission values correlated with a rise in vaccine-induced immunity. Observed carriage dynamics could be mimicked by populations containing 20% of super spreaders with 2.3-fold higher effective contact rates. We conclude that spread of this hypervirulent ST-11 meningococcal clone depends on the levels of effective contacts and immunity rather than genomic variability. Additionally, we propose that super-spreaders enhance meningococcal transmission and that a 70% MenACWY immunization level is sufficient to retard, but not fully prevent, meningococcal spread in close-contact populations.

Funding source: This work was supported by the Medical Research Council (MRC) (MR/M020193/1) awarded to CB. JH was supported by the Biotechnology and Biological Sciences Research Council (BBSRC) (BB/T00746X/1).

#S10 Acute Bacterial Meningitis: epidemiology dynamic in the last 3 decades in a latinamerican pediatric center

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Keywords: Meningitis, epidemiology, prevention, vaccines, sequelae

Introduction: to defeat meningitis by 2023 is a goal of the World Health Organization and to know its dynamic is essential to guide public health strategies. The aim of this study was to describe the epidemiology of acute bacterial meningitis (ABM) in a Latin-American pediatric center.

Methods: retrospective study in children <15years, diagnosed with ABM, discharged between 1993 and 2020. Demographic, epidemiological, laboratory and clinical variables were studied. Descriptive statistics and Stata 15 analysis were used.

Results: 564 ABMs were registered, 63%, 18.8% and 18.2% between 1993/2000, 2001/2010 and 2011/2020, respectively, with an average of cases/year of 39,4; 9,2 and 7,8 in the same periods. The main etiologies were *N. meningitidis* (48%), *S. pneumoniae* (16.4%), Hib (6,7%) and *S. agalactiae* (5,1%). Not known etiology occurred in 16.3%. According to age, 42% were <1 year; 32% between 1 and 4; and 25% > 5years. Overall case fatality rate was 4.2%, concentrated in 1993/2000, <5years and due to *S. pneumoniae*. Sequelae was evidenced in 16%, corresponding to 13.3%, 15.5% and 26% of the cases between 1993/2000, 2001/2010 and 2011/2020, respectively; mainly in *S. pneumoniae* (40.9%), *S. agalactiae* (33.3%) and Hib (31.3%). The percentage of sequelae according to the age of ABM onset was 25% in <1 year; 9.2% 1 – 4years and 7.8% > 5years, regardless the etiology. Hib and *S. pneumoniae* cases predominated in <5 years, while *N. meningitidis* was homogeneously distributed in all age groups. All of them decreased after the introduction of conjugate vaccines. *S. agalactiae* increased between 2011/2020. Cases without etiology were more frequent in <1year, with no decrease from 2001 onwards.

Conclusions: Despite the decrease in cases and mortality after the introduction of vaccines against some etiologies, the pediatric burden of disease and rate of sequelae is still high and other agents such as *S. agalactiae* have increased their frequency. Molecular techniques could optimize etiological diagnosis.

Funding source: none

Support and care for people affected by meningitis

#SC1: Rebuilding Futures after Meningitis

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Keywords: Meningitis, wellbeing, support, aftercare, after-effects

The impact of meningitis can be devastating, leaving families bereaved and individuals living with life changing after-effects. In 2019 Meningitis Now launched its Rebuilding Futures Fund to help address the support needs of those affected by meningitis.

Aim: To provide a flexible and bespoke fund enabling each person or family to apply for up to £1,000 towards the support or practical help they need most. The fund comprises of four award categories:

- Health and Wellbeing
- Opportunities
- Specialist Equipment
- Bereavement.

The First Year: During the first year 82 awards, totalling over £63,000, were made. Awards covered all four categories with funding provided for talking therapies, complementary therapies, mobility aids, IT equipment, training and tuition, contributions towards funeral costs and headstones.

Evaluation: To determine the outcomes and impact of the Rebuilding Futures Fund, data was collected on the application form (baseline) and evaluation form. This included the Measure Yourself Concerns and Wellbeing (MYCaW) (1) questionnaire.

People applying were asked to think about how meningitis had affected them and state one or two specific concerns that they most wanted help with. People were also asked about their wellbeing by using the question "How are you feeling in yourself?"

Concerns and wellbeing were rated for severity using a seven-point Likert scale with 0 meaning "not concerned at all" to 6 meaning 'bothers me greatly'.

In-depth phone interviews were also conducted with 16 people who had received support through the fund.

Key Outcomes: Full evaluation data was received from 55 people. Meningitis Now commissioned Chrysalis Research UK to independently analyse this data (2)

- 98% of people said that the support they received via the Rebuilding Futures Fund helped them; 93% of respondents stated that it had 'helped a lot'
- 95% of people felt that their award had made a difference to them and their life, with 91% stating that it made a big difference
- Concerns negatively affecting people's lives and/or wellbeing were fully or partially alleviated with a 2.7-point decrease on the MYCaW severity of issues scale.
- There was evidence of a noticeable improvement to the wellbeing of award recipients and their family members with a 1.7 increase on the MYCaW wellbeing scale.

Conclusion: The evidence from the evaluation data has demonstrated that the Rebuilding Futures Fund has made a significant positive impact on individuals and families affected by meningitis. Meningitis Now will continue to offer the Rebuilding Futures Fund as an important part of its support services.

Funding source: Meningitis Now has received donations from many funders to support this new programme, including The Worshipful Company of Butchers, Royds Withy King, Sobell Foundation and The Hospital Saturday Fund. A full list of funders can be provided upon request.

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#SC2 Sequelae at hospital discharge in 49 children with invasive meningococcal disease, Chile, 2009-2019:

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Keywords: *Neisseria meningitidis*, meningococcal infection, sequelae, pediatric

Background: Invasive meningococcal disease (IMD) is an infection caused by *Neisseria meningitidis* with fatal outcomes. Twenty percent of survivors may experience permanent or long-term sequelae. The aim of this study was to describe the sequelae at hospital discharge caused by IMD in children between years 2009-2019.

Methods: Cross-sectional study performed with medical records in two pediatric public hospitals of Santiago, Chile. Patients with diagnosis of IMD from 2009-2019 were included. Bivariate analysis and logistic regression were performed.

Results: The records of 52 patients were reviewed, 3 patients died in the first 24 hours, so we performed statistical analysis with 49 patients. Sixty-nine% were male, median age 9 months [IQR-19.5], 67% were admitted to intensive care unit. Serogroups W and B were identified in 30 and 17 cases, respectively. Significant differences were found comparing patients with/without sequelae: shock 73%vs15% ($p=0.0001$), drowsiness/irritability 60%vs26% ($p=0.02$), neurological deficit 53%vs21% ($p=0.0001$), meningitis+meningococemia 57%vs10% ($p=0.001$), septic arthritis 23%vs0% ($p=0.02$), and meningeal signs 57%vs21% ($p=0.01$) increased the risk of having sequelae 20 times [CI95% 1.44-277]. Patients without sequelae had more bacteremia 47.3%Vs3.3% ($p=0.001$) which was protective factor (OR 0.01 [CI95% 0.00-0.33]). Thirty (61%) patients had any sequelae. The most frequent: 1. Neurologic 63%, including psychomotor developmental delay 32% (10/31), speech impairment 22% (7/31), seizures with hyper/hypotonia 16% (5/31) each and attention deficit hyperactivity disorder 6% (2/31); 2. Hearing loss 33%, and 3. Osteoarticular 30%.

Conclusions: We found a high proportion of sequelae in patients studied. Neurological sequelae were the most prevalent. It's necessary to implement multidisciplinary follow-up programs to reduce their long-term impact.

Funding source: None

Advocacy and engagement

#A1 Public Misconceptions around Invasive Meningococcal Disease and Meningococcal Vaccines

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Keywords: Misconceptions, vaccines, meningitis, IMD, public

Meningococcal meningitis is a subset of Invasive meningococcal disease (IMD) that affects 1.2 million per annum globally,¹ with children under 5 years old being the most likely to contract IMD.² Whilst IMD caused by meningococcal strains A, B, C, W and Y can be prevented through vaccination, common public misconceptions regarding both meningitis and meningococcal vaccination have been shown to have a negative impact on vaccine coverage rates (VCRs).³

Herein we discuss some of the common misconceptions around meningitis and meningococcal vaccines, as well as strategies that healthcare professionals (HCPs) can utilise to help support public understanding of these topics and help improve VCRs. Some misconceptions include:

- Understanding of the broad term 'meningitis'
- Awareness of the causes and transmission of meningitis
- Who should be vaccinated against IMD

Below we have explored two of these misconceptions in further detail:

MYTH: There is just one type of meningitis

Pathogen	Examples
Bacteria	Meningococcal, pneumococcal, <i>Haemophilus influenzae type b</i>
Viruses	Herpes Simplex Virus, Human Immunodeficiency Virus, Mumps Virus
Fungi	Cryptococcus, Candida, Blastomyces
Parasites	Angiostrongylus cantonensis, Baylisascaris procyonis

Table 1: pathogens that can cause meningitis⁶

Meningitis can be caused by a variety of different pathogens (table 1) and currently, it is only possible to directly vaccinate against 5 (of at least 12 identified) serogroups of *Neisseria meningitidis*, which causes most cases of bacterial meningitis. MMR, PCV13 and Hib vaccination may also reduce risk of meningitis caused by these pathogens.

Whilst some meningitis types currently have no specific vaccines, preventive measures such as good respiratory hygiene and minimizing overcrowding could help reduce the likelihood of contracting the non-vaccine strains of meningococci, pneumococci, and *Haemophilus influenzae*.

MYTH: Meningitis is easy to diagnose Early stages of meningitis can be hard to recognise and often gets mistaken for influenza with fever and headache. Additionally, different types of meningitis may have the same presentation and thus choosing treatment can be challenging. Medical help should be sought urgently if meningitis is suspected.

What can HCPs do to Support their Patients? To ensure that the public is fully aware of the key aspects of meningitis, visual aids and education leaflets should be made available for parents and carers as well as adolescents and adults being vaccinated. HCPs also require adequate training on early detection of meningitis and access to early referral and treatment.

Work could also be done to support schools to send letters if cases present to assist parents with early detection and prevent uniformed rumours, as well as providing text messages with link to NHS information. Parents and teenagers need to be fully informed in order to consent to vaccination.

Funding source: Sanofi Pasteur

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#A2 MEVacP : a public engagement website about meningitis and vaccine policy

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Keywords: Public engagement, meningitis, vaccine, website, epidemiology

One of the public health goals set by the WHO is to eradicate meningitis by 2030. To achieve this, researchers and health professionals are sparing no effort to improve diagnostic methods and means of communication and awareness, especially in sub-

Saharan Africa where meningitis epidemics are still reported. It is in this context that a website MEVacP (Molecular Epidemiology Vaccine Policy, <https://maidenlab.zoo.ox.ac.uk/mevacp-homepage>) has been created to improve our understanding of bacterial meningitis in Africa

A multidisciplinary team composed of researchers from the University of Oxford and from Africa including the Centre Suisse de Recherche Scientifique (CSRS) (scientists, physicians, social scientists and public health specialists) has been set up to run this website. The targets are threefold: teachers and parents, doctors and health professionals, and researchers and laboratory personnel. The main aspirations of this website include: promoting awareness of meningitis, improving surveillance and our understanding of the epidemiology of meningitis and the prevention of infection through vaccination. Thus, this website details aspects of meningitis ranging from the causes, symptoms and what is meningitis. It also offers opportunities to understand vaccination policies that are implemented around the world. This is a bilingual website existing in English and French with some parts still in development. However, detailed documentation is presented on the 4 most virulent bacteria in terms of bacterial meningitis, namely *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* and *Haemophilus influenzae*. This includes disease manifestations, carriage, serogroups or serotypes and prevention.

The consequences of late treatment such as deafness, brain damage, learning disabilities and loss of limbs are presented. Continuous improvement of this site, which is intended to be interactive and accessible to all, is envisaged for use in teaching and awareness-raising events. The ultimate goal of this scientific contribution is to raise awareness of the need to vaccinate in order to defeating meningitis in worldwide.

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#A3 Interactive Web-based Visual Exploration of Invasive Meningococcal Disease

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Keywords: IMD, Storyboard, Interactive, Web-based, PubMLST

Invasive Meningococcal Disease (IMD) is caused by the human-associated bacterium *Neisseria meningitidis* when it invades the blood, causing septicemia, and/or the meninges, causing meningitis. IMD affects most nations and age groups, though age distribution is not uniform, with the highest rates in infants, children and teenagers. Epidemiological information is crucial for the public health response.

Microbial genomics and associated technologies enable improved diagnosis of existing disease and the development of effective and targeted treatment strategies. They also provide opportunities to support the detection, surveillance, tracking, monitoring, and assessment of infectious diseases. Furthermore, they support the development and assessment of vaccines, the analysis and prediction of anti-microbial resistance, and studies of invasive potential and virulence. There is an explosion of highly valuable genomic data. There are reference databases of genomic data, including PubMLST.org, which has been developed to facilitate open access. PubMLST contains extensive curated databases that integrate population sequence data with provenance and phenotype information for over 100 different microbial species and genera.

The large size and complexity of these rich genomic databases mean that it is very difficult to gain insight into, and understanding of, the information they contain.

Visual Analytics (VA) provides an effective means of interactively extracting and representing information that enables users to research and gain insight into, and understanding from, data so as to develop informative contextual views of what is happening. The research challenge in designing an interactive VA systems is to decide how to transform inherently non-visual data, such as genomic IMD data, into a natural, intuitive and easily accessible visual form, suitable for a wide range of users.

We have developed an interactive web-based 'Storyboard' (<https://maidenlab.zoo.ox.ac.uk/introduction-invasive-meningococcal-disease-imd>) using data from PubMLST that provides information on IMD occurrence in England, for public engagement and disease surveillance. It supports user exploration and analysis of the time-evolution of, and detail about, the changes in, and distribution of, IMD. Users can interactively explore the epidemiological years, serogroup, clonal complex, geographical region and age group, and thus, for instance, discern patterns and trends of disease. The Storyboard enables users of all levels and types to explore and understand the complex information in an easy and intuitive manner, and without the need for training or a user manual. Users can be the public, policy makers, decision makers, epidemiologists, researchers, genomics specialists and others.

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