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An analysis of *Neisseria meningitidis* strains causing meningococcal septic arthritis in England and Wales: 2010–2020

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SUMMARY

Objectives: To analyze clinical meningococcal strains associated with meningococcal septic arthritis cases in England and Wales, and to identify associations between patient age, the synovial joint affected and strain characteristics.

Methods: IMD cases confirmed by the Meningococcal Reference Unit (UK Health Security Agency) between January 2010 and December 2020 were included in the analysis. Septic arthritis cases were defined as those featuring detection and/or isolation of *N. meningitidis* from an articular site. Capsular grouping was performed by serology on clinical isolates and/or real-time PCR on clinical samples.

Results: We identified 162 cases of meningococcal septic arthritis, representing 2% of all invasive meningococcal disease cases during the study period. The knee and the hip were the most commonly affected joints, with the former significantly more frequent in adults and the latter seen more commonly in children and adolescents. Group B strains were between 2 and 6 times less likely to cause septic arthritis in relation to groups W, C and Y strains.

Conclusions: Meningococcal septic arthritis remains a rare manifestation of invasive meningococcal disease. Strain and age associations identified in this study remain unexplained. Future analyzes including clinical case information may help to explain these findings.

Introduction

Neisseria meningitidis, a coloniser of the nasopharynx in humans, is the cause of invasive meningococcal disease (IMD); often characterised by severe systemic infection with relatively high morbidity and mortality.[1] Meningococcal strains are classified into twelve capsular groups but, in England and Wales (E&W), groups B, C, W and Y cause the majority of invasive disease.[2] Most IMD cases present as septicaemia, meningitis or both. Secondary localised infections such as myocarditis, endocarditis, pericarditis, pneumonia, and septic arthritis are less frequently observed.[3]

Meningococcal septic arthritis (MSA) occurs when *N. meningitidis* present in the blood colonises the synovial joints such as the knees, hips, ankles or wrists. Colonization can also occur following penetrative injury or surgery. A recent review suggested that around 10% of all septic arthritis cases are caused by *N. meningitidis*.[4] MSA can manifest as primary (in the absence of systemic symptoms), secondary (in addition to systemic disease), or tertiary (accompanying chronic disease) syndromes.[4,5] In the literature, MSA case reports predominantly focus on primary manifestation, as secondary infection is often seen as peripheral to wider systemic presentation. Whilst primary MSA typically presents with mild symptoms such as localised pain, inflammation and reduced range of movement, in rare cases, primary MSA can result in damage to the articular cartilage. Meningococcal colonization of syn-

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ovial joints also poses a risk of systemic disease should infection seed/reseed the blood (including repeat cases/ chronic disease).

Most reported cases involve a monoarticular presentation with large joints such as the knee and/or hip being the most common site of infection, although polyarticular presentation has been reported.[4,6] Treatment of MSA typically involves arthroscopic wash out or aspiration to dryness of the joint and antimicrobial administration, commonly Penicillin G and/or third-generation Cephalosporins.[4]

The majority of case reports/series provide limited meningococcal strain characterization with most typing to the serogroup level only, whilst several only report the species. Here we describe a large collection of English and Welsh meningococcal strains from MSA cases confirmed by the UK Health Security Agency's Meningococcal Reference Unit (UKHSA MRU) over an eleven-year period.

Materials and methods

Case ascertainment

The UKHSA MRU provides strain characterization services on clinical meningococcal isolates submitted from local microbiology laboratories in E&W. The MRU also provides a free meningococcal PCR detection service for submitters in E&W. IMD cases confirmed between 1st January 2010 and 31st December 2020 (inclusive) were used in this analysis. Information on clinical sample isolation site and other clinical details are supplied by submitting laboratories. Antimicrobial susceptibility of isolates against Penicillin G, Ciprofloxacin, Rifampicin and Cefotaxime was determined using Etest method as previously described.[7] Interpretative breakpoints described in the European Committee on Antimicrobial Susceptibly Testing (EUCAST) v10.0 scheme were used.

Additional data on sampling site was obtained through routine follow up of confirmed cases of IMD by the UKHSA Immunisation and Vaccine Preventable Diseases Division based on information provided by the Health Protection Team managing the case and General Practice.

Strain characterization

Serogrouping of clinical isolates was performed as previously described.[8] Genogrouping from clinical samples (genogroups B, C, W and Y) was performed by real-time PCR.[9] Genomic data were obtained from the Meningitis Research Foundation Meningococcus Genome Library which contains fully annotated draft genomes for all invasive meningococcal isolates received by the MRU since July 2010.[10]

Associations between capsular group and the joint infected were assessed using Chi-Squared test. A multivariate logistic regression analysis was performed to estimate the odds of septic arthritis among different capsular groups controlling for age group (Jamovi v.2.2.5.0). A significance level of 0.05 was used.

Results

Case ascertainment

Between January 2010 and December 2020, the MRU laboratory-confirmed 8081 cases of English, Welsh and Northern Irish IMD cases. Of these, 162 cases (2.0%) featured identification/detection of *N. meningitidis* from one or more synovial joints. Across the eleven years studied, the proportion of IMD cases involving isolation/detection of *N. meningitidis* from synovial fluid varied from 0.95% to 3.33%. Of the 162 MSA cases, 124 (76.5%) yielded a viable meningococcal isolate with the remaining 38 cases confirmed using real-time PCR detection only.

Clinical site analysis

The most common joint site of isolation/detection was the knee with 92 cases, representing more than half of all MSA cases (56.8%). Other joints of isolation/detection were the hip (22/162, 13.6%), the ankle (13/162, 8.0%), the wrist (9/162, 5.6%), the elbow (8/162, 4.9%), the shoulder (5/162, 3.1%) and the intervertebral disk (1/162, 0.6%) (Table 1). For ten cases, the strains were recorded as being isolated/detected from synovial fluid, but the precise clinical site/joint is not known. In two cases, meningococcal isolation/detection was attained in two separate joints: one from the wrist and ankle, and another from the shoulder and knee (Table 1).

For the majority of MSA cases only synovial fluid samples were submitted (117/162, 72.2%). Systemic infection was confirmed in 23 cases (14.2%), with meningococci detected from blood ($n = 17$), cerebrospinal fluid (CSF) ($n = 3$) or both ($n = 3$). In 21 cases (13.0%), isolation/detection was achieved from synovial fluid only with blood samples testing negative, suggesting a localised infection only. One case involved detection from a knee joint with a negative CSF PCR result.

Patient analysis

Patients with MSA ranged from 4 months to 95 years of age (median = 50.3, SD = 29.1) with 49.0% identified as female. More than half of MSA cases (88/162, 54.3%) occurred in patients aged ≥45 years with numbers generally increasing with age but with an early peak in the 1–4 years age group (23/162, 14.2%) (Fig. 1).

The joint of isolation/detection varied significantly by age group (adults (>19 years) vs. children/adolescents. $X^2 = 49.4$, $p < .001$). MSA of the knee was strongly associated with adults (>19 years), as opposed to children and adolescents (80.4% vs. 19.6% of cases, respectively. $P < .001$). Conversely, cases of MSA of the hip were more frequently observed in children and adolescents than adults (86.4 vs. 13.6% of hip cases, respectively. $P < .001$). No significant age associations with other joints were observed.

Capsular group analysis

The majority of MSA cases were caused by group W strains (40.7%), followed by group B (26.5%), group Y (20.4%), group C (11.7%) and group E (0.6%) strains (Supplementary Table 1).

Numbers of group W MSA cases were relatively low between 2010 and 2014 (Fig. 2) despite increasing group W disease through that period. Group W cases peaked in 2015 with 15 cases, representing over half (53.6%) of all MSA cases in that year. Group W cases then fell overall in the following years, after the introduction of the MenACWY teenage vaccination program, accounting for 3 of only 8 (37.5%) cases in 2020[18]. In the same period MSA case numbers due to group B remained relatively stable, ranging from 2 to 7 cases each year (Fig. 2).

Despite group W being the most common group among MSA cases (40.7%), only 16% of all IMD cases were caused by this capsular group during the study period. Conversely, group B represented 67.0% of all IMD cases but caused only 26.5% of MSA cases (Supplementary Table 1). The proportions of all IMD caused by groups Y and C were 10.6% (vs 20.4% of MSA only) and 4.8% (vs 11.7% of MSA only), respectively.

Group W strains caused the majority (63.0%, $n = 34/54$) of MSA cases among children and adolescents (≤19 years old), followed by group B (27.8%, $n = 15$), group C ($n = 3$) and group Y ($n = 2$) (Fig. 3). Among cases not featuring MSA (non-MSA cases), the vast majority in children and adolescents were caused by group B (82.7%). In adults, the distributions between MSA and non-MSA cases showed greater similarity, although group B was again under-

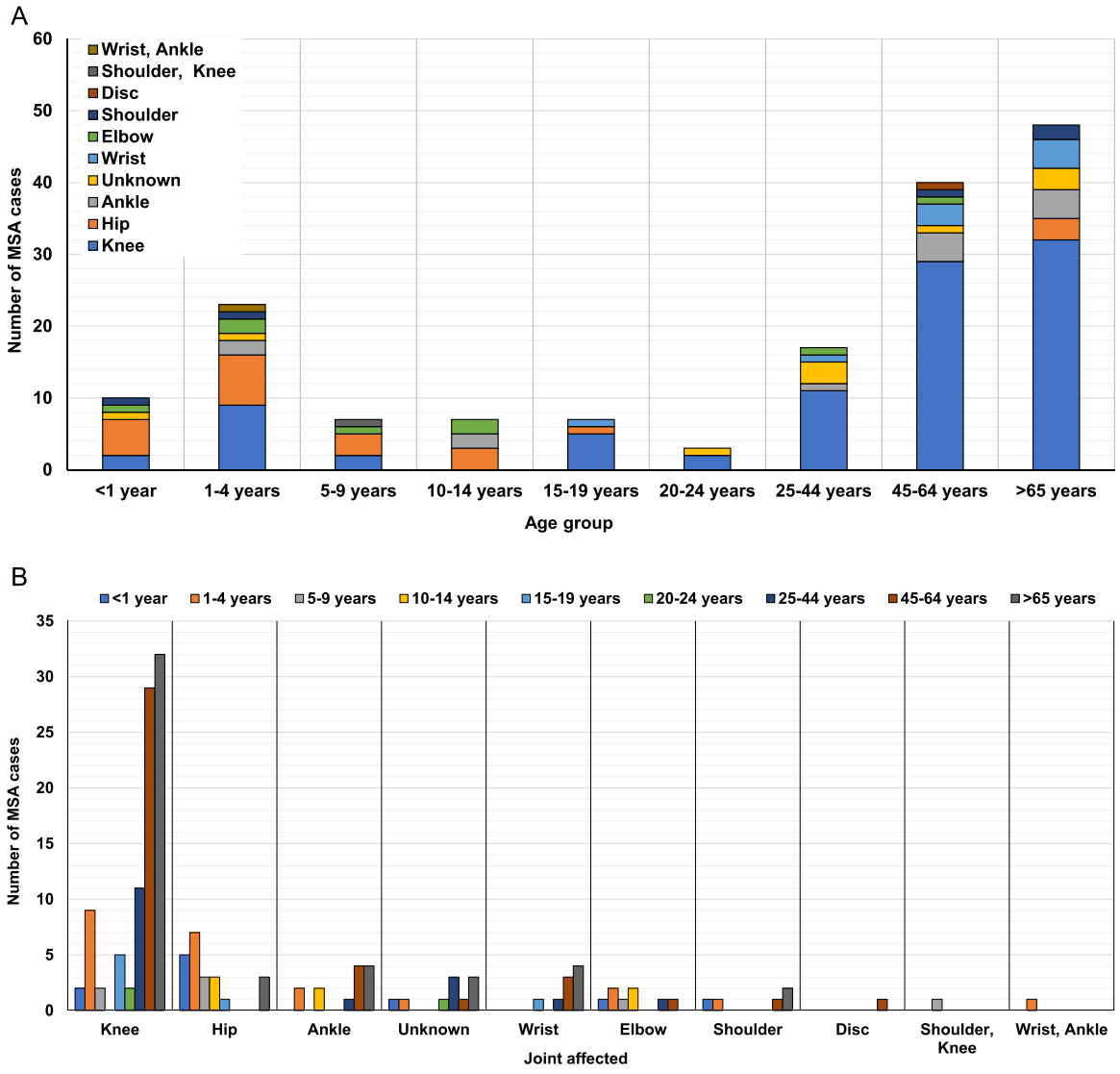

Fig. 1. Number of MSA cases by age group and joint affected. (A) Stacked bar chart showing joint distribution among each patient age group. (B) Clustered bar chart showing age distribution of MSA patients by joint affected.

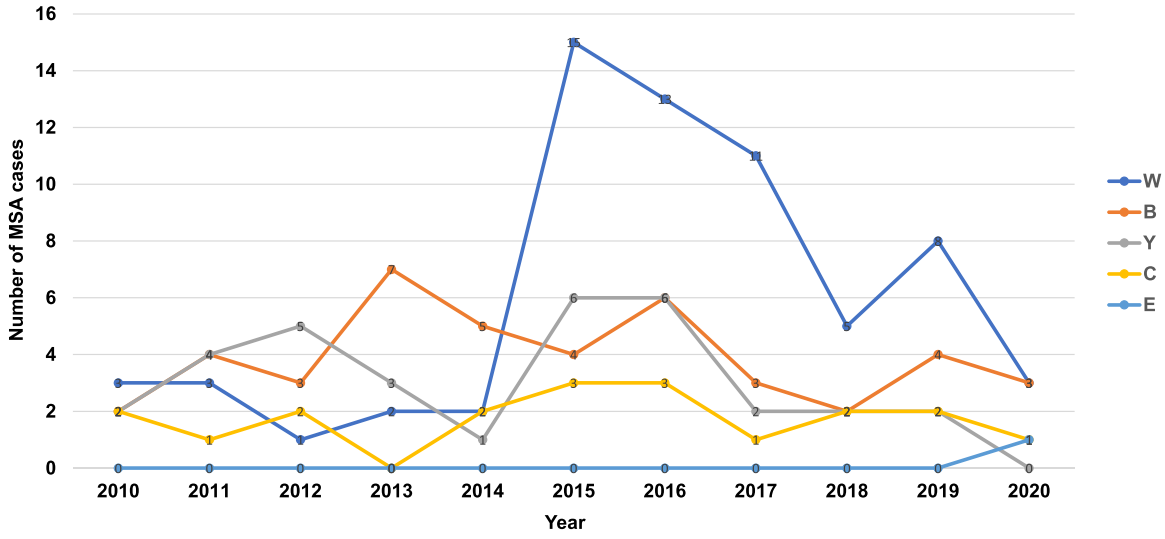

Fig. 2. Numbers of MSA cases caused by each capsular group by year of diagnosis.

Table 1
Frequency of MSA cases by joint affected and description of corresponding samples submitted.

Joint of isolation/detection	Type and positivity of samples submitted						Total
	SF +	SF + Blood +	SF + CSF +	SF + Blood + CSF +	SF+ Blood -	SF+ CSF -	
Knee	67	11	1	2	10	1	92
Hip	16	1	1	0	4	0	22
Ankle	10	1	0	0	2	0	13
Wrist	7	0	0	0	2	0	9
Elbow	6	1	0	0	1	0	8
Shoulder	4	0	0	0	1	0	5
Spinal Disk	1	0	0	0	0	0	1
Wrist & Ankle	1	0	0	0	0	0	1
Shoulder & Knee	1	0	0	0	0	0	1
Not known	4	3	1	1	1	0	10
Total	117	17	3	3	21	1	162

*SF= synovial fluid.

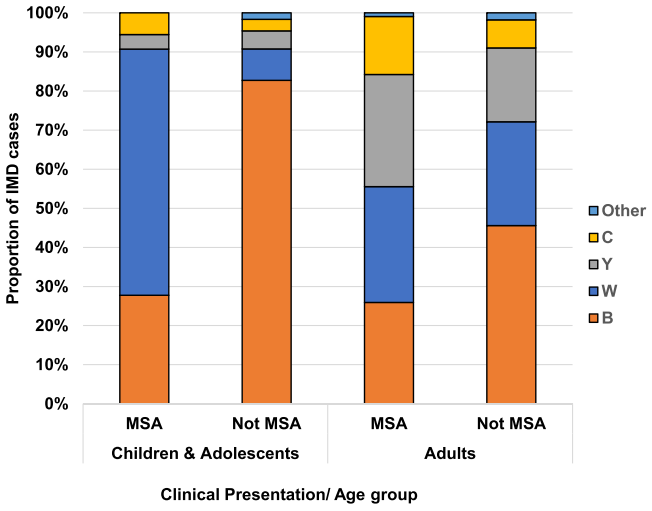

Fig. 3. Distribution of major capsular groups among children & adolescents (≤19 years old) and Adults (>19 years old) stratified by clinical presentation.

represented in the MSA group compared to the non-MSA group (25.9% vs. 45.6%, respectively. Fig. 3).

Across the eleven years studied, 5.1% of all group W cases featured isolation/detection of meningococci from joint fluid (range: 1.7–12.5% per year). The corresponding values for groups C and Y were similar at 4.9% and 3.9%, respectively. Interestingly, however, MSA was seen in only 0.8% of group B cases (range: 0.2–1.6% per year).

A regression analysis controlling for age group indicated that group W strains were almost six times more likely to cause septic arthritis than group B (odds ratio: 5.7, 95% confidence interval (CI): 3.7–8.7). Similarly, group Y and group C strains produced odds ratios of 4.1 (CI: 2.5–6.8) and 5.1 (CI: 2.9–9.0), respectively, when using group B as a baseline.

No statistically significant associations were observed between capsular group and any specific joints. Group W was the most frequent group among strains from all joints. Interestingly, no group B strains were isolated from the ankle, despite being the second-most commonly isolated group overall.

Meningococcal isolates: clonal complex distribution

Of the 124 MSA cases yielding a culturable isolate, 122 had corresponding whole genome sequencing data available. The vast majority of the group W isolates (91.8% (n = 45/49)) belonged to clonal complex (cc) 11 (Fig. 4). The group C and Y isolates were predominantly cc11 (81.8% (n = 9/11)) and cc23 (93.3% (n = 28/30)), respectively. Eight clonal complexes were identified among the group B isolates with cc41/44 being by far the most common (12/31, 38.7%) (Fig. 4). Six isolates had sequence types that were not assigned to any clonal complexes (ST-1111, ST-1345, ST-5330, ST-11234, ST-11301 and ST-15842).

In order to improve differentiation of the group W cc11 MSA strains, cgMLST was performed. The MSA strains were distributed randomly among a large panel of diverse non-MSA group W cc11 isolates with no evidence of phylogenetic clustering (data not shown).

Meningococcal isolates: antimicrobial susceptibility

Nine of the MSA isolates exhibited penicillin resistance (MIC > 0.25 mg/L) (listed in Table 2). The majority were cc11 strains of group C and W. Two group Y isolates and a group B strain of no assigned clonal complex were also found to be resistant. None of the isolates exhibited resistance to other tested antimicrobials.

Discussion

Among E&W IMD cases confirmed between 2010 and 2020, 2% featured meningococcal isolation and/ or detection from one or more joint samples. This figure is similar to that of a study of MSA strains in France between 1999 and 2002 in which 1.2% of meningococcal strains received by the reference laboratory were isolated or detected from a joint.[11] In contrast, however, studies which include clinical details report a higher prevalence of joint involvement in IMD cases. In 2012, Cabellos et al. reported MSA among 7.5% of all IMD diagnosed in a Barcelona hospital between 1977 and 2010.[12] A 2006 report on the Dutch Meningitis Cohort Study identified arthritis among 7% of all-cause meningitis cases identified, and 12.5% of meningococcal meningitis cases.[13] This suggests that a substantial proportion of IMD cases involving joint infection were not recorded as MSA in this analysis because joint samples were not tested.

Most MSA cases in this analysis were confirmed from the knee or hip, reflecting similar findings elsewhere.[4] The vast majority of cases were confirmed from samples taken from a single joint; suggestive of monoarticular infection. This is consistent with cases presented in the literature, however, the prevalence of polyarticular episodes could be under-estimated here as samples may have been taken only from a single joint, despite infection of multiple joints.[4]

Identification of primary or secondary septic arthritis could not be confirmed for all cases in this study. Twenty-two MSA cases (13.5% of total) were confirmed from the joint in the absence of systemic infection (i.e., primary MSA). A similar number of MSA

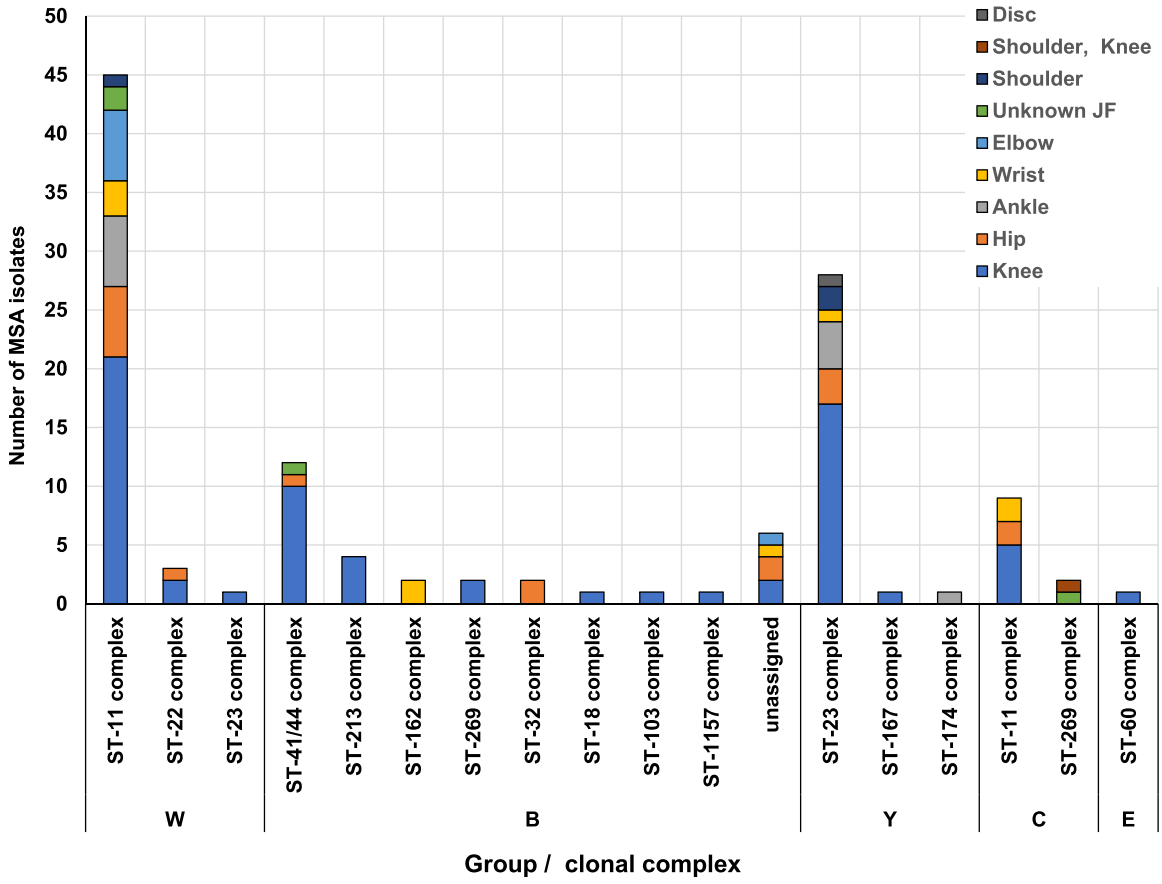

Fig. 4. A stacked bar chart showing the joint of isolation among MSA isolates of each clonal complex ($n = 122$). The clonal complexes are grouped into the capsular group of the isolates.

cases were identified as secondary MSA (i.e., accompanying systemic infection). The majority of cases (~70%) were laboratory-confirmed from synovial fluid samples alone, suggestive of primary septic arthritis, however, some of these cases may have presented with systemic infection but no systemic sample was submitted to the MRU. Similarly, as noted above, systemic IMD cases featuring joint involvement may not have been included in the MSA dataset because synovial samples were not taken/ submitted. Future collation and analysis of corresponding clinical details would be informative in order to definitively determine the prevalence of MSA (primary and secondary) in E&W and accurately determine the joints involved.

The age distribution analysis revealed peaks in cases among older adults (>45 years) and young children (<5 years). This contrasts with a recent literature review which reported a peak of cases in adolescents/ young adults, however, the case reports may vary geographically and therefore be impacted by differences in epidemiology and clinical diagnosis.[4]

In this analysis, significant variation was observed in the joints affected across different age groups. Infection of the hip was associated with children and adolescents, whilst MSA of the knee was most frequently observed in older adults. The cause of this age-related pattern is unclear, however, 'irritable hip' (IH) is a complaint often observed among children under 15, most-commonly resulting from a transient synovitis.[14] We hypothesize that joint sampling may be more frequent in these younger age groups due to IH resulting in greater MSA case ascertainment, but future assessment of clinical data would be required to confirm this.

Group W was the most common serogroup among the MSA strain collection, particularly in cases in children and adolescents. Group B strains showed a significantly lower propensity for causing MSA with <1% of all group B strains being detected/ isolated from the joint. Group W, C and Y strains showed similar likelihoods of joint infection and were found to be between 4 and 6 times more likely cause MSA compared to group B.

The reasons for this variation in presentation between capsular groups are not fully understood. In relation to other capsular groups, group B MSA strains were much more diverse with isolates belonging to eight different clonal complexes (in addition to several "singletons") identified. Conversely, the vast majority of group W and C strains belonged to cc11, and the group Y isolates were predominantly cc23 strains. We hypothesize therefore that strains of these two clonal complexes may possess unique virulence factors that facilitate invasion of the synovial space. An association between group W strains and MSA was highlighted in a previous study of French MSA cases.[11] In this study, the authors attributed this association to an increase in cc11 (ET-37) strains in the early 2000's. In 2009, a group W cc11 strain originating in South America was introduced into the UK and resulted in a dramatic increase in cases over the subsequent years.[15] This sub lineage has an established association with atypical clinical presentations such as gastrointestinal symptoms, septic arthritis, pneumonia and epiglottitis.[3,16] The group Y MSA cases in this study were observed predominantly in older adults. This highly age-specific pattern is well documented feature for group Y strains (primarily cc23).[17] Together these previous observations support the hypothesis that yet undetermined virulence factors/ host interactions specific to cc11 and cc23 strains may result in an enhanced ability to colonize and propagate within atypical clinical sites such as joints.

Table 2
Details of penicillin resistant MSA isolates.

Lab ID	Year collected	Site of isolation	Joint Affected	Group	Subtype	Sequence Type	Clonal complex	Penicillin MIC (mg/L)	*penA* allele
M10 240671	2010	Blood	Knee	W	P1.5, 2	11	ST-11 complex	0.38	9
M12 240784	2012	Synovial fluid	Ankle	Y	P1.7-2, 13-15	1466	ST-174 complex	0.50	9
M14 240541	2014	Synovial fluid	Wrist	B	P1.12-1, 13	1111	unassigned	0.38	540
M17 240467	2017	Synovial fluid	Knee	W	P1.5, 2	11	ST-11 complex	0.38	9
M18 240166	2018	Synovial fluid	Knee	W	P1.5, 2	11	ST-11 complex	0.50	14
M19 240101	2019	Synovial fluid	Knee	Y	P1.21, 16-31	23	ST-23 complex	0.38	19
M19 240212	2019	Synovial fluid	Wrist	C	P1.5-1, 10-8	11	ST-11 complex	0.38	179
M19 240668	2019	Synovial fluid	Knee	C	P1.5-1, 10-8	11	ST-11 complex	0.38	179
M19 240698	2019	Synovial fluid	Elbow	W	P1.5, 2	11	ST-11 complex	0.38	14

Nine of the 124 meningococcal isolates (7.3%) obtained from MSA cases exhibited penicillin resistance. A recent analysis of antimicrobial resistance in English and Welsh IMD isolates collected over the same study period identified 3% as penicillin resistant[19]. The greater proportion of resistance among MSA cases is likely to be underpinned by a large representation of cc11 isolates in the dataset. Willerton et al. found that *penA* alleles associated with penicillin resistance has increased in cc11 strains since 2015.[19] Indeed, five of the nine resistant isolates were cc11 strains isolated since 2015.

Whilst this study was limited by the reliance on samples submitted, such microbiological analyzes are important for identifying strain associations which can inform preventative strategies. We observed variation in the propensity of different capsular groups to cause MSA, with a strong association between joint infection and group W, Y and C strains. Further study may reveal underlying strain-specific factors that explain this association. Comprehensive collection and analyzes of clinical data in MSA cases in future is likely to help better elucidate the incidence and impact of MSA in E&W.

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Declaration of Competing Interest

GGB, SAC, AW, LW, LLW, JL, XB and RB have performed contract research on behalf of the UK Health Security Agency for Pfizer, GlaxoSmithKline and Sanofi-Pasteur, but received no personal renumeration. No other authors have any conflict of interest to declare.

CRediT authorship contribution statement

George Gyamfi-Brobbey: Conceptualization, Investigation, Writing – review & editing. **Stephen A. Clark:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Helen Campbell:** Investigation, Writing – review & editing. **Aiswarya Lekshmi:** Investigation, Writing – review & editing. **Sonia Ribeiro:** Investigation. **Andrew Walker:** Investigation. **Anna Mensah:** Investigation. **Laura Willerton:** Investigation. **Lloyd Walsh:** Investigation. **Jay Lucidarme:** Investigation, Writing – review & editing. **Xilian Bai:** Investigation, Writing – review & editing. **Shamez N Ladhani:** Conceptualization, Supervision. **Saad Ahmed:** Conceptualization, Writing – review & editing. **Tom Walton:** Conceptualization, Writing – review & editing. **Ray Borrow:** Conceptualization, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.07.019.

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