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Risk of invasive pneumococcal disease during pregnancy and postpartum and association with adverse maternal and foetal outcomes: A prospective cohort study, England, 2014-19

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SUMMARY

Background: Pneumococcal infections are associated with significant morbidity and mortality, especially at the extremes of age and in those with underlying conditions. Little is known about the risks, presentations or outcomes of invasive pneumococcal disease (IPD) during pregnancy or the postpartum period.
Methods: The UK Health Security Agency conducts enhanced national surveillance of IPD in England. We used national surveillance data to calculate IPD risk and outcomes in pregnant, postpartum and non-pregnant women of childbearing age with IPD over a five-year period in England.
Findings: There were 1701 IPD cases in women aged 15–44 years between 1 July 2014 and 30 June 2019, including 123 (7.2%) pregnant, 38 (2.2%) postpartum and 1540 (90.5%) non-pregnant women. IPD incidence in pregnant women (0.048/1000 woman-years) was not significantly different compared to non-pregnant women (0.041/1000 woman-years; Incidence Rate Ratio [IRR]: 1.17; 95%CI 0.96–1.40; p=0.11). When stratified by trimester, however, women in their third trimester had a 2.27-fold (95%CI 1.80–2.85, $p < 0.001$) increased risk of IPD, compared to non-pregnant women (IRR 2.27, 95%CI 1.78–2.85, $p < 0.001$), while those in the first (IRR 0.49, 95%CI 0.28–0.80) and second trimester (IRR 0.71, 95%CI 0.47–1.04) had a lower risk, albeit only statistically significant for the first trimester. Postpartum women (0.144 per 1000 woman-years), on the other hand, had a 3.49-fold (95%CI 2.46–4.81, $p < 0.001$) higher IPD risk than non-pregnant women.

Most pregnant women developed IPD during their third trimester (80/123, 65.0%), with all but one pregnancy resulting in a live birth. IPD in the second trimester was associated with live birth in 77.8% of cases (21/27), while 22.2% experienced a miscarriage (5/27, 18.5%) or stillbirth (1/27, 3.7%). IPD in the first trimester was associated with live birth in 41.7% of cases (5/12), miscarriages in 41.7% (5/12), and termination in 16.7% (2/12) cases. Only three neonates (3/142) had confirmed IPD. There were no deaths in pregnant women with IPD compared to 5.5% (85/1540) in non-pregnant women.
Interpretation: While pregnant women overall did not appear to have an increased risk of IPD compared to non-pregnant women, those infected in third trimester or postpartum appeared to have more than twice the incidence. Most pregnant and postpartum women had a live birth, and subsequent neonatal infection was rare, occurring in 2% of live births.

Introduction

Streptococcus pneumoniae is a major cause of serious bacterial infections, including pneumonia, septicaemia and meningitis, and is associated with significant morbidity and mortality across all age-groups.[1,2] While the increased risk at the extremes of age and in individuals with specific underlying conditions such as immunosuppression is well-documented, little is known about the risks and burden of IPD during pregnancy and the postpartum period. Pregnancies complicated by serious bacterial infections are associated with poorer pregnancy outcomes, including preterm birth, stillbirth, and ICU admissions for the mother and newborn,

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with as much as 15% of early miscarriages and 66% of late miscarriages reported to be attributable to infections.[3–5] One small case series of 12 women found that severe pneumonia during late second and third trimester resulted in 17% intrauterine death, 50% preterm birth, 50% undergoing emergency delivery, including five requiring emergency caesarean section, and a 17% maternal fatality rate.[6] The postpartum period has also been associated with increased risk of various infections, often due to physiologic and iatrogenic trauma to genitourinary tract or abdomen during childbirth or abortion.[7]

An estimated 5–7% of women have an infection in postpartum period,[8] which is typically due to group B streptococcus (GBS) but has also been reported for IPD.[9,10] Additionally, *S. pneumoniae* is a rare cause of neonatal sepsis but outcomes, as reported mainly from case reports prior to introduction of pneumococcal conjugate vaccines (PCVs) can be severe, with reported case-fatality rates (CFRs) of up to 50%.[11,12] Vaginal colonisation in the mother, though rare for *S. pneumoniae*, has been implicated as a possible source of transmission, indicating a very high invasion-to-colonisation ratio, unlike GBS which commonly colonises the female genital tract without causing disease in the neonate.[11]

The introduction of PCVs into national childhood immunisation programmes has led to large and sustained reductions in vaccine-serotype invasive pneumococcal disease (IPD) in vaccinated children and, through indirect (herd) protection, across all ages.[13] In the UK, infants received the 7-valent PCV (PCV7) from 2006 and the 13-valent PCV (PCV13) from 2010 at a 2+1 schedule (8 weeks, 16 weeks and 1 year of age) until the end of 2020, after which time the schedule was reduced to a 1+1 schedule (12 weeks and 1 year of age).[14,15] In pregnancy, a US study conducted in the pre-PCV13 period did not identify any increase in the risk of IPD during pregnancy or peripartum, with incidence estimates of 0.04 cases per 1000 woman-years compared to 0.05 cases in 1000 woman-years in non-pregnant women but did find a small increased risk in postpartum women (0.15 cases per 1000 woman-years).[9] Little is known about IPD risks in this vulnerable group since PCV13 implementation.

Here, we assessed the risk of IPD in pregnant, postpartum and non-pregnant women of reproductive age during the post-PCV13 era, and describe the clinical characteristics, serotype distribution and outcomes of IPD in pregnant and postpartum women and their infants in England over a 5-year surveillance period.

Methods

IPD Surveillance

UK Health Security Agency (UKHSA, formerly Public Health England) has been conducting national IPD surveillance in England for more than three decades. The UKHSA Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) provides a national reference service for the confirmation and serotyping of invasive pneumococcal isolates routinely referred by all hospital laboratories across England. Reported cases without an isolate submitted for serotyping are actively followed-up with the respective hospital laboratory. Following PCV7 introduction in 2006, UKHSA enhanced the national laboratory-based IPD surveillance to follow-up all cases in vaccine-eligible children with a postal questionnaire sent to their general practitioner (GP), requesting information about clinical presentation, underlying comorbidities, complications and outcomes of IPD at hospital discharge. Since 2013, surveillance was extended to all age groups. Questionnaires not returned or incomplete were actively followed up through reminder letters, emails and telephone calls to the GPs or, if necessary, the hospital clinician responsible for the patient.

Definitions

IPD is defined as isolation of *S. pneumoniae* from a normally sterile site, or detection of pneumococcal DNA by PCR in cerebrospinal (CSF) or pleural fluid. Microbiological and clinical assessment of clinical presentations of meningitis, pneumonia, other focus and bacteraemia were as defined previously and briefly described here.[16] Invasive pneumonia was defined as detection of *S. pneumoniae* (by culture/PCR) in pleural fluid or isolation of *S. pneumoniae* in the blood, in conjunction with clinical features indicative of pneumonia in the patient. Meningitis was defined as detection of *S. pneumoniae* (by culture/PCR) in CSF or isolation of *S. pneumoniae* in the blood, in conjunction with clinical features indicative of meningitis in the patient. Septicemia was defined as isolation of *S. pneumoniae* from the blood without any discernible focus of infection. *S. pneumoniae* detected in other normally sterile sites was categorised under the 'other' category. Where multiple clinical presentations were reported, the primary clinical presentation was selected based on the following hierarchy: meningitis, pneumonia, other, and bacteraemia (without a focus). Comorbidities were based on clinical risk groups for pneumococcal disease as defined in the "Green Book" on Immunisation Against Infectious Disease.[17] Malignancy and immunosuppression categories were combined in the final analyses. Ectopic pregnancies were categorised within the 'miscarriage' pregnancy outcome.

The pregnant group included women with IPD who were at least 4 weeks pregnant at diagnosis (sample date) and up to one day after delivery to include peripartum women whose infection was most likely to be associated with pregnancy. The first trimester was defined as weeks 1 to 12 of gestation, the second trimester as weeks 13 to 26, and the third trimester as weeks 27 to 42. Postpartum women with IPD were defined as women who had IPD from 2–30 days inclusive after delivery. Neonatal IPD was defined as IPD confirmed within 28 days of birth. PPV23 vaccination status was determined from PPV dose dates, with categorised as vaccinated if their vaccination date occurred more than 14 days prior to the sample date.

Data sources

We used enhanced national surveillance data during 2014–2019 to calculate IPD risk during pregnancy in women aged 15–44 years in England. We also assessed maternal and foetal outcomes following IPD. Laboratory reports, including serotypes, and questionnaire data are routinely imported, matched and de-duplicated in a Microsoft Access (Microsoft Corporation, Redmond, Washington) database as part of national surveillance. The final reconciled dataset, including laboratory-confirmed IPD cases in women aged 15–44 years and their pregnancy status within 30 days of IPD diagnosis between 2014/15 and 2018/19 (epidemiological years, from 01 July to 30 June the following year), was imported into Stata version 15.1 (StataCorp LLC, Texas) for analysis. The Hospital Episode Statistics (HES) dataset, which is part of an administrative database used primarily for payment purposes but containing some clinical information about diagnoses and operations for all admissions, outpatient appointments and A&E attendances at NHS hospitals in England, was used to further enrich the IPD dataset, including the pregnancy or postpartum status, comorbidities and hospitalisation outcomes. After deterministic linkage using NHS number and date of birth, 80.0% (1359/1701) of cases were found to have associated HES admission records. Within this group, the International Classification of Diseases, 10th Revision (ICD-10) codes in the diagnosis fields were used to supplement comorbidity status, pregnancy status as well as labour and postpartum outcomes. Denominators to calculate relative risk in pregnant, non-pregnant and postpartum women were obtained from the Office for National Statistics (ONS) annual statistics on live births, abortions and miscarriages.[18]

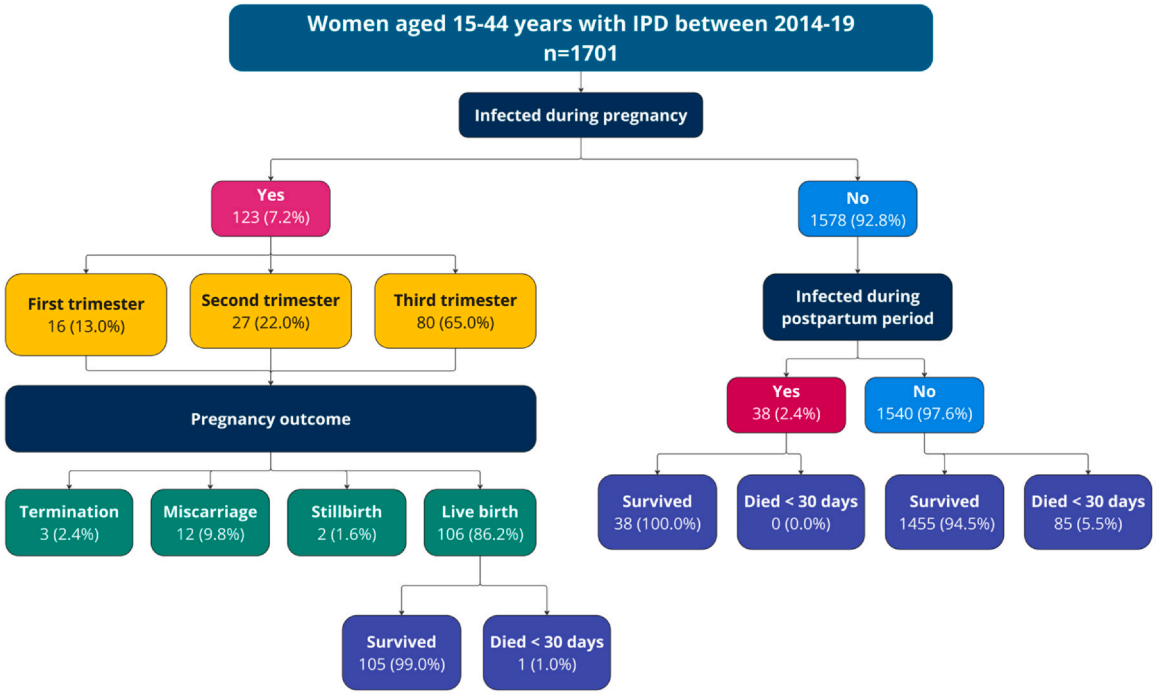

Fig. 1. Flowchart of women aged 15–44 years with IPD.

Statistical analyses

The data presented are largely descriptive. Median ages across pregnancy status groups were compared for statistical significance using the Kruskal-Wallis test; where a significant difference was observed across the three groups, pairwise comparisons were performed using the Dunn test with Bonferroni correction to identify specific groups showing significant differences in median age. Using methodology similar to previously described,[9] IPD incidence rate in pregnant women was calculated by dividing the number of IPD cases in pregnant women during 2014/15–2018/19 by total person-time in woman-years, which was calculated by multiplying live births, abortions and miscarriages in England during the same period by nine-twelfths and one-sixth, assuming that nearly all pregnancies last 9 months and abortions and miscarriages last 2 months, respectively. To calculate the pregnancy denominator, live births for each corresponding year were added to the number of abortions and miscarriages. The denominators for trimester groups were determined by multiplying the pregnancy denominator by the respective number of days within each trimester for a full-term pregnancy. This involved dividing the total days between 30.5 days and the end of the standard pregnancy length, to approximate the time at risk for each specific trimester. Similarly, IPD incidence rate in non-pregnant women was calculated by dividing the number of IPD cases in non-pregnant women by subtracting the sum of live-births, abortions and miscarriages from the population size of women aged 15–44 years in England, multiplied by nine-twelfths. P-values for incidence rate ratios were calculated using two-tailed Fisher's exact test. Finally, we fitted a multinomial logistic regression model including pregnancy status as the dependent variable and age group, ethnic group, comorbidity status, clinical presentation as independent variables, to assess characteristics associated with being pregnant or postpartum.[18] The STROBE reporting guidelines for cohort studies were followed in this research.[19]

Results

Between 1 July 2014 and 30 June 2019 (five epidemiological years), there were 1701 laboratory-confirmed IPD cases among women aged 15–44 years in England. IPD cases in this cohort included 123 (7.2%) pregnant, 38 (2.2%) postpartum and 1540 (90.5%) non-pregnant women (Fig. 1). Pregnant women (median (IQR): 31 (26–35), $p < 0.001$) and postpartum women (30; 25–34; $p < 0.001$) were both younger than non-pregnant women (36; 30–41) (Table 1). In univariate analysis, pregnant women (27/123, 23.1%) were 21.1% less likely to have comorbidities compared to non-pregnant women (491/1233, 39.8%); while postpartum (10/32, 27.8%) did not appear to have a significantly different comorbidity prevalence compared to non-pregnant women (p=0.33). Among pregnant women with an underlying comorbidity, chronic respiratory disease (12/123, 9.8%), immunosuppression/malignancy (6/123, 4.9%), diabetes mellitus (4/123, 3.3%), chronic renal disease (2/123, 1.6%) were the only conditions reported. Among postpartum women with reported comorbidities, chronic respiratory disease (6/32, 18.8%), immunosuppression/malignancy (3/32, 9.4%), chronic liver disease (1/32, 3.1%), chronic renal disease (1/32, 3.1%) were the only conditions reported. Where reported, pneumonia was the most common clinical presentation among all three groups: pregnant (64/106, 60.4%), postpartum (16/32, 50.0%) and non-pregnant women (69.0%, 835/1210). The serotype group distribution in pregnant and postpartum women was similar to that in non-pregnant women, with the additional PPV23 serotypes contributing to most of the IPD cases with serotyped isolates (1111/1578, 70.4%), while NVT serotypes contributed the lowest (205/1578, 13.0%). Of PCV13-type IPD cases, only a small number were attributed to PCV7 serotypes (1/123 of pregnant women and 29/1420 non-pregnant women). The proportion of cases with prior PPV23 vaccination was slightly higher among non-pregnant women (164/1212, 13.5%) compared to pregnant (10/117, 8.6%) and postpartum (0/32, 0.0%) women but neither of these differences was statistically significant (p=0.131, p=0.982, respectively). The majority of cases were of White ethnic group (886/1235, 71.7%) and ethnicity distribution was similar among non-pregnant, pregnant and the postpartum cohorts. There were no significant differences in specific comorbidities between the groups by pregnancy status with exception of chronic liver disease, which was significantly less common among pregnant women compared to non-pregnant women (p=0.031).

Table 1
Characteristics of pregnant, postpartum and non-pregnant women.

Characteristic	Pregnant, n = 123	Postpartum, n = 38	Non-pregnant, n = 1540
Age (year)[a]	31 (26 - 35)	30 (25 - 34)	36 (30 - 41)
Age group (year)	n=123	n=38	n=1540
< 30	53 (43.1%)	19 (50.0%)	378 (24.6%)
30–34	24 (19.5%)	10 (26.3%)	283 (18.4%)
35–39	36 (29.3%)	9 (23.7%)	378 (24.6%)
40+	10 (8.1%)	0 (0.0%)	501 (32.5%)
Ethnic group	n=112	n=30	n=1093
White	83 (74.1%)	21 (70.0%)	782 (71.6%)
Asian	11 (9.8%)	1 (3.3%)	72 (6.6%)
Black	3 (2.7%)	4 (13.3%)	84 (7.7%)
Mixed	2 (1.8%)	1 (3.3%)	44 (4.0%)
Other	13 (11.6%)	3 (10.0%)	111 (10.2%)
Comorbidity status	n=117	n=32	n=1233
Comorbid	27 (23.1%)	10 (27.8%)	491 (39.8%)
Healthy	90 (76.9%)	22 (72.2%)	742 (60.2%)
Serotype group	n=123	n=35	n=1420
PCV13	22 (17.9%)	8 (22.9%)	232 (16.3%)
PPV23	87 (70.7%)	21 (60.0%)	1003 (70.6%)
NVT	14 (11.4%)	6 (17.1%)	185 (13.0%)
Comorbidities	n=117	n=32	n=1233
Chronic respiratory disease	12 (9.8%)	6 (18.8%)	179 (14.3)
Chronic heart disease	0 (0.0%)	0 (0.0%)	27 (2.2%)
Chronic liver disease	0 (0.0%)	1 (3.1%)	67 (5.4%)
Chronic renal disease	2 (1.6%)	1 (3.1%)	35 (2.8%)
Immunosuppression/ malignancy	6 (4.9%)	3 (9.4%)	153 (12.4%)
CSF leaks	0 (0.0%)	0 (0.0%)	14 (1.1%)
Asplenia	0 (0.0%)	0 (0.0%)	8 (0.7%)
Sickle-cell disease	0 (0.0%)	0 (0.0%)	7 (0.6%)
Diabetes mellitus	4 (3.3%)	0 (0.0%)	58 (4.7%)
Cochlear implants	0 (0.0%)	0 (0.0%)	2 (0.2%)
Coeliac disease	0 (0.0%)	0 (0.0%)	2 (0.2%)
Clinical presentation	n=106	n=32	n=1210
Meningitis	2 (1.9%)	1 (3.1%)	130 (10.7%)
Pneumonia	64 (60.4%)	16 (50.0%)	835 (69.0%)
Other	13 (12.3%)	5 (15.6%)	105 (8.7%)
Bacteraemia	27 (25.5%)	10 (31.3%)	140 (11.6%)
PPV23 vaccination status	n=117	n=32	n=1212
Yes	10 (8.6%)	0 (0.0%)	164 (13.5%)
No	107 (91.5%)	32 (100.0%)	1048 (86.5%)

Note: Due to rounding, percentages may not total to 100%.
[a] Median (IQR); n (%).

IPD Incidence

IPD incidence in pregnant women was 0.048 per 1000 woman-years, which was not significantly different than the incidence of 0.041 per 1000 woman-years in non-pregnant women (Incidence Rate Ratio (IRR): 1.17; 95%CI 0.96–1.40; p=0.107) (Table 2). When stratified by trimester at time of infection, those in their third trimester had more than twice the risk of IPD compared to non-pregnant women (IRR 2.27, 95%CI 1.78–2.85, p < 0.001), while those in the first and second trimester had a lower risk of IPD (IRR 0.49, 95%CI 0.28–0.80 and IRR 0.71, 95%CI 0.47–1.04, respectively) albeit only statistically significant for the first trimester. Postpartum women (0.144 per 1000 woman-years), on the other hand had more than three times the risk of IPD compared to non-pregnant women (IRR 3.49, 95%CI 2.46–4.81, p < 0.001).

Maternal and foetal outcomes

Among pregnant women, 65.0% (80/123) of infections occurred in the third trimester, followed by the second trimester (27/123, 22.0%) and first trimester (16/123, 13.0%) (Table 3). Overall, 86.2% (n=106) IPD cases in pregnant women experienced a live birth - including 78 (63.4%) at term, 21 (17.1%) at preterm, and 7 (5.7%) at unknown timing - while 9.8% (12/123) had a miscarriage, stillbirth (2/123, 1.6%). Pregnant women with IPD in the third trimester – with the exception of one woman who had a stillbirth (1/80) – all subsequently had a live birth (Fig. 2); where gestational age at birth was known (74/80), most delivered at term (82.4%, 61/74), followed by preterm (20.3%, 12/74) (Table 3). Among women infected during the second trimester, 77.8% (21/27) had live births, with 51.9% (14/27) reaching full-term. Notably, 18.5% (5/27) experienced a miscarriage and 3.7% (1/27) had a stillbirth. Pregnancy outcomes of 12 women, who had IPD during their first trimester, with known gestational age (12/16), were more varied and included term birth (3/12, 25.0%), preterm birth (2/12, 16.7%), miscarriage (5/12, 41.7%), and termination (2/12, 16.7%). Overall, among 106 pregnant women who had a live-birth, 27.4% (29/106) of pregnant women developed IPD on the same day or within 1 day of the birth while 56.6% (60/106) delivered more than 28 days after IPD. The length of stay in hospital (median 4 (IQR: 2–8) days) was not statistically significant by pregnancy status (Table 3).

In the multinomial regression models, pregnant women were significantly less likely to be aged ≥40 years (Relative Risk Ratio [RRR]: 0.14, 95%CI 0.07–0.31, compared with 30 years) and be of Black ethnicity (RRR: 0.23 95%CI 0.05–0.96, compared to White ethnicity), but significantly more likely to present with bacteraemia (RRR: 2.25, 95%CI 1.31–3.86, compared with pneumonia) and healthy (RRR: 1.88, 95%CI 1.16–3.05), when compared to non-pregnant women. Postpartum women were 3.28 times (95%CI 1.37–7.88, p=0.008) more likely to present with bacteraemia than pneumonia as compared with non-pregnant women (Fig. 3). All pregnant and postpartum women survived their infection. In contrast, 85/1540 (5.5%) non-pregnant women died within 30 days of IPD (Table 3).

Neonatal IPD

Except for one baby born to a pregnant woman at term who died within 30 days of birth with a congenital malformation, there were no other neonatal deaths. Of the 144 live births, three newborns (2.1%) whose mothers developed IPD in the third trimester or postpartum, had confirmed IPD following birth. Two neonates presented with bacteraemia, one had bacteraemic pneumonia and all had neonatal intensive care admission and prolonged hospital stays. In two neonates, the infecting serotype (3, 35F) was confirmed to be same as their mother's, while the third baby had serotype 8 IPD, whose mother had serotype 3 IPD. All three babies survived their infection.

Table 2
Incidence of IPD among pregnant, postpartum and non-pregnant women.

Pregnancy status	Cases	Person-time (years)	Incidence Rate (IR), per 1000 woman-years	Incidence Rate Ratio (IRR)	95% CI	P-value
Pregnant women	123	2,550,247	0.048	1.17	0.96–1.40	0.107
First trimester	16	784,692	0.020	0.49	0.28–0.80	< 0.001
Second trimester	27	915,473	0.030	0.71	0.47–1.04	0.070
Third trimester	80	850,082	0.094	2.27	1.80–2.85	< 0.001
Postpartum women	38	263,329	0.144	3.49	2.46–4.81	< 0.001
Non-pregnant women	1540	37,208,117	0.041	Reference		

Table 3
Maternal and foetal outcomes by trimester and postpartum period.

Characteristic	First trimester, n = 16	Second trimester, n = 27	Third trimester, n = 80	Postpartum, n = 38	Non-pregnant, n = 1540
Age (year)[a]	29 (23 - 36)	33 (28 - 36)	31 (25 - 35)	30 (25 - 34)	36 (30 - 41)
	n=16	n=27	n=80	n=38	n=1540
Admitted to hospital	12 (75.0%)	24 (89.9%)	58 (72.5%)	26 (68.4%)	1120 (72.7%)
Length of hospital stay[a]	3 (2–4)	4 (3–8)	4 (3–6)	4 (2–7)	4 (2–8)
	n=11	n=15	n=54	n=22	n=906
Admitted to ICU	1 (9.1%)	1 (6.7%)	8 (14.8%)	5 (22.7%)	220 (24.3%)
Clinical presentation	n=13	n=24	n=69	n=32	n=1210
Meningitis	1 (7.7%)	0 (0.0%)	1 (1.5%)	1 (3.1%)	130 (10.7%)
Pneumonia	8 (61.5%)	15 (62.5%)	41 (59.4%)	16 (50.0%)	835 (69.0%)
Other	3 (23.1%)	4 (16.7%)	6 (8.7%)	5 (15.6%)	105 (8.7%)
Bacteraemia	1 (7.7%)	5 (20.8%)	21 (30.4%)	10 (31.3%)	140 (11.6%)
Pregnancy outcome	n=16	n=27	n=80	n=38	-
Full-term birth	3 (18.8%)	14 (51.9%)	61 (76.3%)	15 (39.5%)	-
Preterm birth	2 (12.5%)	7 (25.9%)	12 (15.0%)	1 (2.6%)	-
Live birth (unknown term)	1 (6.3%)	0 (0.0%)	6 (7.5%)	22 (57.9%)	-
Miscarriage	7 (43.8%)	5 (18.5%)	0 (0.0%)	-	-
Stillbirth	0 (0.0%)	1 (3.7%)	1 (1.3%)	-	-
Termination	3 (18.8%)	0 (0.0%)	0 (0.0%)	-	-
	n=12	n=27	n=80	n=38	n=1540
Death (< 30 days)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	85 (5.5%)

Note: Due to rounding, percentages may not total to 100%.
[a] Median (IQR); n (%).

Discussion

Pregnant women in their third trimester and postpartum women had low but significantly increased risk of IPD compared to non-pregnant women. Over the five-year surveillance period, the 123 pregnant women contributed to only 7% of IPD cases among women of reproductive age while the 38 postpartum women contributed to 2%, indicating the burden of IPD in pregnant and postpartum women is low. Pregnant women were younger and healthier than non-pregnant women but did not appear to differ by some other characteristics – ethnic group or serotype group distribution – which were comparable across the pregnancy status groups. Pregnant and postpartum women with IPD were, however, more likely to develop bacteraemia than pneumonia compared to non-pregnant women. Reassuringly, all pregnant and postpartum women with IPD survived their infection, with no evidence of a prolonged hospital stay compared to non-pregnant women with IPD. Neonatal IPD following maternal infection was rare, occurring in 2.1% (3 cases) of live births among women who developed IPD near the time of delivery. All three infants recovered following treatment in hospital but required extended hospital stays of up to 13 days.

There are very few population-based studies assessing IPD risk during pregnancy and the postpartum period, especially after implementation of highly effective PCVs in national immunisation programmes, One US study covering 2007–09 surveillance period, reported a 3.0-fold higher incidence rate of IPD in postpartum women (0.15 per 1000 woman-years) compared to non-pregnant women, similar to our 3.3-fold increased rate (0.14 per 1000 woman-years). While they also identified no overall increased risk of IPD during pregnancy, unlike our study, they did not stratify their cases by trimester. In our larger cohort, we found that the risk in the third trimester was more than twice as high as that of non-pregnant women, which was masked in the overall estimate due to the comparatively lower risks observed during the first two trimesters of pregnancy.

These findings suggest that the risk of IPD and adverse foetal outcomes are comparatively lower than for certain other maternal infections including invasive group B Streptococcus and non-typeable *Haemophilus influenzae* (ntHI), which were associated with an increased rate ratio of 2.0 and 17.2 when compared with non-pregnant women, respectively.[9,20] Almost a third of pregnant women with IPD in the third trimester delivered on the same day or

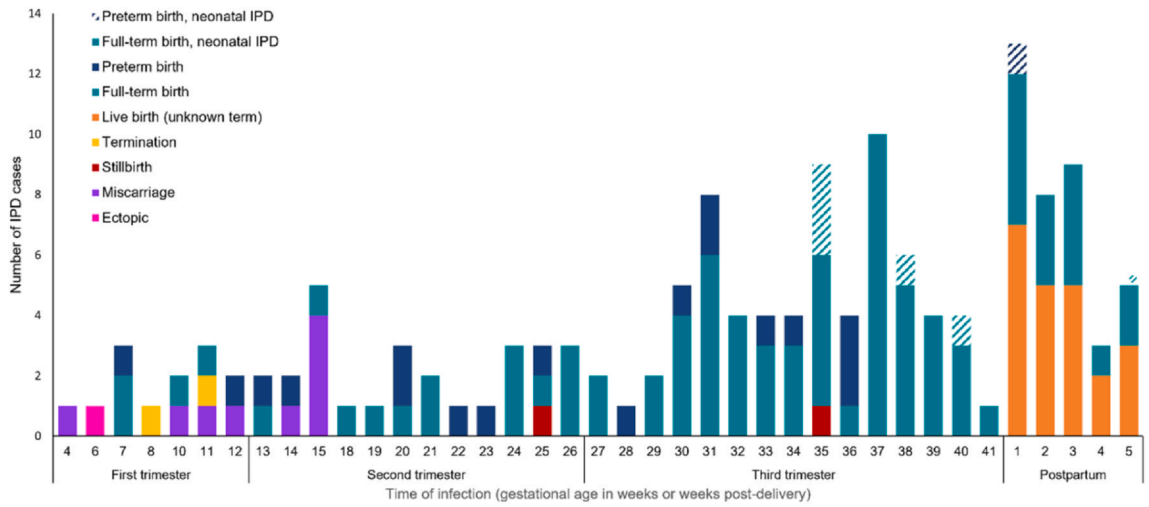

Fig. 2. Timeline of pregnant and postpartum IPD cases by gestational age (weeks) or weeks postpartum at time of infection and foetal outcomes. *One infant born to a pregnant case at full-term died within 30 days due to an unrelated cause.

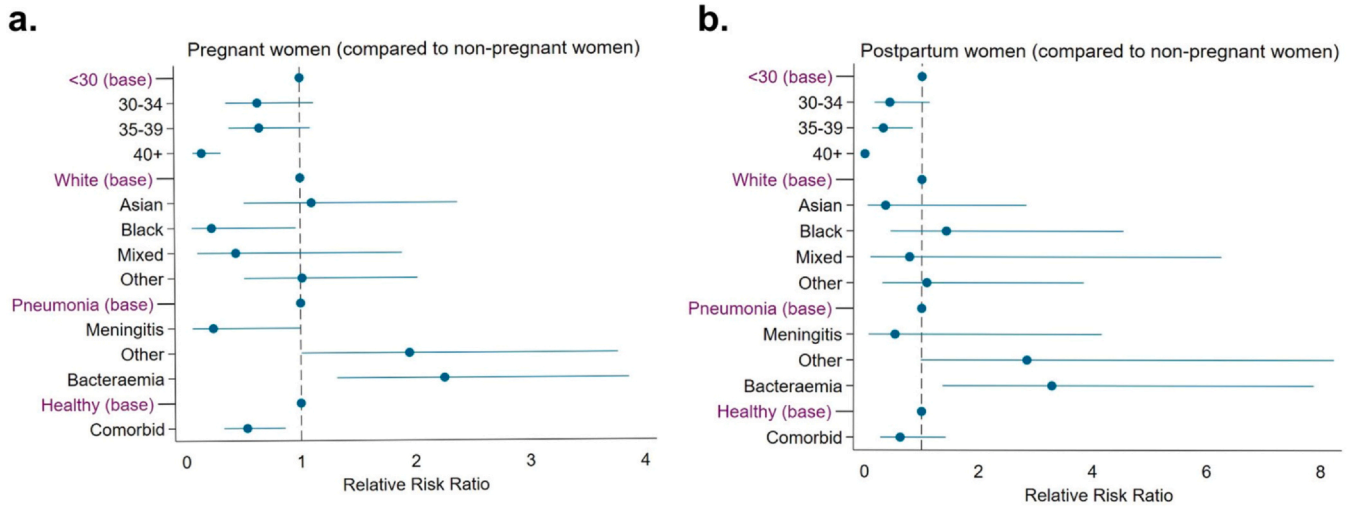

Fig. 3. Multinomial logistic regression models of characteristics associated with pregnant (a) and postpartum (b) women compared to non-pregnant women (reference group).

a day after infection, suggesting the possibility that severe infection in the mother could have contributed toward a need for induction of labour or an emergency caesarian section, likely because of poor condition of the mother and/or the foetus.[21]

Whilst most pregnant women with IPD survived their infection and went on to deliver at term, a substantial proportion (31%) had a miscarriage, stillbirth or premature live-birth. Aligned with our findings, which showed that 11% of pregnant and postpartum women had stillbirth, termination, or miscarriage without any cases of neonatal death linked to IPD, the study conducted in the US similarly reported only 8% of cases with stillbirth or termination without neonatal death.[9] There was otherwise a paucity of research or case reports on pregnant women with IPD and their pregnancy outcomes in the literature.

The relatively immature immune systems of the foetus and newborn also play an important role in their increased susceptibility to particular infections, with uteroplacental circulation between mother to foetus providing the means for passing infection to the neonate, however neonatal sepsis due to the streptococcus is known to be uncommon, with vaginal colonisation rarer still (< 0.03%).[22,23] It is worth noting that, postpartum women who were subjected to a caesarean section, particularly those who were in labour before the surgery, have a higher risk of postpartum infection compared to those who have a vaginal delivery.[24]

We also found that pregnant and postpartum women were more likely to present with bacteraemia than non-pregnant women who were more likely to develop bacteraemic pneumonia. This may be because pregnant women were significantly less likely to have underlying conditions which may increase the risk of specific focal infections such as pneumonia or meningitis.[25,26] Notably, unlike the US study, we did not observe any significant association between ethnic group and IPD risk, with the only association observed being that Black women with IPD were 88% less likely to be pregnant than non-pregnant than White women with IPD.[9]

We have previously reported that premature infants had an increased risk of IPD compared to infants born at term, with the risk being highest in the neonatal period.[27] Maternal immunisation with PCVs could potentially protect newborns against early-onset pneumococcal infections in immune-naïve neonates but, unlike other infectious diseases with successful maternal (influenza, pertussis) and neonatal (hepatitis B) immunisation programmes, the very small number of cases, which included infections due to non-vaccine pneumococcal serotypes – albeit the proportion of vaccine-serotype IPD make up the majority – would suggest that antenatal vaccination would be unlikely to be cost-effective[28,29]; one Cochrane review recently concluded that there was insufficient evidence to assess whether pneumococcal vaccination during pregnancy could reduce infant infections.[30] Furthermore, with the use of newer higher-valent PCVs, such as PCV15 and PCV20, it is also important to consider the serotype coverage they provide, which would be slightly lower than PPV23. In the case of PCV20, 9N one of the commonest serotypes which made up 5% of cases among women in this cohort is excluded, while PCV15 would only have 25% coverage of all infecting serotypes within this cohort. Given these limitations, newer vaccines may not offer any greater cost-effectiveness.

Strengths and limitations

This is the largest study on the risk of IPD among pregnant and postpartum women. A strength of the current study is the long-standing surveillance of IPD in England and the high case ascertainment of invasive *Streptococcus pneumoniae* infections, which is legally notifiable in the UK; the surveillance itself has also been enhanced in recent years to collect additional information on the outcomes of pregnancy and the postpartum period. The collection of pregnancy and postpartum status was, however, challenging because it was not always reported in the surveillance questionnaire by the GP. We therefore had to rely on using multiple data sources to ascertain the information. It is, however, still possible that women in early pregnancy may not have been captured in the surveillance. Similarly, some pregnancy women with IPD may have experienced a pregnancy loss after the infection, which may not have been captured by our surveillance. These are, however, rare events and, therefore, unlikely to affect our findings. Linkage of the surveillance data to HES was particularly useful for enriching the final datasets, especially by providing additional data on underlying conditions, hospitalisation for IPD, and pregnancy outcomes. This is particularly important because blood cultures are routinely only performed in hospital settings in patients with suspected sepsis, who are invariably hospitalised for further management, including initiation of empiric antibiotics whilst awaiting culture and other results. Our estimates of neonatal infections in infants born to mothers with IPD are also likely to be underestimated because we only included confirmed neonatal IPD cases and it is likely that we missed some cases where microbiological investigations may be negative because of maternal receipt of antenatal antibiotics, for example. Also, while we report on adverse pregnancy outcomes such as miscarriage, stillbirth and premature birth, were unable to comment on whether these events were directly associated with IPD. Additionally, with limited information regarding parity, birth order, and other

household exposures – particularly the presence of young children, among whom carriage is known to be highest – meant it was not possible to ascertain the potential routes of carriage and acquisition among these women and whether they varied by pregnancy status.

Finally, we used Office for National Statistics (ONS) population estimates and live births, miscarriages and abortions figures, to estimate the denominator of the pregnant and postpartum population in England which may be subject to some error.

Conclusion

Pregnant women in their third trimester and postpartum women have an increased risk of IPD compared to non-pregnant women, but the serotypes responsible for IPD were similar. All pregnant and postpartum women with IPD survived their infection, but some infections were associated with miscarriage and stillbirths. Infection in neonates born to mothers with IPD was rare and associated with favourable outcomes.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SNL holds the position of Associate Editor at the Journal of Infection and will not take part in the editorial review or determination of publishing for this article. ZAC, MB, FB, CLS, SDE, DJL, NKF and SNL report providing vaccine manufacturers with post-marketing surveillance reports, which the companies are required to submit to the UK licensing authority in compliance with their risk management strategy. In accordance with UK Health Security Agency policy, a cost recovery charge is made for these reports payable to the Immunisation and Vaccine Preventable Diseases Division. No other disclosures were reported.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106363.

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