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Trends in invasive *Haemophilus influenzae* serotype b (Hib) disease in England: 2012/13 to 2022/23

Erjola Hani [a], Fariyo Abdullahi [a], Marta Bertran [a], Seyi Eletu [b], Joshua D'Aeth [b], David J. Litt [b], Norman K. Fry [a,b], Shamez N. Ladhani [a,c,*]

[a] Immunisations and Vaccine Preventable Diseases Division, UK Health Security Agency, United Kingdom
[b] Vaccine Preventable Bacteria Section, Respiratory and Vaccine Preventable Bacteria Reference Unit, UK Health Security Agency (UKHSA), 61 Colindale Avenue, London NW9 5EQ, United Kingdom
[c] Centre for Neonatal and Paediatric Infection (CNPI), St. George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom

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SUMMARY

Introduction: *Haemophilus influenzae* serotype b (Hib) conjugate vaccines have been highly successful in reducing the Hib disease worldwide. Recently, several European countries have reported an increase in invasive Hib disease. We aimed to describe the epidemiology, clinical characteristics, genomic trends, and outcomes of invasive Hib disease over the past 11 years in England.

Methods: The UK Health Security Agency (UKHSA) conducts national surveillance of invasive *H influenzae* disease and hosts a national reference laboratory for confirmation and serotyping. General practitioners are contacted to complete a surveillance questionnaire for confirmed Hib cases. Invasive Hib isolates routinely undergo whole genome sequencing.

Results: During 2012/13–2022/23, there were 6881 invasive *H. influenzae* infections, of which 5852 (85%) were serotyped; most isolates (4881, 83%) were non-typeable *H. influenzae*, followed by Hif (591, 10%), Hie (189, 3%), Hib (118, 2%) and Hia (54, 1.0%). The median age for invasive Hib disease was 51 years, and most cases (84%, 99/118) were in adults. Children accounted for 19 cases (16%), including 13 (11%) in < 1 year-olds and 6 (5%) in 1–5-year-olds. Bacteraemic pneumonia was the most common diagnosis (66/118, 56%). Hib case-fatality rate was 5.9% (7/118), with the last fatality reported in 2016. Among 64 sequenced strains during 2016/17–2022/2023, most (56/64, 88%) belonged to the CC6 lineage (representing ST6 and single locus variants of ST6).

Conclusions: In England, invasive Hib disease remains rare with no evidence of any increase in incidence and is rarely fatal, affecting mainly adults with underlying conditions, who typically develop pneumonia.

Introduction

A number of European countries with established national *Haemophilus influenzae* type b (Hib) vaccination programmes have recently reported an increase in invasive Hib disease, mainly in infants and toddlers, with cases increasing in both unvaccinated individuals and in fully-vaccinated children.[1–3] *H. influenzae* can be distinguished into six distinct serotypes (a-f), based on their unique capsular polysaccharide, or can be non-encapsulated (also known as non-typeable *H. influenzae*, NTHi).[4] Prior to routine immunisation, Hib was a major cause of serious bacterial infections worldwide, especially in children aged < 5 years, where it was the most important cause of bacterial meningitis.[5] In England, the Hib conjugate vaccine was implemented as a three-dose infant schedule at 2, 3 and 4 months of age in 1992,[4] and a booster given as a combined Hib/MenC conjugate vaccine added in 2006.[4] Since then, the programme has been highly successful in maintaining a very low incidence of invasive Hib disease across all age groups through a combination of direct and indirect (herd) protection.[3,6]

Between 2012–2016, there were 67 Hib cases (including 9 in < 5 year-olds) in England and Wales (incidence < 0.05/100,000), accounting for 2.3% (67/2883) of all laboratory-confirmed invasive *H. influenzae* infections.[7] Given the recent increase in Hib cases reported in several European countries including France, the Netherlands and Portugal, we investigated the epidemiology, clinical characteristics, genomic trends, and outcomes of invasive Hib

* Correspondence to: Immunisations and Vaccine Preventable Diseases Division, UK Health Security Agency, 61 Colindale Avenue, London NW9 5EQ, United Kingdom.
E-mail address: shamez.ladhani@ukhsa.gov.uk (S.N. Ladhani).

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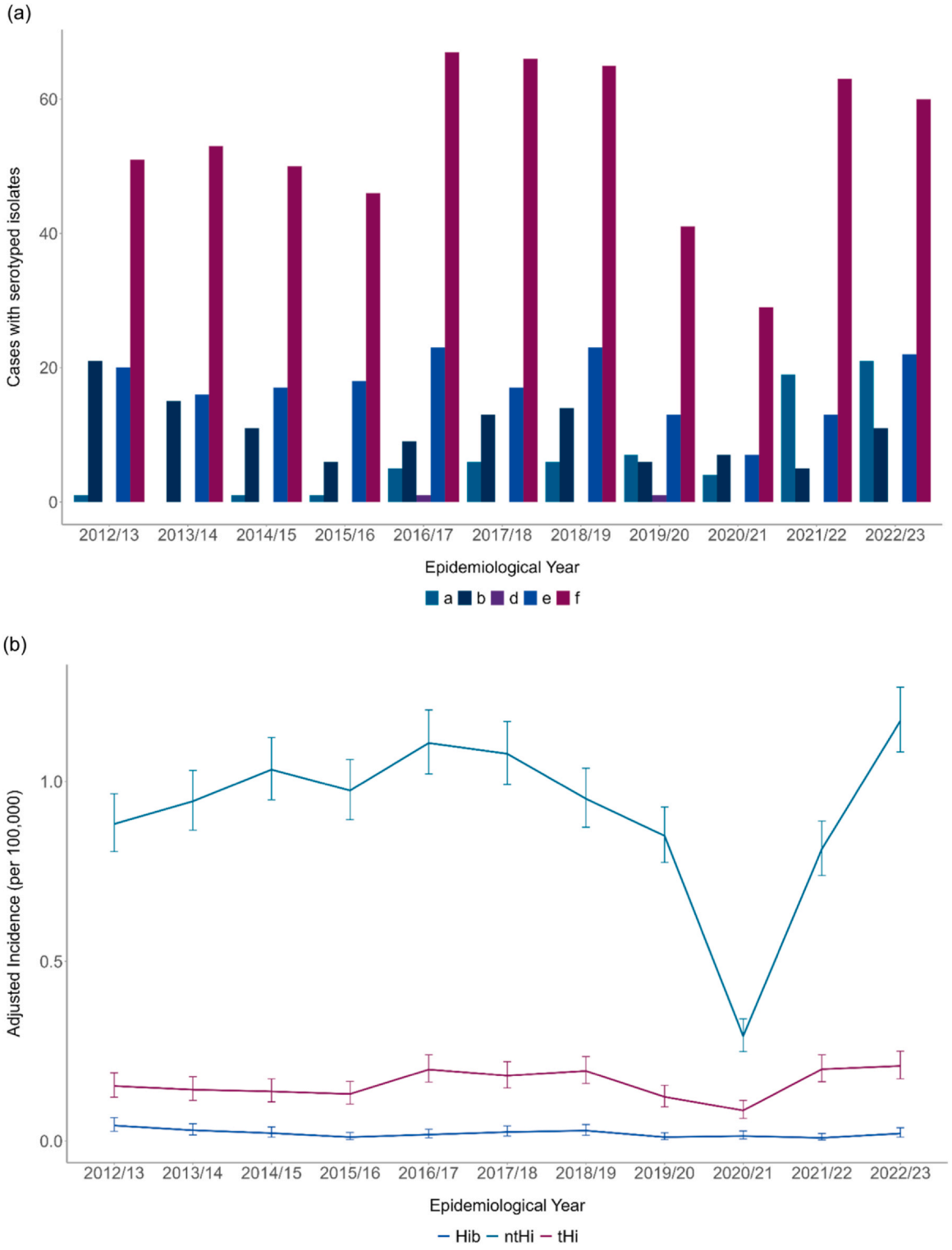

Fig. 1. (a) Number of invasive *H. influenzae* cases by serotype (there were no Hic cases), 2012/13–2022/23 (b) Adjusted incidence of *H. influenzae* b, non-typed *H. influenzae* and other typed *H. influenzae* and 95% confidence intervals for adjusted incidence, 2012/13 – 2022/23.

disease during the most recent eleven epidemiological years in England (2012/2013–2022/2023).

Methods

The UK Health Security Agency (UKHSA) conducts enhanced national surveillance of invasive *Haemophilus influenzae* infections in England. Invasive disease is defined as isolation of *H. influenzae* from a normally sterile site. In England, all laboratories performing a primary diagnostic role must notify UKHSA on the confirmation of a notifiable organism, which includes invasive *H. influenzae*. Notifiable infections are routinely reported to the UKHSA electronically through the Secondary Generation Surveillance System (SGSS). Hospital laboratories also routinely submit invasive isolates to the UKHSA national reference laboratory for confirmation and serotyping, which is only performed at the reference laboratory. Cases

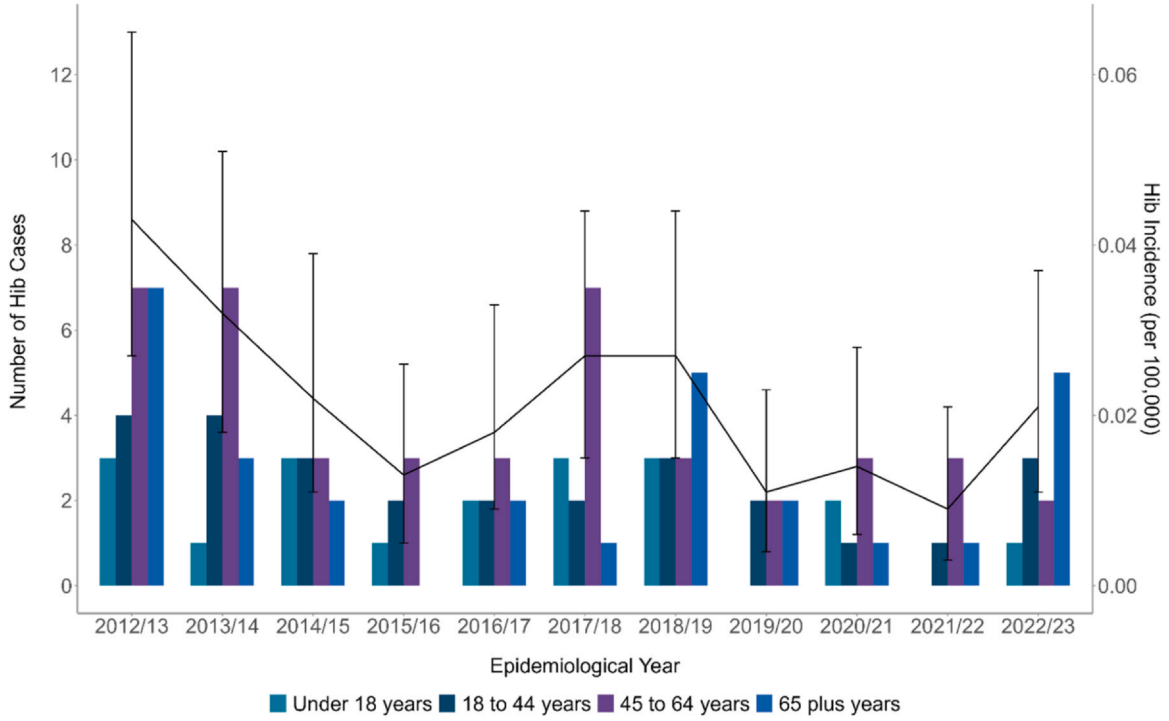

Fig. 2. Number of *H. influenzae* b cases by age group and epidemiological year, with a secondary axis showing the adjusted incidence and 95% confidence intervals for adjusted incidence of Hib cases per 100,000, 2012/13 – 2022/23.

notified to UKHSA without sample submission are actively followed-up by UKHSA with the reporting laboratory. UKHSA also follows up all confirmed Hib cases by requesting their general practitioners to complete a short surveillance questionnaire on demographics, underlying conditions, vaccination history, clinical diagnosis and outcomes.

All laboratory-confirmed, invasive *H. influenzae* cases in residents of England during 01 July 2012 to 30 June 2023 were included and analysed by epidemiological year (01 July to 30 June). Meningitis was defined as *H. influenzae* identified in the cerebrospinal fluid or from blood with clinical and/or radiological evidence of meningitis. Classification of other clinical diagnoses (bacteraemic pneumonia, septic arthritis, osteomyelitis, epiglottitis, and cellulitis) was based on isolation of *H. influenzae* from a normally sterile site with symptoms and signs consistent with that clinical presentation. Bacteraemia was defined as *H. influenzae* isolated from the blood with no focal symptoms or signs. Vaccination status was assessed in children aged < 18 years (the age group for whom UKHSA routinely request vaccination status from the general practitioner) and categorised as age-appropriate if the correct number of Hib-containing vaccine doses were administered at least two weeks prior to developing invasive Hib disease.

Invasive Hib isolates obtained during 2016/17–2022/23 underwent whole genome sequencing. Isolates were cultured and sequenced as described previously,[8] with reads produced from Illumina HiSeq2500 and NextSeq1000 first being demultiplexed and then trimmed using trimmomatic.[9] The multi-locus sequence type (MLST) of these isolates was then determined using MOST[10] with the reference *H.influenzae* MLST database from pubMLST.[11] Reads were then *de novo* assembled using Shovill v0.9.0.[12] Assemblies from the clonal complex (CC) 6 lineage were then aligned to a reference ST6 isolate (NCBI RefSeq Accession: GCF_900635795.1) using ska2 v0.3.4.[13] A phylogeny of these CC6 isolates was then formed using Gubbins v3.3.0[14] to remove recombination and infer a phylogeny using RAxML v8.2.12.[15]

Data analysis

Epidemiological surveillance data are routinely inputted into Microsoft Access, linked with laboratory surveillance data, cleaned and deduplicated regularly. The combined dataset was extracted into Stata 17 (Statcorp, TX) for analysis. To calculate incidence, mid-year age-group-specific population estimates published by the Office for National Statistics (ONS) were used as denominators. The adjusted incidence of invasive Hib disease by age group was calculated by assuming that the proportion of isolates not serotyped attributed to Hib was the same as the proportion among serotyped isolates.[16] The corresponding confidence intervals were calculated using Poisson distribution.

Results

There were 6881 laboratory-confirmed cases of invasive *H. influenzae* disease during the 11-year surveillance period (2012/2013–2022/23), and 5852 (85%) isolates were serotyped. Of these, 83% (4881/5852) were NTHi, 10% (591/5852) type f (Hif), 3% (189/5852) type e (Hie), 2% (118/5852) Hib, 1% (54/5852) type a (Hia), 0.3% (19/5852) type d (Hid) and no type c (Hic) cases (Fig. 1a). NTHi cases declined by 68% after COVID-19 pandemic restrictions were implemented in March 2020, from 425 cases in 2019/20 (incidence, 0.9/100,000) to 136 in 2020/21 (incidence, 0.3/100,000), and then increased to 576 cases in 2022/23 (incidence, 1.2/100,000) (Fig. 1b). Invasive Hia infections have been increasing since 2016/17, albeit with a small decline in cases during the 2020/21 pandemic restrictions, with 21 cases reported in 2022/23 compared to five cases in 2016/2017 (Fig. 1a).

Hib cases fluctuated between 5–21 per epidemiological year. The adjusted Hib incidence decreased from 0.043/100,000 (n = 23) in 2012/2013 to 0.014/100,000 (n = 8) during 2020/21, decreasing further after pandemic restrictions were lifted to 0.009/100,000 (n = 6) in 2021/22, before increasing to 0.021/100,000 (n = 12) during 2022/23, similar to pre-pandemic levels (Fig. 2). The median age of Hib

Table 1
Demographic and clinical variables of *Haemophilus influenzae* serotype b (Hib) cases, 2012/13 to 2022/23 in England.

	Age < 18 years, n = 19 (%)[a]	Age 18-44 years, n = 27 (%)	Age 45-64 years, n = 43 (%)	Age ≥65 years, n = 29 (%)[b]	Total, n = 118 (%)
Sex					
Female	8 (44)	7 (26)	19 (44)	16 (55)	51 (43)
Male	19 (56)	20 (74)	24 (56)	13 (45)	67 (57)
Comorbidities					
Any Comorbidity	2 (11)	9 (33)	20 (47)	16 (34)	47 (40)
Chronic lung diseases	(0)	1 (9)	6 (30)	2 (13)	9 (19)
Chronic liver or gastrointestinal disease	(0)	(0.00)	2 (10)	(0)	2 (4)
Chronic heart disease	(0)	(0.00)	(0)	1 (6)	1 (2)
Chronic renal disease	(0)	1 (9)	(0)	3 (19)	4 (9)
Metabolic disease	(0)	2 (19)	5 (25)	4 (25)	11 (23)
Malignancy or immunosuppression	1 (50)	4 (37)	6 (30)	5 (31)	16 (34)
Congenital chromosomal abnormality	1 (50)	(0.00)	(0)	(0)	1 (2)
Other Comorbidity	(0.00)	3 (28)	1 (5)	1 (6)	3 (6)
Main clinical Diagnosis					
Meningitis	4 (21)	(0.00)	2 (5)	1 (3)	7 (6)
Pneumonia	6 (32)	18 (67)	20 (47)	22 (76)	66 (56)
Other focus[c]	7 (37)	6 (22)	14 (33)	4 (14)	31 (26)
Septicaemia	2 (11)	3 (11)	7 (16)	2 (7)	14 (11)
Vaccinated for Age					
Not eligible due to age	2 (11)	n/a	n/a	n/a	n/a
Partially Vaccinated	6 (32)	n/a	n/a	n/a	n/a
Fully Vaccinated	7 (37)	n/a	n/a	n/a	n/a
Not Vaccinated	4 (21)	n/a	n/a	n/a	n/a

[a] Children with invasive Hib disease were aged < 1 year (n = 13) and 1-5 years (n = 6) with no cases diagnosed in 6-17 years.
[b] Older adults in their age group were aged 65-74 years (n = 18), 75-84 years (n = 3), 85-94 years (n = 7) and ≥95 years old (n = 1).
[c] Other clinical diagnoses included epiglottitis, septic arthritis, and cellulitis.

cases was 51 (interquartile range, 37–64) years and most cases (84%, 99/118) were in adults (≥18-year-olds). Children (age < 18 years) accounted for 19 cases (16%), with 13 cases (11%) in infants aged < 1 year and 6 cases (5%) in toddlers aged 1–5 years; there were no cases in 6–17-year-olds. The median age of children with invasive Hib disease was 2 (interquartile range, 0 months – 2 years) months (Table 1).

The most common clinical diagnosis was bacteraemic pneumonia (56%, 66/118), which was more common in adults (61%, 60/99) than in children (32%, 6/19) (Table 1). In contrast, "other" clinical diagnoses (37%, 7/19) were common in children and included epiglottitis (43%, 3/7), cellulitis (43%, 3/7), and septic arthritis (14%, 1/7) (Table 1). Hib meningitis was rare overall (6%, 7/118), with four of the seven cases occurring in children aged ≤5 years, where meningitis accounted for 21% (4/19) of cases.

Most children (89%, 17/19) were previously healthy, except for one infant with a chromosome disorder and one toddler with a malignancy. In contrast, 33% (9/27) of 18–44-year-olds, 47% (20/43) of 45–64 year-olds and 55% (16/29) of ≥65-year-olds had at least one comorbidity. The most common comorbidities in 18–64-year-olds were malignancy or immunosuppression (34%, 10/29), metabolic disorders (24%, 7/29) and chronic lung disease (24%, 7/29) (Table 1). In ≥65-year-olds, the most common comorbidities were malignancy or immunosuppression (31%, 5/16), metabolic disorder (25%, 4/16) and chronic renal disorders (19%, 3/16).

In children, 37% (7/19) were fully vaccinated for their age, 32% (6/19) were partially vaccinated and 21% (4/19) were eligible for at least one dose but were unvaccinated (Table 1). Two infants were too young for vaccination, including one who developed meningitis and another with bacteraemic pneumonia.

Fatalities were rare (7/118, case-fatality rate, 5.9%) and included two deaths in 18–64-year-olds (2/70; case-fatality rate 2.8%) and five among ≥65-year-olds (5/29, 17.2%) with the last reported death in any age group occurring in 2016. There were no childhood Hib deaths during the surveillance period.

Most Hib strains typed by MLST (45/64, 70%) belonged to ST6, with the CC6 lineage (representing ST6 and single locus variants of ST6) containing 56 of the 64 isolates (Fig. 3a). A phylogeny created from the CC6 isolates revealed no clustering of isolates based on year of isolation (Fig. 3b). Hib strains responsible for nine cases in children aged < 5 years were also found sporadically around the phylogeny, with no evidence of a single strain circulating predominantly in children or in adults.

Discussion

In England, invasive Hib disease remains extremely rare across all age groups, with NTHi accounting for the majority of invasive *H. influenzae* cases, followed by Hif, Hie and Hia. Hid is extremely rare, and there were no Hic cases during the 11-year surveillance period. We have reported on the recent increase in invasive Hia disease in England, which we are monitoring closely.[8] Most Hib cases occurred in adults, who typically had underlying medical conditions and were diagnosed with bacteraemic pneumonia. In contrast, nearly all children with invasive Hib disease were previously healthy and had more varied clinical presentations. In particular, half the meningitis cases occurred in children aged 0–5 years. Reassuringly, Hib case-fatality rates remain very low across all age groups, irrespective of age, underlying condition, or clinical presentation, with no deaths reported in any age group since 2016. Genomic analysis identified invasive Hib isolates as belonging to the ST6 lineage, with no evidence of clustering of a single strain by age group or over time.

The recent increase in invasive Hib disease reported in several European countries is concerning. In France, the Hib immunisation programme was changed from a 3+1 to a 2+1 schedule at 2, 4 and 11 months in 2013, and despite maintaining very high vaccine coverage, cases of invasive Hib disease increased in the absence of any known risk factors.[3] During 2017–19, there were 56 invasive Hib cases confirmed in France, including 25 cases confirmed in 2019 alone, with most cases (37/56; 66%) diagnosed among children aged < 5 years (median age, 0.8 years) who most commonly presented with meningitis (16/37; 43%).[3] Of the 37 childhood Hib cases, 24 were fully-vaccinated (9 had received all three doses) or partially-vaccinated (15 had received one or two doses), while 13 were unvaccinated.[3] Further investigations identified that all vaccine failure cases with available acute serum samples had very low vaccine-

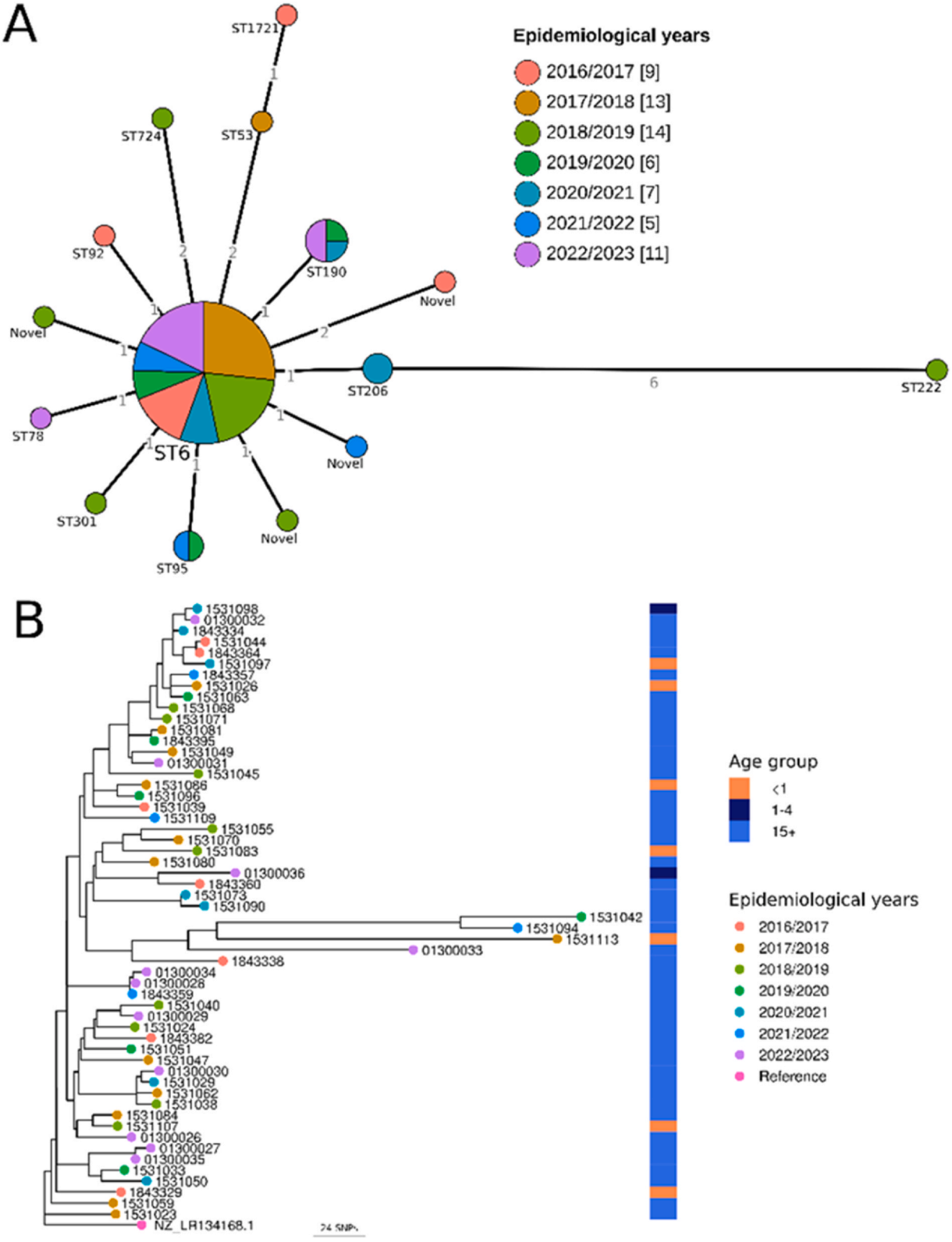

Fig. 3. Relatedness of Hib isolates. A) Minimum spanning tree formed from the MLST profiles of 64 Hib isolates. Nodes are coloured by epidemiological year of isolation. Branches are labelled with number of loci differences between MLSTs. B) Maximum likelihood phylogeny of 56 Hib and reference ST6 isolate, generated from the nonrecombinant regions of the 57-isolate alignment. Tips are coloured by the epidemiological year of isolation. The coloured bar represents the age group of patients an isolate was sampled from.

induced IgG antibody levels against the Hib polyribosylribitol phosphate polysaccharide capsule (anti-PRP IgG).[3] In a French seroprevalence study, the median anti-PRP IgG antibody levels and the proportion of children who achieved the putative short-term protective threshold of 0.15 μg/ml were lower in children who had received the 2+1 schedule compared to those who had received the 3+1 schedule, especially at two years of age.[3] The authors found that there was limited boosting of anti-PRP IgG antibodies after the third

dose in children receiving the 2+1 schedule compared to a sharp rise in antibody titres after the fourth dose in those receiving the 3+1 schedule, leading the authors to speculate that the lower antibody levels after the booster following the reduced schedule in children not only increased their risk of invasive Hib disease but also allowed carriage and transmission of Hib in the community.[3]

In the Netherlands, Hib incidence increased during 2020 and 2021 despite the implementation of COVID-19 pandemic restrictions, with 40% of invasive Hib cases reported in children aged < 5 years.[2] In this age group, Hib incidence increased from 2.0/100,000 in 2019 to 3.3/100,000 (n = 28) in 2020 and 2.6/100,000 (n = 15) within the first 8 months of 2022.[2] In 2019, the choice of combination vaccine in the Netherlands was changed from the pentavalent DT3aP-HBV/Hib vaccine introduced in 2011 to a hexavalent DT5aP-HBV/Hib vaccine, which differed in the composition of the conjugate carrier protein, the adjuvant used and length of the Hib antigen component in the vaccine.[2] Additionally, the childhood immunisation schedule was reduced from 3+1 (2–3-4 & 11 months) to 2+1 (3–5 & 11 months) in 2020. Despite these changes, vaccine effectiveness remained consistently high and consequently, vaccine failure rates remained low, with most of the recent increase in Hib cases reported in unvaccinated and partially vaccinated children and young adults.[2] It is possible that the changes in the national immunisation programme continued to provide direct protection against Hib disease in fully vaccinated children but may be less effective in preventing carriage and transmission.[2]

In Portugal, where infants received four doses of a Hib-containing vaccine at 2–4-6 and 18 months of age, national surveillance identified 41 invasive Hib cases in 0–17-year-olds over 12 years (2010–2021), including 19 (73%) in < 5-year-olds; of these, 26 (63%) were vaccine failures. Despite very high childhood vaccine uptake rates, the incidence of both invasive Hib disease and Hib vaccine failure increased in the latter six years compared to the first six years of the surveillance period.[1] The authors speculated that antenatal vaccination with a pertussis-containing combination vaccine that was implemented in 2016 may have resulted in potential blunting of infant vaccine responses or, alternatively, there may be potential interference between concomitant infant vaccines, but this has not been observed in other countries with similar immunisation programmes. The authors proposed that, since almost a quarter of the vaccine failure cases occurred in 12–17-month-olds, moving the booster earlier from 18 months to 12 months of age could potentially prevent at least some of the vaccine failure cases.[1]

Optimising the timing, coadministration and scheduling of Hib combination vaccines is not only important for direct protection of vaccinated children against invasive Hib disease but also to prevent carriage acquisition in vaccinated toddlers and, therefore, onward transmission to others, which is critical for maintaining population (herd) protection. In England, a 3+1 Hib vaccination schedule has been in place since 2006, with the 12-month booster given as a combined Hib/MenC conjugate vaccine. The infant vaccine was changed from DTaP/IPV/Hib (Pediacel®) to hexavalent DTaP/IPV/Hib/HepB (Infanrix-Hexa®) in 2017, but this has so far not affected direct or indirect protection against Hib. Notably, though, the UK will soon be replacing the 12-month Hib/MenC dose with an 18-month Hexavalent combination vaccine booster,[17] so ongoing enhanced national surveillance will be important for rapidly detecting early changes in disease epidemiology.

Another possible explanation for the increase in Hib cases in some European countries was the emergence of a vaccine-escape strain. All three countries reporting an increase in Hib cases, however, identified the responsible isolates as belonging to ST-6 or its derivatives, consistent with other European countries with low Hib incidence, including England.[1–3] Interestingly, the Dutch authors identified a shift in subclusters within this sequence type which they postulate might render them more efficient colonisers or increase their invasiveness, but this requires further investigation.[2]

Strengths and limitations

The strength of this study is the use of data from long-term national surveillance for invasive *H. influenzae* via a national reference laboratory nationally responsible for confirmation and serotyping all invasive isolates in England. Serotyping rates have remained consistently high, allowing for surveillance of even the most uncommon serotypes over time, such as the recent detection of a national increase in invasive Hia disease.[8] The availability of whole genome sequencing for monitoring isolate lineages additionally provides more detailed insight into the pathogens responsible for invasive disease. We also had 100% completion of the enhanced surveillance questionnaires for all invasive Hib cases, allowing us to assess vaccination status, underlying conditions, clinical diagnoses, and outcomes.

However, as not all isolates are serotyped, we may have missed some of the very rare *H. influenzae* serotypes. Another limitation is that our surveillance questionnaire requested limited clinical data on confirmed cases to keep the questionnaire short in order to maximise questionnaire return rates; hence, we cannot comment on disease severity, clinical course of illness or treatment. Finally, our surveillance only includes invasive disease, and therefore, we cannot comment on the epidemiology or trends in non-invasive *H. influenzae* disease, particularly non-bacteraemic pneumonia.

Conclusion

Several European countries have reported a small but sustained increase in the incidence of invasive Hib disease, especially in young children, but cases remain very low in England and mainly in adults with underlying conditions who developed bacteraemic pneumonia. With the proposed changes to the scheduling and choice of a Hib combination vaccine in the national infant immunisation schedule in England, ongoing surveillance will be critical.

Ethics approval

UKHSA has legal permission to process confidential information for national surveillance of communicable diseases without individual patient consent (Regulation 3 of Health Service Regulations 2002) and, as such, ethics committee approval is not required.

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Declaration of Competing Interest

None.

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