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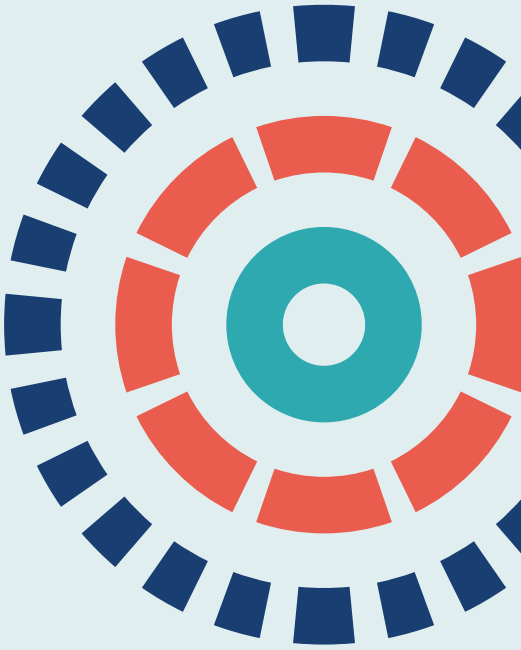

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Developing a serocorrelate of protection against invasive group B streptococcus disease in pregnant women: a feasibility study

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This report

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Abstract

Developing a serocorrelate of protection against invasive group B streptococcus disease in pregnant women: a feasibility study

Clara Carreras-Abad,[1] Madeleine Cochet,[1] Tom Hall,[1] Laxmee Ramkhelawon,[1] Asma Khalil,[2] Elisabeth Peregrine,[3] Latha Vinayakarao,[4] Sharmila Sivarajan,[5] Rosol Hamid,[6] Tim Planche,[7] Elizabeth Sheridan,[8] Stephen Winchester,[9] Jane Plumb,[10] Abdelmajid Djennad,[11] Nick Andrews,[11] Kirsty Le Doare[1]* and Paul Heath[1]

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Background: Group B streptococcus is the leading cause of infection in infants. Currently, intrapartum antibiotic prophylaxis is the major strategy to prevent invasive group B streptococcus disease. However, intrapartum antibiotic prophylaxis does not prevent maternal sepsis, premature births, stillbirths or late-onset disease. Maternal vaccination may offer an alternative strategy. Multivalent polysaccharide protein conjugate vaccine development is under way and a serocorrelate of protection is needed to expedite vaccine licensure.

Objectives: The ultimate aim of this work is to determine the correlate of protection against the major group B streptococcus disease-causing serotypes in infants in the UK. The aim of this feasibility study is to test key operational aspects of the study design.

Design: Prospective cohort study of pregnant women and their infants in a 6-month period (1 July to 31 December 2018).

Setting: Five secondary and tertiary hospitals from London and South England. National iGBS disease surveillance was conducted in all trusts in England and Wales.

Participants: Pregnant women aged ≥ 18 years who were delivering at one of the selected hospitals and who provided consent during the study period. There were no exclusion criteria.

Interventions: No interventions were performed.

Main outcome measures: (1) To test the feasibility of collecting serum at delivery from a large cohort of pregnant women. (2) To test the key operational aspects for a proposed large serocorrelates study. (3) To test the feasibility of collecting samples from those with invasive group B streptococcus.

Results: A total of 1823 women were recruited during the study period. Overall, 85% of serum samples were collected at three sites collecting only cord blood. At the two sites collecting maternal, cord and infant blood samples, the collection rate was 60%. A total of 614 women were screened for group B streptococcus with a colonisation rate of 22% (serotype distribution: 30% III, 25% Ia, 16% II, 14% Ib, 14% V and 1% IV). A blood sample was collected from 34 infants who were born to colonised women. Maternal and infant blood and the bacterial isolates for 15 newborns who developed invasive group B streptococcal disease during the study period were collected (serotype distribution: 29% III, 29% II, 21% Ia, 7% Ib, 7% IV and 7% V).

Limitations: Recruitment and sample collection were dependent on the presence of research midwives rather than the whole clinical team. In addition, individualised consent limited the number of women who could be approached each day, and site set-up for the national surveillance study and the limited time period of this feasibility study limited recruitment of all eligible participants.

Conclusions: We have verified the feasibility of collecting and processing rectovaginal swabs and blood samples in pregnant women, as well as samples from those with invasive group B streptococcal disease. We have made recommendations for the recruitment of cases within the proposed GBS3 study and for controls both within GBS3 and as an extension of this feasibility study.

Future work: A large case–control study comparing specific immunoglobulin G levels in mothers whose infants develop invasive group B streptococcal disease with those in colonised mothers whose infants do not develop invasive group B streptococcal disease is recommended.

Trial registration: Current Controlled Trials ISRCTN49326091; IRAS project identification number 246149/REC reference number 18/WM/0147.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 23, No. 67. See the NIHR Journals Library website for further project information.

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Glossary

GBS3 A multicentre prospective two-arm, parallel, cluster randomised controlled trial to test women for group B streptococcus colonisation in late pregnancy or labour compared with the current risk based strategy, with internal pilot and feasibility evaluation and parallel economic modelling for testing women.

List of abbreviations

BPAIIG	British Paediatric Allergy, Immunity and Infection Group
CI	confidence interval
CoP	correlate of protection
CPS	capsular polysaccharide
ECM	enriched culture medium
EOD	early-onset disease
GBS	group B streptococcus
HRA	Health Research Authority
IAP	intrapartum antibiotic prophylaxis
iGBS	invasive group B streptococcal disease
IgG	immunoglobulin G
LAT	latex agglutination test
LOD	late-onset disease
neonIN	Neonatal Infection Network
NIHR	National Institute for Health Research
PCR	polymerase chain reaction
RCOG	Royal College of Obstetrics and Gynaecology
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture

Plain English summary

Group B streptococcus is often carried by healthy women and usually causes no problems. Group B streptococcus may be passed from mother to child, primarily through the birth canal, and, in rare cases, can cause serious disease (i.e. pneumonia, sepsis or meningitis) and even death in babies. It may be possible to prevent group B streptococcus disease in babies by giving a vaccine to pregnant women. The reason for vaccinating the mother is so that she can pass on protection (antibodies) during the pregnancy to her baby. A vaccine is currently being developed against group B streptococcus that aims to boost this protection. To help vaccine development progress faster, we need to find out how much antibody is actually needed to protect babies from group B streptococcus disease. A large study is needed to address this question; therefore, we have performed a feasibility study to assess the practicalities of performing this large study. Specifically, we will assess (1) women's willingness to participate in a swabbing and cord blood study, (2) the ability to collect swabs and cord blood once recruited, (3) the ability to identify group B streptococcus disease in this population and (4) the laboratory processing of samples.

We recruited 1823 pregnant women from five maternity units in England in a 6-month period: 22% of all women delivering at all sites and 74% of those women who were approached. In three hospitals, cord blood samples from 85% of 1201 women were collected. In two hospitals, we collected 60% of maternal blood samples, 53% of cord blood samples and 99% of swabs from the vagina and rectum from 622 women. A total of 22% of these women carried group B streptococcus in their vagina or gut and we collected blood samples from 34 healthy babies born to these women. During the study, we collected samples from 15 babies who had developed severe group B streptococcus disease; four babies were born to women participating in the study and the rest were identified through national surveillance.

In conclusion, we have verified the feasibility of collecting and processing swabs from the vagina and rectum and blood samples in pregnant women, as well as samples from babies who developed group B streptococcus disease. In addition, we have identified a number of strategies that could be adopted in a future study in order to increase recruitment and sample collection.

Scientific summary

Background

Group B streptococcus is the leading cause of sepsis and meningitis in newborns and young infants worldwide. The most common clinical presentation is early-onset disease (i.e. occurring in newborns aged < 7 days). Most cases can be prevented with antibiotics given in labour (intrapartum antibiotic prophylaxis). However, intrapartum antibiotic prophylaxis does not prevent late-onset disease, stillbirths, preterm births or maternal sepsis. Furthermore, the UK has experienced an increase in group B streptococcus in infants in recent years (from 0.72 to 0.95 per 1000 live births between 2000 and 2014), despite a national prevention strategy that was introduced in 2003. Therefore, alternative strategies, such as maternal vaccination, are being explored to provide greater protection against all clinical presentations, as well as to reduce the use of antibiotics and their potential negative consequences on infant immune development and antimicrobial resistance.

There is evidence that maternally derived serotype-specific antibodies against group B streptococcus can protect newborns and young infants against disease. To facilitate group B streptococcus vaccine licensure, a serocorrelate of protection against the major group B streptococcus serotypes causing disease is needed.

Objectives

The overall aim of this study is to facilitate a national serocorrelate of protection against group B streptococcus disease study in 2020 embedded within the National Institute for Health Research GBS3 trial. The objective of this feasibility study was to test the key operational aspects of such a study.

The primary objective was to test the feasibility of collecting serum at delivery (maternal, cord or both) from a large cohort of pregnant women.

First, we tested the following key operational aspects: enrolment rate of eligible women who were willing to participate in the delivery blood collection study, maternal and/or cord blood collection rate, key clinical data collection rate, and infant invasive group B streptococcal disease surveillance consent rate. Several substudies were embedded, including rectovaginal swab consent and collection rates, rectovaginal group B streptococcus colonisation rate and rectovaginal group B streptococcus serotype-specific colonisation rate, infant blood sample consent rate, infant Guthrie card consent rate, and infant Guthrie card collection rate.

Second, we tested the feasibility of collecting samples (maternal and infant blood samples and the bacterial isolate) from invasive group B streptococcal disease cases from the study cohort and from national surveillance.

Finally, we assessed laboratory parameters important for the main study: the impact of timing of processing and blood sample storage conditions on total immunoglobulin G concentrations; the serotype-specific group B streptococcus anticapsular polysaccharide immunoglobulin G concentrations in maternal serum and cord blood in subjects colonised with group B streptococcus at delivery; and the correlation between two different culture techniques for detection of group B streptococcus in rectovaginal swabs: enrichment culture medium and direct plating using selective agar.

Methods

We carried out a prospective cohort study of pregnant women and their infants over a 6-month period between 1 July and 31 December 2018. Participants were recruited from five maternity units in London and South England (i.e. Croydon, East Surrey, Kingston, Poole and St George's hospitals). The inclusion criteria were all pregnant women aged ≥ 18 years delivering at one of the five selected hospitals during the study period. As this was a feasibility study, there were no exclusion criteria. At Kingston and St George's hospitals, women consented to provide maternal and cord blood samples as well as a rectovaginal swab. In addition, they were invited to participate in the infant blood sample collection substudy in which infants from colonised mothers were randomised at 1, 2 or 3 months. Furthermore, we asked for consent to track their Guthrie cards if they had group B streptococcus-positive swabs and/or group B streptococcus disease. At Croydon, East Surrey and Poole hospitals, women were asked to participate in the cord blood collection study only. Maternal blood samples were collected only if cord blood was not obtained.

A telephone call follow-up was made at 90 days after birth to assess whether or not infants had developed invasive group B streptococcal disease. In addition, national surveillance was set up after the study started to increase the number of cases detected and to test the feasibility of using national surveillance data to identify cases.

All data were collected on Research Electronic Data Capture (REDCap; 8.1.8, Vanderbilt University, Nashville, TN, USA) and we undertook a descriptive analysis using Stata® version 15 (StataCorp LP, College Station, TX, USA). McNemar's test was used to assess the exploratory objective comparing the two group B streptococcus culture methods.

Results

During the study period, 1823 women were recruited, which was 22% (95% confidence interval 21% to 23%) of all women delivering at the five selected hospitals. A total of 1201 were recruited at the three sites collecting cord blood only, where the serum sample collection rate was 85%. At two sites collecting maternal, cord and rectovaginal swabs, 622 women were recruited and the serum sample collection rate was 60%. The rectovaginal sample collection rate was 99% (614/622). We found a colonisation rate of 22% with the following serotype distribution: 30% III, 25% Ia, 16% II, 14% Ib, 14% V and 1% IV. Furthermore, 34 infants born to colonised mothers were randomised at 1, 2 or 3 months for blood sample collection.

Key clinical data were collected and recorded on REDCap in 90–100% of cases, except for two items that were related to antibiotic prescription, at 65% and 54%, respectively. Owing to the short period of the study, we made 16% of the 90-day follow-up telephone calls. However, the consent rate for making calls was 100%. We collected maternal and infant blood and the bacterial isolate from all 15 infants who developed invasive group B streptococcal disease. The serotype distribution in cases was 29% III, 29% II, 21% Ia, 7% Ib, 7% IV and 7% V.

There was no impact of time of spinning on total immunoglobulin G concentrations for periods of time from 6 hours to 1 week. The serotype-specific group B streptococcus anticapsular polysaccharide immunoglobulin G concentrations in maternal serum and cord blood in subjects colonised with group B streptococcus at delivery demonstrated that we were able to identify antibodies in these women and that antibodies generally declined between delivery and 3 months of life.

We found a significant difference ($p < 0.001$) between direct plating and enriched culture medium culture methods for detection of group B streptococcus. Using an enriched culture medium before plating onto selective agar identified 97% (116/120) of the total positive rectovaginal swabs, whereas direct plating onto selective agar identified 75% (90/120).

Conclusions

The feasibility study has been able to assess key operational aspects that are needed to define the correlates of protection against invasive group B streptococcal disease in a future study. We identified a number of factors that may account for the variability in recruitment and sample collection rates between sites. The need for consenting on labour wards and the engagement of all clinical staff were identified as two key factors.

Future work

To define the serocorrelates of protection against the major disease-causing group B streptococcus serotypes will require a case–control study of adequate size. We have previously estimated that this could be achieved with around 150 cases of invasive group B streptococcal disease and 450 matched controls.

Cases

A sample size of 150 cases will require a cohort of > 180,000 women (based on the known national incidence) and this is well within the sample size predicted for the GBS3 trial. We therefore propose that cord samples are obtained from this number of women. We will discuss further with the GBS3 team whether this would apply to all women in the trial or only those in particular groups (e.g. standard of care group). The latter would be preferred as this group may well have a higher rate of invasive group B streptococcal disease. Within the feasibility study we have been able to define the practical issues around collecting, spinning, storing and transferring these samples. We have also identified the issues around consenting women for this, and have identified retrospective consent as an acceptable and effective method. We would also like to propose consideration of an opt-out approach, whereby pregnant women receive information about cord blood collection, which is then undertaken unless the woman elects not to participate. We will explore this approach further through parent groups, health-care worker discussions and ethics committee advice.

Controls

As previously demonstrated, we require a control group of around 450 colonised women (3 : 1 matched to cases). To obtain 450 controls requires swabs from 5000 women. Importantly, such women must not have received intrapartum antibiotics. Again, within the feasibility study we have been able to define, in detail, the practical issues around collecting these samples as well as the issues around consenting women. We now have a network of hospitals that are able to undertake a study to collect samples from controls.

We believe that completing the recruitment of the control group within the GBS3 trial will be difficult. One of the major reasons for this is that the majority of women in GBS3 who are identified as group B streptococcus-colonised will go on to receive intrapartum antibiotic prophylaxis. They will not therefore be suitable as controls. It is also clear from the GBS3 team that actually identifying women who have received intrapartum antibiotic prophylaxis (on an individual level) will be problematic, as their current strategy is to define antibiotic exposure on a unit level and they do not currently envisage capturing individual-level data.

We therefore wish to propose completing recruitment to the control group through the network of units that we have established during the feasibility study. This will ensure that we have a complete and well-defined control group in preparation for case collection during the GBS3 trial. The extension will also allow completion of the kinetics substudy and will ensure that the methods for collecting cases are finalised.

Trial registration

This trial is registered as ISRCTN49326091 and as IRAS project identification number 246149/REC reference number 18/WM/0147.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Group B streptococcus (GBS) is the leading cause of neonatal sepsis and meningitis in most countries. GBS is also an important cause of disease in pregnant women, immunocompromised adults and elderly people.[1] The highest incidence of invasive group B streptococcal disease (iGBS) is in the first 3 months of life and the condition is traditionally divided into early-onset disease (EOD) (i.e. occurring in infants aged < 7 days) or late-onset disease (LOD) (i.e. occurring in infants aged 7–89 days). GBS is an encapsulated bacterium and 10 serotypes are described; five serotypes (i.e. Ia, Ib, II, III, V) account for 97% of iGBS.[2]

Overall, EOD accounts for 60–80% of iGBS in the first 3 months of life. Maternal colonisation with GBS in the gastrointestinal or genital tract is a prerequisite for EOD, with vertical transmission occurring during or just before birth. Around 20% of pregnant women are colonised with GBS[3] and 1–2% of neonates who are born to colonised women develop invasive disease in the absence of intrapartum antibiotic prophylaxis (IAP).[4] EOD can occur rapidly, with signs evident at birth or within 12 hours in most cases, typically presenting with sepsis, pneumonia and/or meningitis.[5]

Group B streptococcus is present in all regions of the world and an estimated 21.7 million pregnant women are colonised at any one time.[3] In 2015, it was estimated that annually worldwide there were at least 319,000 infants aged < 3 months with iGBS, resulting in 90,000 infant deaths and at least 10,000 children with disability related to GBS meningitis. Additionally, 33,000 maternal cases and 57,000 stillbirths are attributed to GBS disease each year.[6]

The global burden of group B streptococcus is therefore high and represents an unmet public health need

Intrapartum antibiotic prophylaxis can reduce the incidence of EOD, and many high-income countries have established IAP policies. The incidence of EOD in the USA has declined significantly in the era of IAP and the incidence is also generally declining in other countries adopting a swab-based screening policy.[7,8] However, in some countries, particularly those adopting a risk-based IAP strategy, such as the Netherlands[9] and the UK,[10] recent increases in disease burden have been reported.

It is clear that even strict and universal implementation of IAP guidelines does not eliminate EOD,[11,12] as disease can occur because of limitations to IAP administration (e.g. in precipitate labour), in infants of mothers who were negative on screening and where no risk factors are evident in labour.[13] Most significantly, IAP has no impact on GBS-related prematurity or stillbirths or LOD, where the burden of disease is substantial. The majority of GBS meningitis occurs after the first week of life, so this particular burden remains. In the USA and the UK, GBS is now the most common cause of bacterial meningitis in children aged < 5 years.[14,15]

Given the very early onset of neonatal GBS disease, the shortcomings of IAP-based prevention strategies and the evidence that suggests that maternal antibodies acquired after natural exposure (when transmitted transplacentally to the fetus) may protect the young infant from invasive infection,[16] the prospect of protecting mothers and their infants through vaccination in pregnancy is an attractive one. Possible candidates for an effective vaccine include one or more of the conserved surface proteins or the capsular polysaccharide (CPS).[17]

Multiple studies of CPS–protein conjugate vaccines in non-pregnant and, more recently, in pregnant women have established the immunogenicity and safety of these candidates.[17] Recent estimates suggest that an effective GBS maternal vaccine (> 80% efficacy), with high (90%) global coverage, could prevent 231,000 infant and maternal GBS cases, 41,000 stillbirths and 66,000 infant deaths annually.[6]

Several obstacles exist in moving the most advanced vaccines into Phase III clinical trials. The first is that, given the relative rarity of GBS disease in Europe and the USA, large numbers of infants would need to be recruited to determine vaccine efficacy.[18] Second, obstacles exist in determining what concentration of antibody is required to protect the infant for the duration of the at-risk period (i.e. the first 3 months of life), as there are currently no internationally recognised standards with which to interpret individual study results.[1] Licensure and policy decisions would be significantly accelerated if an immune marker, measured in an analytically and clinically validated assay, was established as a correlate of protection (CoP). Licensure in such a scenario would come with a commitment to establish effectiveness post licensure in a Phase IV study. This was the approach used for licensure of meningococcal C and meningococcal B vaccines.[19]

Correlates of protection against invasive disease

The association between serotype-specific capsular antibody levels and iGBS in newborns was initially characterised in 1976 by Baker and Kasper.[16] In the majority of subsequent studies, levels of CPS serotype-specific antibodies in maternal delivery sera of women who had neonates with EOD caused by that serotype were low, compared with levels in sera from women delivering infants who remained healthy.[1] However, different 'protective' levels have been defined in different studies as well as for the different serotypes.

In a meta-analysis undertaken to compare the proportions of cases and controls with antibody levels of ≥ 2 µg/ml, the odds of contracting iGBS were 6.6 [95% confidence interval (CI) 2.1 to 20.6] and 2.4 (95% CI 1.2 to 4.7) times greater in infants whose mothers had antibody levels of < 2 µg/ml for serotypes III and Ia, respectively.[20] A threshold of 1 µg/ml has also been proposed as a CoP for serotypes Ia and III.[8] Thresholds are much higher in other studies using different case–control designs and different enzyme-linked immunosorbent assay methods,[21,22] which makes direct comparisons difficult.

Interpretation of studies is confounded by the different assay methods used and the lack of standardised reference reagents for serotype-specific antibody levels. Therefore, further studies using standardised methods are warranted.[23]

Defining a correlate of protection against invasive group B streptococcal disease

There is considerable evidence that serum immunoglobulin G (IgG) can protect infants against iGBS and that this IgG is maternally derived as a result of natural maternal infection (i.e. colonisation). It is essential to know precisely what level of serum IgG in women at delivery is protective so that this can be targeted through vaccination. Protective levels can be estimated by comparing IgG from babies who are exposed to GBS (through maternal colonisation) and go on to develop iGBS (cases), with IgG from babies who are exposed to GBS (through maternal colonisation) but do not develop iGBS (controls). To do this, there needs to be sufficient numbers of cases and controls to be able to define the protective level of IgG (the CoP) with sufficient precision. Although the level of IgG in women at delivery is most often proposed as the CoP, there is a predictable decline in IgG level from the mother to the fetus (transplacental transfer ratio) and, subsequently, to the infant over the first 3 months of life (reflecting the half-life of maternal IgG). Measuring IgG in the cord blood and at different time points in the infant can allow these concentrations to be compared with maternal IgG to calculate the rate of antibody decline during the at-risk period of the first 3 months of life. The level of IgG in the infant will be of particular relevance in cases of LOD where the median age at disease onset is around 21 days.[24]

To generate a CoP, maternal delivery/cord sera from a cohort of mothers/babies must be collected prospectively. When an infant subsequently develops iGBS the relevant delivery samples can be retrieved for that infant and the antibody levels can be compared with those of suitable controls. The antibody levels in the infant at the time of iGBS can also be obtained and may also be used to predict the levels present at the time of delivery as it is not expected that these will change significantly between birth and the onset of iGBS, at least for EOD.[25]

Study rationale

From a UK perspective, we have recently seen an increasing burden of disease, despite a national (risk-based) policy for IAP,[10] and the UK National Screening Committee has recently recommended not to introduce a national screening programme.[26] The clinical effectiveness and cost-effectiveness of screening for GBS in pregnancy is the objective of another Health Technology Assessment application (17/86, GBS3). Conversely, the UK population has widely accepted the concept of maternal vaccination, with high coverage of maternal pertussis vaccination (> 70%) and the first demonstration of its effectiveness, to our knowledge.[27] The UK is therefore in an excellent position to pursue the development, licensure and implementation of a maternal vaccine against GBS.

Licensure and policy decisions for a candidate GBS vaccine would be significantly accelerated if an immune marker was established as a CoP. Regulatory bodies, including the European Medicines Agency and the Food and Drug Administration,[28] have made it clear that they would now consider this approach to licensure if robust evidence can be developed. Additionally, the UK Joint Committee on Vaccination and Immunisation has indicated it would consider a recommendation for routine implementation of a vaccine licensed on the basis of CoP – as it has for other recent vaccines (e.g. meningococcal C[19]).

The two critical gaps that have to be filled to make decisions on the use of such vaccines (both at the regulatory and at the recommending body level) are (1) the development of a standardised immunoassay to measure antibody levels that act as the correlates of natural immunity, supported by measurement of functional antibody assays, and (2) a large biobank of sera to establish the correlate using these new standardised assays. The first of these gaps is being addressed by a consortium of groups from academia, public health and industry (led by co-applicant KLD, OPP1153630), and the second is the basis of this study.

Given the anticipated size and logistical complexities of the serocorrelates study that would be needed to address this gap in knowledge, the aim of this initial feasibility study is to test key operational aspects of the study design for the collection of a large bank of serum in the UK.

Chapter 2 Objectives

Primary objective

To test the feasibility of collecting serum at delivery (maternal, cord or both) from a large cohort of pregnant women.

Secondary objectives

To test the key operational aspects for a proposed large serocorrelates study:

- enrolment rate [the rate (proportion) of eligible women who are willing to participate in the delivery blood collection study]
- maternal and/or cord blood collection rate
- key clinical exclusion data collection rate [weeks' gestation at birth, receipt of IAP in labour (yes/no), type of IAP (list), time between administration of IAP and delivery (in hours)]
- infant iGBS surveillance consent rate.

In a substudy of the main study above to assess:

- rectovaginal swab consent rate
- rectovaginal swab collection rate
- rectovaginal GBS colonisation rate
- rectovaginal GBS CPS serotype-specific colonisation rates.

In the substudy above, where samples of maternal/cord blood and rectovaginal swabs are all available, to assess:

- infant blood sample consent rate
- infant Guthrie card consent rate
- infant Guthrie card collection rate.

To test the feasibility of collecting samples from iGBS cases:

- maternal blood and rectovaginal swab, and the baby blood consent and collection rate from the participants of the iGBS study
- maternal and baby blood sample consent and collection rate from national surveillance (all NHS trusts in England and Wales).

Exploratory objectives

To assess:

- the impact of timing of processing and blood sample storage conditions on total IgG concentrations
- the serotype-specific GBS anti-CPS IgG concentrations in maternal serum and cord blood in subjects colonised with GBS at delivery
- the correlation between two different culture techniques for detection of GBS in rectovaginal swabs – enrichment culture medium and direct plating using selective agar.

Chapter 3 Study design and methods

Study design

This was a prospective cohort study of pregnant women and their infants. The study design is shown in *Figures 1* and *2*.

Participants

Inclusion criteria

- Those who were pregnant.
- Those who were aged ≥ 18 years.
- Those who were delivering at one of the selected hospitals.
- Those who consented to participate during the study period.

Exclusion criteria

As this was a feasibility study, there were no exclusion criteria other than inability to fulfil the inclusion criteria above.

Ethics approval and research governance

Ethics approval for the study was given by the West Midlands – Solihull Research Ethics Committee (REC) on 15 June 2018 with the reference number 18/WM/0147. The study was also approved by the Health Research Authority (HRA) and Care Research Wales on 15 June 2018. Site-specific capacity and capability was then given at the different research and governance departments of St George's University Hospitals NHS Foundation Trust, Kingston Hospital NHS Foundation Trust, Poole Hospital NHS Foundation Trust, Surrey and Sussex Healthcare NHS Trust and Croydon Health Services NHS Trust.

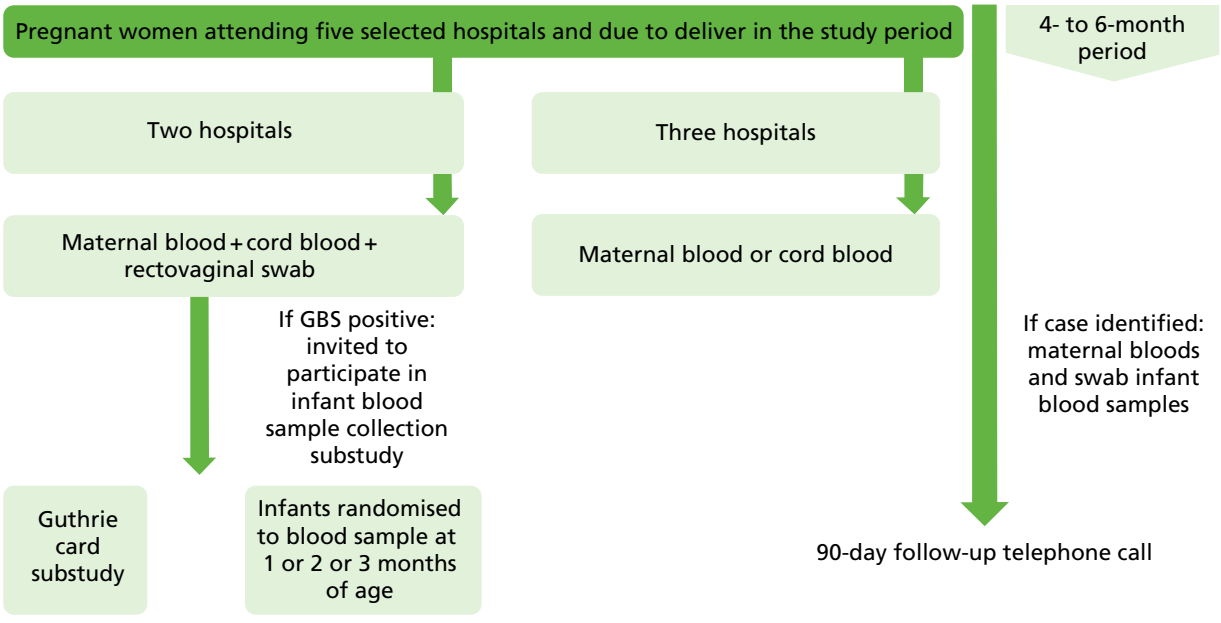

FIGURE 1 Flow chart for the feasibility study in five hospitals in London and the South East.

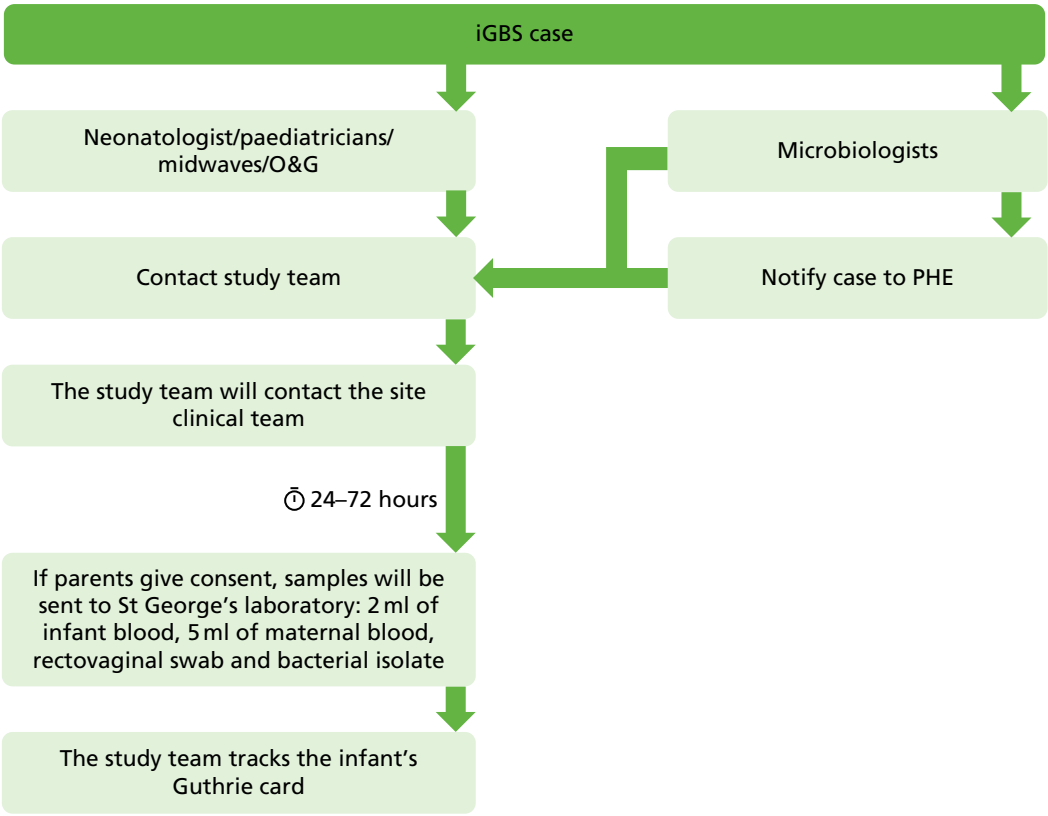

FIGURE 2 Flow chart for the national surveillance of iGBS. O&G, obstetrics and gynaecology; PHE, Public Health England.

The Antenatal and Newborn Research Advisory Committee approved the Guthrie card substudy on 3 October 2018.

During the study period, the protocol was amended three times, as follows.

Amendment 1 (5 July 2018)

1. Retrospective consent: permission was granted for retrospective written consent for sample collection in those cases where there was insufficient time to obtain this before delivery and verbal consent was previously recorded in the participant's medical notes.
2. The GBS surveillance was extended to all the trusts of England and Wales to increase the number of neonates and infants with iGBS recruited.

Amendment 2 (25 September 2018)

1. Permission was granted for the bacterial isolate from the national iGBS surveillance to be sent to the St George's microbiology laboratory to fully characterise the GBS strain.

Amendment 3 (9 October 2018)

1. Permission was granted to extend the study until 31 December 2018.
2. Permission was granted for consent to trace the Guthrie cards of those infants with iGBS included in the national surveillance subset through their NHS number.

Recruitment procedure

Patient recruitment at a site commenced after REC, HRA and local approvals and all subjects were screened and consented by delegates of the chief investigator.

Study information was available on social media, posters on notice boards, institutional and GBSS websites [https://gbss.org.uk/recent-research (accessed 30 January 2018)], letters, text messages or through direct approach in antenatal clinics. Women had the opportunity to ask questions of the research team by telephone or e-mail. If a woman was interested in participating, this was recorded on handheld notes to ensure that delivery staff were aware of her interest.

Collection of delivery bloods

Following confirmation of consent, blood samples were obtained from the mother at any time during labour (or within 48 hours of delivery) and/or from the cord once the placenta was delivered. At Kingston and St George's hospitals, both maternal blood and cord blood were collected. At other sites, maternal blood was obtained if it was not possible to obtain a sample of cord blood after delivery.

Collection of swabs

At Kingston and St George's hospitals only, pregnant women were asked to take part in the colonisation study and a single vaginorectal swab was collected.

Collection of infant blood

At Kingston and St George's hospitals, women who were participating in both the delivery blood collection study and the colonisation study, and who were shown to be colonised with GBS, were also invited to participate in the infant antibody kinetics substudy. A home visit or hospital appointment was undertaken to collect an additional blood sample from the infant at 4, 8 or 12 weeks of age.

Collection of Guthrie cards

At Kingston and St George's hospitals, women who were participating in both the delivery blood collection study and the colonisation study were also invited to participate in the infant Guthrie card collection substudy. Women were asked for consent to access their babies' routine Guthrie card from the National Screening Laboratory.

Invasive group B streptococcal disease surveillance

When a case of iGBS occurred at any participating hospital in England or Wales, the relevant paediatrician was contacted by the study team and asked to recruit the mother and baby to the iGBS substudy. Women were approached in the hospital and asked to provide a maternal and an infant blood sample.

Follow-up of babies

A follow-up telephone call was made to all consenting parents 90 days after their baby was born to confirm whether or not their child had developed iGBS during this time period.

Informed consent

Informed consent from the participant, the legally authorised representative or the parents/guardians/person with legal responsibility for children was obtained following explanation of the aims, methods, benefits and potential hazards of the study.

Information about the study was given by one of the research midwives/clinical team and women had the opportunity to ask questions. There was no minimum period between receiving information and providing consent. Initially, formal written consent for participation in the study was taken at enrolment and then confirmed with the mother verbally at, during or following delivery. In some cases, there was insufficient

time to obtain written informed consent from participants who were presenting and being consented in labour, although appropriately sensitised to the study. Following an amendment submitted to and approved by the ethics committee (on 5 July 2018), we amended the protocol so that we were able to obtain retrospective written consent after sample collection during delivery if verbal consent was previously recorded in the participant's notes. Written consent could be taken retrospectively within 24 hours of birth. No data were collected until written informed consent was obtained and participants could withdraw at any time.

Parents of infants identified as having a positive culture for GBS from a normally sterile site (blood or cerebrospinal fluid) from participating hospitals in England and Wales were approached for consent to obtain blood samples from the mother and baby during the acute admission and for collection of the GBS isolate. Samples were collected when parents had had time to consider the information they had received about the study and had given full written informed consent to the local study team.

A copy of the signed informed consent form along with a copy of the most recently approved patient information sheet were given to the study participant. An original signed and dated consent form was retained in the investigator site file and a third copy was placed in the medical notes.

Sample procedures

Delivery blood samples

Blood was obtained from the mother at any time during labour (or within 48 hours of delivery) and/or from the cord once the placenta was delivered. A total of 5 ml of blood was collected into a BD® serum separator tube (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Blood samples were transported to the laboratories to be processed and the serum was collected into Eppendorf tubes (Thermo Fisher Scientific, Waltham, MA, USA) and frozen at –20 °C to –80 °C for later processing.

Relevant clinical information was extracted from the mother's handheld or hospital notes onto the case report form. This included baby/babies gestation at birth (weeks), receipt of IAP (yes/no), type of IAP (list), time between administration of first IAP and delivery (hours), recent blood transfusion (in last 3 months), and elective caesarean section (yes/no).

Vaginal and rectal swabs

At Kingston and St George's hospitals only, a single double-head rectovaginal swab was obtained at any time from 35 weeks' gestation up to (and including) delivery, either by the study midwife or by the mother herself (with appropriate written guidance). The swab was inserted into the lower half of the vagina and turned slowly clockwise once before removing and inserting past the anal sphincter into the low rectum. The swabs were processed for GBS using validated methods (in an NHS laboratory) and reported using standard NHS clinical pathways. In addition, we used a second, well-established, method for identification of GBS recommended by the Centers for Disease Control and Prevention (but not currently in use in the UK): one head of the swab was inserted into a transport media tube and transported to the local clinical laboratory for processing in accordance with standard methods (direct plating onto selective agar), and the other head was inserted into Lim broth (an enrichment culture media), sent to the research laboratory, incubated for 6–24 hours and plated onto selective agar. The results (positive/negative) were communicated to the site research midwives and the mother was informed by telephone (if GBS positive) and by letter (if positive or negative). If GBS positive, women were subsequently managed in accordance with the Royal College of Obstetrics and Gynaecology (RCOG) Greentop Guideline and were offered IAP if results were available before delivery.[29] Positive results were also serotyped with a latex agglutination test (LAT) or polymerase chain reaction (PCR), if non-typeable by a LAT.

Collection of infant blood

At Kingston and St George's hospitals only, women who were participating in both the delivery blood collection study and the colonisation study and who were shown to be colonised with GBS were also

invited to participate in the infant antibody kinetics substudy. In this substudy, babies born to colonised mothers were randomised to have one blood sample obtained at 4, 8 or 12 weeks of age. Blood sampling was undertaken by doctors using venepuncture or capillary sampling (2 ml) before blood was processed and stored, as described above.

Collection of Guthrie cards

At Kingston and St George's hospitals only, women who were participating in both the delivery blood collection study and the colonisation study and had not received IAP were invited to participate in the infant Guthrie card collection substudy. In this substudy, mothers were asked for permission to obtain a single blood spot from the Guthrie card, which is obtained routinely in all babies at around 5 days of age. This will be obtained from the National Screening Laboratory and stored for antibody analysis.

Antibody testing

Prior to the start of the study, serum samples were collected from 10 healthy non-pregnant volunteers to assess the impact of timing of processing of blood samples and storage conditions on total IgG concentrations. The effect on total IgG concentration was assessed at different times between sample collection and sample processing (6 hours/10 hours/18 hours/24 hours/48 hours/72 hours/5 days/7 days).

Antibodies against the GBS-CPS were quantified using Luminex® multiplex assays (Luminex Corporation, Austin, TX, USA) performed at St George's, University of London, laboratories using the standardised assays that have been established as part of a Gates Foundation-funded collaboration led by Kirsty Le Doare.

Infant follow-up

A follow-up telephone call was scheduled at 90 days after the baby's birth to establish whether or not the infant developed iGBS during this time period. This telephone call was made by the research midwives at each site in order to keep personal data locally.

National invasive group B streptococcal disease surveillance

Microbiologists and paediatricians at all NHS trusts from England and Wales were informed about the study through established research and clinical networks [British Paediatric Allergy, Immunity and Infection Group (BPAIIG), Public Health England, the Neonatal Infection Network (neonIN) and the UK Paediatric Vaccine Group]. Paediatricians and microbiologists were asked to make contact with study staff when a case of iGBS occurred at their hospital. After having set up the site, the relevant paediatrician provided study information to the parents and sought their permission for inclusion in the study. Following consent from the parent, a sample of blood was obtained from the mother and from her baby and processed as above. The participating mother was also asked to provide a single rectovaginal swab, taken either by the midwife or by mother herself, to be processed as above. Furthermore, the study team contacted the microbiology laboratory and asked for the bacterial isolate in order to culture and fully characterise the GBS strain. These samples and the bacterial isolate were sent to and stored at St Georges, University of London, in a linked anonymised fashion. In addition, parents were asked for their permission to collect the Guthrie card of the infant.

Data collection

To standardise recruitment processes across the study sites and maximise data quality, we used Research Electronic Data Capture (REDCap; 8.1.8, Vanderbilt University, Nashville, TN, USA)[30] hosted at St George's, University of London. A range of data validation checks were carried out in both REDCap and Stata® version 15 (StataCorp LP, College Station, TX, USA)[27] to minimise erroneous or missing data.

Statistical design

Sample size

There is no formal sample size calculation as this is a pragmatic study conducted among a representative network of hospitals that is intended to assess the feasibility of approaching a much larger network of hospitals needed to achieve the main objective of this research. The proportions achieved against the various study end points will allow sample size calculations to be made for the main study.

Statistical analysis

For the main end point of this feasibility study, we have undertaken a descriptive analysis. All analysis is unadjusted. McNemar's test was used to assess the exploratory objective concerning the two different GBS culture methods.

Extensive efforts were undertaken to identify missing data. All missing data were excluded from the final analyses.

Chapter 4 Results

The analysis for this report is based on data collected from 2 July to 31 December 2018. The total number of participants recruited was 1823, across the five sites (*Table 1*). We had partial recruitment with fewer research midwives from 1 to 31 December. A summary of results is shown in *Figure 3*.

Objective 1

To test the feasibility of collecting serum at delivery (maternal, cord or both) from a large cohort of pregnant women.

TABLE 1 Participants recruited by hospital

Hospital	Start date	End date	Recruitment (*n*)
Croydon Health Services NHS Trust	20 August 2018	31 December 2018	166
Surrey and Sussex Healthcare NHS Trust	8 August 2018	30 November 2018	414
Kingston Hospital NHS Foundation Trust	10 July 2018	31 December 2018	257
Poole Hospital NHS Foundation Trust	11 July 2018	31 December 2018	621
St George's University Hospitals NHS Foundation Trust	2 July 2018	31 December 2018	365
Total	2 July 2018	31 December 2018	1823

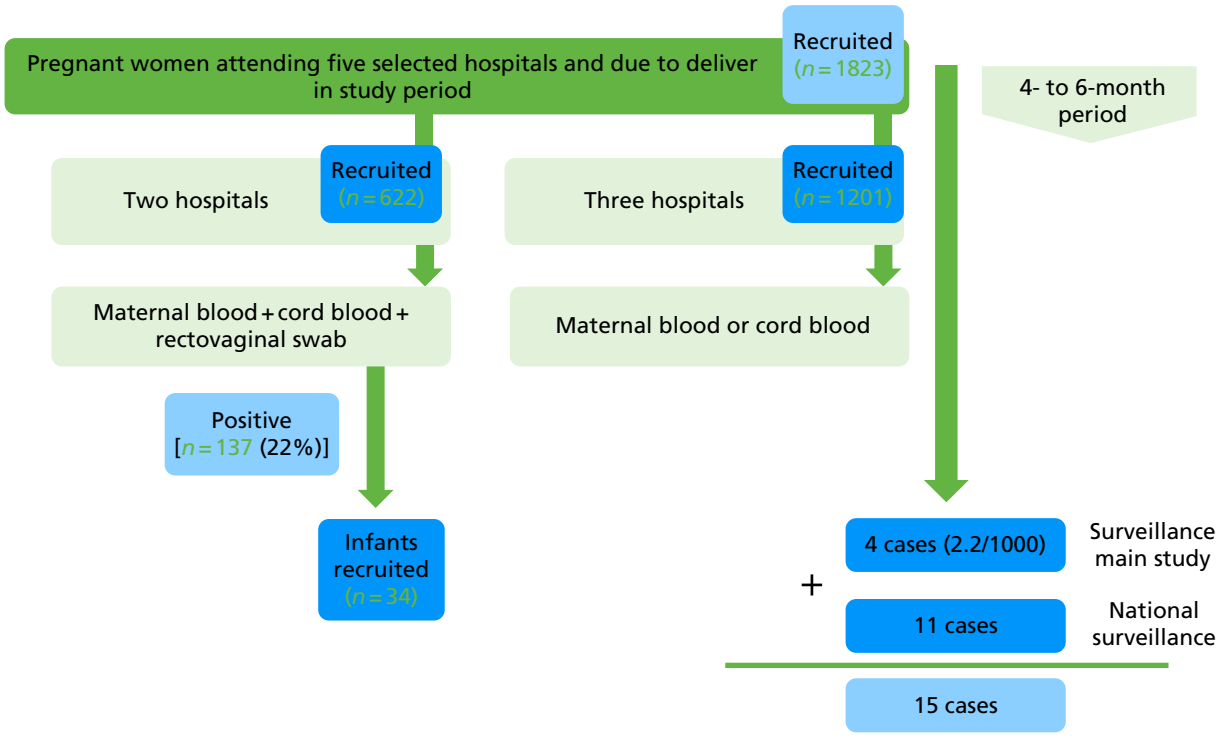

FIGURE 3 Summary of results.

Enrolment rate

Overall, 22% (95% CI 21% to 23%) of all women delivering during the study period consented to take part in the feasibility study. However, when based on the number of women approached, the enrolment rate was 74% (95% CI 71% to 76%) (*Table 2*). Two sites did not collect information on the number of women approached, as the clinical teams approaching women did not accurately record when women declined to participate.

Maternal and cord blood collection rates

In the two sites collecting both maternal and cord bloods, 60% and 53% of those recruited women had samples collected, respectively (*Table 3*). In the three hospitals collecting cord blood only, the collection rate was 85% (95% CI 83% to 87%) (*Table 4*).

TABLE 2 Enrolment rate by hospital

Hospital	Consented/approached women, % (*n/N*)	Consented/total deliveries during study period, % (*n/N*)
Croydon Health Services NHS Trust	49 (166/340)	16 (166/1023)
Surrey and Sussex Healthcare NHS Trust	–	30 (414/1370)
Kingston Hospital NHS Foundation Trust	64 (240/377)	10 (257/2462)
Poole Hospital NHS Foundation Trust	93 (621/667)	32 (621/1942)
St George's University Hospitals NHS Foundation Trust	–	15 (365/2458)
Total	74 (1027/1384)[a] (95% CI 71 to 76)	22 (1823/8340) (95% CI 21 to 23)

a Based on the three sites that were able to record all women who were approached during the study.

TABLE 3 Maternal and cord blood collection rate in the two sites collecting both

Hospital	Maternal blood/total recruited, % (*n/N*)	Cord blood/total recruited, % (*n/N*)
Kingston Hospital NHS Foundation Trust	81 (207/257)	79 (203/257)
St George's University Hospitals NHS Foundation Trust	45 (165/365)	34 (125/365)
Total	60 (372/622)	53 (328/622)

TABLE 4 Cord blood collection rate in the three sites collecting cord blood only

Hospital	Cord blood/total recruited, % (*n/N*)	Maternal blood[a]/total recruited, % (*n/N*)	Maternal or cord blood/ total recruited, % (*n/N*)
Croydon Health Services NHS Trust	73 (121/166)	0 (0/166)	73 (121/166)
Surrey and Sussex Healthcare NHS Trust	94 (389/414)	6 (24/414)	99 (413/414)
Poole Hospital NHS Foundation Trust	76 (469/621)	2 (14/621)	78 (483/621)
Total	82 (979/1201)	3 (38/1201)	85 (1017/1201) (95% CI 83 to 87)

a Maternal blood was collected only if cord blood not obtained.

Key clinical data collection rate

Data on demographic and risk factors for iGBS were recorded in 90–100% of participants. Note that data regarding ethnicity and infant sex were included from 1 November 2018. Data relating to antibiotic administration were more difficult to collect retrospectively and represented a significant challenge to our teams (*Table 5*).

Characteristics of participants recruited to the study are shown in *Table 6*.

If we compare data from recruited women (see *Table 6*) and women delivering at the five sites during the last year (*Table 7*), we can assess the representativeness of our population. Overall, the sample from this study is similar to the general population of pregnant women. With regard to ethnicity, *Tables 6* and *7* show that Croydon Health Services NHS Trust and St George's University Hospitals NHS Foundation Trust have a large non-white population. Regarding delivery type, more women with elective caesarean sections were included in the study than are represented in the total study population.

The GBS-colonised women received benzylpenicillin in 62–85% of cases depending on the hospital site; the first dose was given ≥ 4 hours before delivery in 50% of women with GBS-positive swabs (60/119). The antibiotics given most frequently for reasons other than GBS colonisation were cefuroxime and cefalexin (*Table 8*).

TABLE 5 Key clinical data collection rate

Key clinical data	Collection rate, % (*n*/*N*)
Maternal demographic information	
Maternal age	100 (1823/1823)
Ethnicity	48 (878/1823[a])
Previous pregnancy	99 (1821/1823)
Previous GBS colonisation	99 (1054/1056[b])
Previous baby with iGBS	99 (1050/1056[b])
Birth information	
Time between membrane rupture and delivery	92 (1676/1823)
Delivery type	93 (1690/1823)
Term delivery	93 (1690/1823)
Infant sex	59 (1082/1823[a])
Positive swab before birth	91 (1666/1823)
Antibiotics if positive swab	90 (166/185[c])
Antibiotic timing	54 (100/185[c])
Antibiotics for other reasons	65 (1179/1823[b])

a Collection of this item started after 1 November 2018.
b Number of women with previous pregnancies.
c Number of positive swabs.

TABLE 6 Demographics and risk factors by hospital

Demographic	Croydon Health Services NHS Trust (*N* = 166)	Surrey and Sussex Healthcare NHS Trust (*N* = 414)	Kingston Hospital NHS Foundation Trust (*N* = 257)	Poole Hospital NHS Foundation Trust (*N* = 621)	St George's University Hospitals NHS Foundation Trust (*N* = 365)	Total (*N* = 1823)
Maternal age group (years),* n *(%)						
< 25	18 (10.8)	34 (8.2)	12 (4.7)	96 (15.5)	23 (6.3)	183 (10)
25–34	84 (50.6)	240 (58)	133 (51.8)	371 (59.7)	195 (53.4)	1023 (56.1)
35–41	57 (34.3)	125 (30.2)	107 (41.6)	145 (23.3)	132 (36.2)	566 (31)
> 41	7 (4.2)	15 (3.6)	5 (1.9)	9 (1.4)	15 (4.1)	51 (2.8)
Ethnicity,* n *(%)	**N = *120***	**N = *4***	**N = *31***	**N = *587***	**N = *136***	**N = *878***
White British	36 (30[a])	1 (25)	14 (45)	484 (82.5)	65 (47.8)	600 (68.3)
Black British	3 (2.5)	0 (0)	0 (0)	0 (0)	8 (5.9)	11 (1.3)
Asian British	7 (5.8)	2 (50)	4 (12.9)	2 (0.3)	6 (4.4)	21 (2.4)
Other white	23 (19.2)	0 (0)	11 (35.5)	42 (7.2)	23 (16.9)	99 (11.3)
Other black	20 (16.7)	0 (0)	0 (0)	3 (0.5)	2 (1.5)	25 (2.8)
Other Asian	24 (20)	0 (0)	1 (3)	12 (2)	6 (4.4)	43 (4.9)
Mixed	2 (1.7)	0 (0)	1 (3)	6 (1)	1 (0.7)	10 (1.1)
Others	5 (4.2)	1 (25)	0 (0)	38 (6.5)	25 (18.4)	69 (7.8)
Missing	46 (27.7)	410 (99)	226 (87.9)	34 (5.5)	229 (62.7)	945 (51.8)
Previous pregnancy,* n *(%)						
Yes	114 (68.7)	253 (61.1)	124 (48.2)	387 (62.3)	178 (48.8)	1056 (57.9)
No	52 (31.3)	160 (38.6)	133 (51.8)	233 (37.5)	187 (51.2)	765 (42)
Missing	0 (0)	1 (0.2)	0 (0)	1 (0.2)	0 (0)	2 (0.1)
GBS colonisation in previous pregnancy,* n *(%)	**N = *114 (68.7)***	**N = *253 (61.1)***	**N = *124 (48.2)***	**N = *387 (62.3)***	**N = *178 (48.8)***	**N = *1056 (57.9)***
Yes	4 (2.4)	23 (5.6)	17 (6.6)	11 (1.8)	13 (3.6)	68 (3.7)
No	87 (52.4)	156 (37.7)	99 (38.5)	367 (59.1)	60 (16.4)	769 (42.2)
Unknown	23 (13.9)	73 (17.6)	8 (3.1)	9 (1.4)	104 (28.5)	217 (11.9)
Missing	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.3)	2 (0.1)
Previous baby with iGBS,* n *(%)	**N = *114 (68.7)***	**N = *253 (61.1)***	**N = *124 (48.2)***	**N = *387 (62.3)***	**N = *178 (48.8)***	**N = *1056 (57.9)***
Yes	1 (0.6)	6 (1.4)	1 (0.4)	4 (0.6)	7 (1.9)	19 (1)
No	90 (54.2)	199 (48.1)	119 (46.3)	371 (59.7)	116 (31.8)	895 (49.1)
Unknown	23 (13.9)	47 (11.4)	4 (1.6)	12 (1.9)	50 (13.7)	136 (7.5)
Missing	0 (0)	1 (0.2)	0 (0)	0 (0)	5 (1.4)	6 (0.3)
Rupture of membranes,* n *(%)						
< 18 hours	131 (78.9)	351 (84.8)	214 (83.3)	414 (66.7)	260 (71.2)	1370 (75.2)
≥ 18 hours	35 (21.1)	57 (13.8)	41 (16)	102 (16.4)	71 (19.5)	306 (16.8)
Missing	0 (0)	6 (1.4)	2 (0.8)	105 (16.9)	34 (9.3)	147 (8.1)
Delivery type,* n *(%)						
Vaginal	86 (51.8)	261 (63)	132 (51.4)	280 (45.1)	214 (58.6)	973 (53.4)
Caesarean section with ROM	43 (25.9)	75 (18.1)	40 (15.6)	95 (15.3)	55 (15.1)	308 (16.9)

TABLE 6 Demographics and risk factors by hospital (*continued*)

Demographic	Croydon Health Services NHS Trust (*N* = 166)	Surrey and Sussex Healthcare NHS Trust (*N* = 414)	Kingston Hospital NHS Foundation Trust (*N* = 257)	Poole Hospital NHS Foundation Trust (*N* = 621)	St George's University Hospitals NHS Foundation Trust (*N* = 365)	Total (*N* = 1823)
Caesarean section without ROM	37 (22.3)	74 (17.9)	83 (32.3)	141 (22.7)	74 (20.3)	409 (22.4)
Missing	0 (0)	4 (1)	2 (0.8)	105 (16.9)	22 (6)	133 (7.3)
Gestational age*, n *(%)						
< 34 weeks	0 (0)	3 (0.7)	1 (0.4)	4 (0.6)	2 (0.5)	10 (0.5)
≥ 34 weeks	166 (100)	408 (98.6)	254 (98.8)	512 (82.4)	340 (93.2)	1680 (92.2)
Missing	0 (0)	3 (0.7)	2 (0.8)	105 (16.9)	23 (6.3)	133 (7.3)
Infant's sex*, n *(%)	***144***	***79***	***120***	***509***	***230***	***1082***
Male	71 (49.3[a])	40 (50.6)	61 (50.8)	248 (48.7)	115 (50)	535 (49.4)
Female	73 (50.7)	39 (49.4)	59 (49.2)	261 (51.3)	115 (50)	547 (50.6)
Missing	22 (13.3)	335 (80.9)	137 (53.3)	112 (18)	135 (37)	741 (40.6)
Positive swab before birth*, n *(%)						
Yes	28 (16.9)	31 (7.5)	28 (10.9)	30 (4.8)	68 (18.6)	185 (10.1)
No	138 (83.1)	380 (91.8)	227 (88.3)	465 (74.9)	271 (74.2)	1481 (81.2)
Missing	0 (0)	3 (0.7)	2 (0.8)	126 (20.3)	26 (7.1)	157 (8.6)

ROM, rupture of membrane.
a Percentage applies to total number where data known.
Note that data regarding ethnicity and infant sex were included from 1 November 2018. This explains the missing data in these two areas.

TABLE 7 Demographics and risk factors for all deliveries by hospital

Demographic	Croydon Health Services NHS Trust	Surrey and Sussex Healthcare NHS Trust	Kingston Hospital NHS Foundation Trust	Poole Hospital NHS Foundation Trust	St George's University Hospitals NHS Foundation Trust	Total
Maternal age (years) (mean)	31	31.8	32	30.5	32.6	31.6
Ethnicity (%)						
White	36	80	63	0	46	56
Asian	14	11	10	0	16	13
Black	17	3	3	0	10	8
Mixed	9	3	1	0	2	4
Other ethnic groups	24	2	7	0	10	11
Not stated	0	1	16	0	16	8
Missing	0	0	0	100	0	20
Delivery type (%)						
Caesarean section	26	30	29	32	25	28
Vaginal	51	70	71	68	75	68
Missing	23	0	0	0	0	4

continued

TABLE 7 Demographics and risk factors for all deliveries by hospital (*continued*)

Demographic	Croydon Health Services NHS Trust	Surrey and Sussex Healthcare NHS Trust	Kingston Hospital NHS Foundation Trust	Poole Hospital NHS Foundation Trust	St George's University Hospitals NHS Foundation Trust	Total
Gestational age (%)						
< 37 weeks	4	9	6	0	9	7
≥ 37 weeks	64	91	94	0	91	85
Missing	32	0	0	100	0	26
Infant's sex (%)						
Male	51	51	0	51	51	51
Female	49	49	0	49	49	49
Missing	0	0	100	0	0	20

Note
Missing values for Poole Hospital NHS Foundation Trust regarding ethnicity and gestational age, as well as missing values for Kingston Hospital NHS Foundation Trust, regarding infant's sex were excluded to calculate total percentages.

TABLE 8 Characteristics of antibiotic administration by hospital

	Croydon Health Services NHS Trust	Surrey and Sussex Healthcare NHS Trust	Kingston Hospital NHS Foundation Trust	Poole Hospital NHS Foundation Trust	St George's University Hospitals NHS Foundation Trust	Total
Antibiotics if positive swab (N)	***28***	***31***	***28***	***30***	***68***	***185***
Yes, *n* (%)	21 (75)	27 (87.1)	22 (78.6)	20 (66.7)	29 (42.6)	119 (64.3)
No, *n* (%)	7 (25)	4 (12.9)	6 (21.4)	10 (33.3)	20 (29.4)	47 (25.4)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	19 (27.9)	19 (10.3)
Antibiotics type (N)	***23***	***29***	***22***	***20***	***26***	***120***
Benzylpenicillin, *n* (%)	13 (61.9)	23 (85.2)	18 (81.8)	17 (85)	21 (72.4)	92 (77.3)
Clindamycin, *n* (%)	3 (14.3)	2 (7.4)	2 (9.1)	1 (5)	1 (3.4)	9 (7.6)
Others, *n* (%)	7 (25)	4 (12.9)	2 (7)	2 (6.6)	4 (5.9)	19 (4.2)
Antibiotics timing if positive swab (N)	***21***	***27***	***22***	***20***	***29***	***119***
< 2 hours before birth, *n* (%)	2 (9.5)	7 (25.9)	6 (27.3)	4 (20)	3 (10.3)	22 (18.5)
2–4 hours before birth, *n* (%)	3 (14.3)	3 (11.1)	4 (18.2)	7 (35)	1 (3.4)	18 (15.1)
> 4 hours before birth, *n* (%)	16 (76.2)	16 (59.3)	12 (54.5)	8 (40)	8 (27.6)	60 (50.4)
Missing, *n* (%)	0 (0)	1 (3.7)	0 (0)	1 (5)	17 (58.6)	19 (16)
Antibiotics for other reasons (N)	***166***	***414***	***257***	***621***	***365***	***1823***
Yes	44 (26.5)	36 (8.7)	48 (18.7)	232 (37.4)	21 (5.8)	381 (20.9)
No	92 (55.4)	219 (52.9)	118 (45.9)	272 (43.8)	97 (26.6)	798 (43.8)
Missing	30 (18.1)	159 (38.4)	91 (35.4)	117 (18.8)	247 (67.7)	644 (35.3)

TABLE 8 Characteristics of antibiotic administration by hospital (*continued*)

	Croydon Health Services NHS Trust	Surrey and Sussex Healthcare NHS Trust	Kingston Hospital NHS Foundation Trust	Poole Hospital NHS Foundation Trust	St George's University Hospitals NHS Foundation Trust	Total
***Antibiotics type for other reasons* (N)**	***43***	***33***	***48***	***230***	***14***	***368***
Benzylpenicillin, *n* (%)	1 (0.3)	7 (1.8)	0 (0)	3 (0.8)	3 (0.8)	14 (3.7)
Clindamycin, *n* (%)	3 (0.8)	1 (0.3)	0 (0)	1 (0.3)	0 (0)	5 (1.3)
Cefalexin, *n* (%)	18 (4.7)	3 (0.8)	0 (0)	7 (1.8)	7 (1.8)	35 (9.2)
Ceftriaxone, *n* (%)	0 (0)	1 (0.3)	0 (0)	2 (0.5)	0 (0)	3 (0.8)
Cefuroxime, *n* (%)	20 (5.2)	21 (5.5)	47 (12.3)	217 (57)	2 (0.5)	307 (80.6)
Co-amoxiclav, *n* (%)	0 (0)	0 (0)	1 (0.3)	0 (0)	2 (0.5)	3 (0.8)
Vancomycin, *n* (%)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)

Note
Total numbers for 'antibiotics type' can be higher than the number of women who received antibiotics because some women received more than one antibiotic.

Infant invasive group B streptococcal disease surveillance

The consent rate for the 90-day follow-up telephone call to be made was 100% (1823/1823).

The telephone calls started 90 days after the first baby was born and, because of the short study period, applied only to those recruited in the first month of the study. No cases of iGBS were detected in the telephone follow-up that had not already been reported by the hospital team (*Table 9*).

TABLE 9 Follow-up telephone call at 90 days

	Croydon Health Services NHS Trust (*N* = 166)	Surrey and Sussex Healthcare NHS Trust (*N* = 414)	Kingston Hospital NHS Foundation Trust (*N* = 257)	Poole Hospital NHS Foundation Trust (*N* = 621)	St George's University Hospitals NHS Foundation Trust (*N* = 365)	Total (*N* = 1823)
Telephone call attempt 1,* n *(%)						
Yes	40 (24.1)	51 (12.3)	20 (7.8)	80 (12.9)	100 (27.4)	291 (16)
No	126 (75.9)	363 (87.7)	237 (92.2)	541 (87.1)	265 (72.6)	1532 (84)
Telephone call 1: successful,* n *(%)	***(N = 40)***	***(N = 51)***	***(N = 20)***	***(N = 80)***	***(N = 100)***	***(N = 291)***
Yes	23 (57.5)	14 (27.5)	6 (30)	35 (43.8)	40 (40)	118 (40.5)
No	17 (42.5)	37 (72.5)	14 (70)	45 (56.3)	60 (60)	173 (59.5)
Telephone call attempt 2,* n *(%)	***(N = 17)***	***(N = 37)***	***(N = 14)***	***(N = 45)***	***(N = 60)***	***(N = 173)***
Yes	17 (100)	32 (86.5)	5 (35.7)	36 (80)	32 (53.3)	122 (70.5)
No	0 (0)	5 (13.5)	9 (64.3)	9 (20)	28 (46.7)	51 (29.5)
Telephone call 2: successful,* n *(%)	***(N = 17)***	***(N = 32)***	***(N = 5)***	***(N = 36)***	***(N = 32)***	***(N = 122)***
Yes	3 (17.6)	4 (12.5)	0 (0)	16 (44.4)	11 (34.4)	34 (27.9)
No	14 (82.4)	28 (87.5)	5 (100)	20 (55.6)	21 (65.6)	88 (72.1)

Rectovaginal swab consent and collection rate

Of the 622 women enrolled at the two hospitals taking part in the colonisation study, rectovaginal consent was 100% and the rectovaginal collection rate was 99% (*Table 10*). The overall GBS colonisation rate was 22% (*Table 11*).

Rectovaginal group B streptococcus serotype-specific colonisation rates

A total of 115 out of 120 positive swabs were serotyped with a rapid LAT and PCR was performed when the sample was found to be non-typeable by LAT. The most common serotype was serotype III (30%), followed by Ia (25%), II (16%), Ib (16%), V (14%) and IV (1%) (*Figure 4*).

TABLE 10 Rectovaginal swab consent and collection rate

Hospital	Rectovaginal swab study consent rate, % (*n/N*)	Rectovaginal swab collection rate, % (*n/N*)
Kingston Hospital NHS Foundation Trust	100 (257/257)	99 (255/257)
St George's University Hospitals NHS Foundation Trust	100 (365/365)	98 (359/365)
Total	100 (622/622)	99 (614/622)

TABLE 11 The GBS colonisation rate

Hospital	GBS positive/swabs analysed, % (*n/N*)	Known positive swab/all swabs,[a] % (*n/N*)	GBS positive/all swabs, % (*n/N*)
Kingston Hospital NHS Foundation Trust	20 (49/247)	3 (8/255)	22 (57/255)
St George's University Hospitals NHS Foundation Trust	20 (71/350)	3 (9/359)	22 (80/359)
Total	20 (120/597)	3 (17/614)	22 (137/614) (95% CI 19% to 26%)

a Women who were already known to have a positive swab during this pregnancy were also invited to participate but the swab was not repeated.

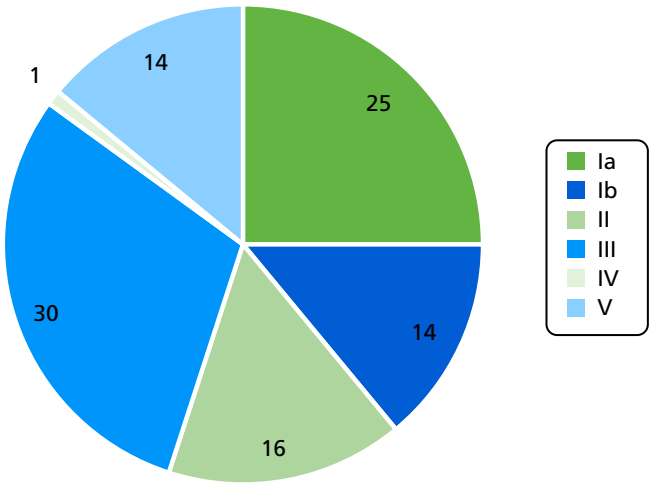

FIGURE 4 The GBS serotype distribution in colonised women.

Risk factors for group B streptococcus colonisation

No statistically significant differences were found between colonised and non-colonised women regarding demographic and risk factors for iGBS except having had a positive GBS swab in a previous pregnancy, which was more common in colonised women (*Table 12*).

TABLE 12 Demographic and risk factors by colonisation status

Demographic	Colonised, *n* (%)	Non-colonised, *n* (%)	Total, *n* (%)	*p*-value
	137 (22.3)	477 (77.7)	614 (100)	
Hospital				***0.984***
Kingston Hospital NHS Foundation Trust	57 (22.4)	198 (77.6)	255 (41.5)	
St George's University Hospitals NHS Foundation Trust	80 (22.3)	279 (77.7)	359 (58.5)	
Maternal age group (years)				***0.159***
< 25	6 (17.1)	29 (82.9)	35 (5.7)	
25–34	66 (20.5)	256 (79.5)	322 (52.4)	
35–41	57 (24.1)	180 (75.9)	237 (38.6)	
> 41	8 (40)	12 (60)	20 (3.3)	
Ethnicity				***0.124***
White British	35 (44.9)	43 (55.1)	78 (12.7)	
Black British	5 (62.5)	3 (37.5)	8 (1.3)	
Asian British	3 (30)	7 (70)	10 (1.6)	
Other white	22 (64.7)	12 (35.3)	34 (5.5)	
Other black	1 (50)	1 (50)	2 (0.3)	
Other Asian	5 (71.4)	2 (28.6)	7 (1.1)	
Mixed	0 (0)	2 (100)	2 (0.3)	
Others	16 (66.7)	8 (33.3)	24 (3.9)	
Missing	50 (11.1)	399 (88.9)	449 (73.1)	
Previous pregnancy				***0.803***
Yes	68 (22.7)	231 (77.3)	299 (48.7)	
No	69 (21.9)	246 (78.1)	315 (51.3)	
GBS colonisation in previous pregnancy	68 (22.7)	231 (77.3)	299 (100)	0.041
Yes	12 (41.4)	17 (58.6)	29 (9.7)	
No	34 (21.5)	124 (78.5)	158 (52.8)	
Unknown	22 (19.8)	89 (80.2)	111 (37.1)	
Missing	0 (0)	1 (100)	1 (0.3)	
Previous baby with iGBS	68 (22.7)	231 (77.3)	299 (100)	0.427
Yes	3 (42.9)	4 (57.1)	7 (2.3)	
No	54 (23.1)	180 (76.9)	234 (78.3)	
Unknown	11 (20.8)	42 (79.2)	53 (17.7)	
Missing	0 (0)	5 (100)	5 (1.7)	

continued

TABLE 12 Demographic and risk factors by colonisation status (*continued*)

Demographic	Colonised, *n* (%)	Non-colonised, *n* (%)	Total, *n* (%)	*p*-value
Rupture of membranes				***0.96***
< 18 hours	106 (22.5)	365 (77.5)	471 (76.7)	
≥ 18 hours	25 (22.7)	85 (77.3)	110 (17.9)	
Missing	6 (18.2)	27 (81.8)	33 (5.4)	
Delivery type				***0.825***
Vaginal	74 (21.6)	268 (78.4)	342 (55.7)	
Caesarean section with ROM	23 (24.5)	71 (75.5)	94 (15.3)	
Caesarean section without ROM	36 (23.1)	120 (76.9)	156 (25.4)	
Missing	4 (18.2)	18 (81.8)	22 (3.6)	
Gestation				***0.349***
< 34 weeks	0 (0)	3 (100)	3 (0.5)	
≥ 34 weeks	133 (22.6)	455 (77.4)	588 (95)	
Missing	4 (17.4)	19 (82.6)	23 (3.7)	
Infant's sex				***0.541***
Male	42 (25.1)	125 (74.9)	167 (27.2)	
Female	38 (22.8)	129 (77.2)	167 (27.2)	
Missing	57 (20.4)	223 (79.6)	280 (45.6)	

Analysis based on an unpaired *t*-test. *p*-values of < 0.05 were considered significant.

Infant blood sample collection rates

In the two hospitals participating in both the colonisation and the blood collection studies, consent to obtain an infant blood sample if the mother was GBS positive and consent to obtain Guthrie card samples were both 100% (*Table 13*). However, we were able to contact the families of 61% of eligible infants and to collect blood samples from 59% of infants whose family we contacted (*Table 14*). Samples were taken from seven infants at 1 month, 14 infants at 2 months and 13 infants at 3 months of life.

TABLE 13 Infant blood sample consent rates

Infant sample	Consent rate, % (*n/N*)
Blood sample	100 (622/622)
Guthrie card	100 (622/622)

TABLE 14 Infant blood sample collection for eligible infants

Hospital	Infants contacted/eligible infants, % (*n/N*)	Infant blood sample collected/infants contacted, % (*n/N*)
Kingston Hospital NHS Foundation Trust	56 (27/48)	48 (13/27)
St George's University Hospitals NHS Foundation Trust	66 (31/47)	68 (21/31)
Total	61 (58/95)	59 (34/58)

Objective 2

To test the feasibility of collecting samples from iGBS cases.

Participants from the feasibility study

There were five notifications of iGBS within the participants of the main study, all from Poole Hospital. The clinical presentation was EOD in all cases, and three cases occurred in conjunction with cases of maternal sepsis. Samples of maternal blood, a rectovaginal swab, infant blood and the bacterial isolate were collected from four mother–infant pairs (*Table 15*). The fifth case was unable to be recruited as the infant was admitted to a different hospital.

Participants from national invasive group B streptococcal disease surveillance

The protocol was amended on 6 September 2018 to include national (England and Wales) surveillance for iGBS. This resulted in 18 notifications, from which 11 cases were recruited into the study (58%). Seven cases were not recruited as there was insufficient time to set up the site before the patient was discharged. All parents approached consented to participation in the study. The clinical presentation was EOD in nine and LOD in two cases (both of which were preterm infants) (*Table 16*).

TABLE 15 The iGBS cases from the feasibility study

Case	Infant's sex	Age at presentation	Weeks' gestation	Duration of ROM	IAP	Time of first dose	Presentation	Isolate serotype
1	Male	15 hours	40.5	> 18 hours	Cefuroxime + metronidazole	< 2 hours	Sepsis	II
2	Female	Birth	39	< 18 hours	Cefuroxime + metronidazole	> 4 hours	Sepsis	V
3	Male	Birth	33.3	> 18 hours	Erythromycin	> 4 hours	Sepsis	Ib
4	Female	Birth	40.4	< 18 hours	Cefuroxime + metronidazole	< 2 hours	Sepsis	II

ROM, rupture of membranes.

TABLE 16 The iGBS cases from the national surveillance

Case	Infant's sex	Age at presentation	Weeks' gestation	Duration of ROM	IAP	Time of first dose	Presentation	Isolate serotype
1	Male	18 hours	40^{+2}	< 18 hours	No	–	Sepsis	III
2	Male	14 hours	42	< 18 hours	Cefuroxime + metronidazole	< 2 hours	Sepsis	II
3	Female	2 hours	41	< 18 hours	No	–	Sepsis	Ia
4	Female	16 hours	38^{+3}	> 18 hours	No	–	Sepsis	Ia
5	Female	< 24 hours	37^{+4}	< 18 hours	No	–	Sepsis + meningitis	Unknown
6	Female	6 hours	39	> 18 hours	No	–	Sepsis	Ia
7	Female	7 hours	40	> 18 hours	No	–	Sepsis	III
8	Male	42 days	30^{+2}	> 18 hours	No	–	Sepsis	III
9	Female	3 days	Term	< 18 hours	No	–	Sepsis	IV
10	Male	5 hours	40	> 18 hours	No	–	Sepsis	III
11	Male	53 days	25	< 18 hours	No	–	Sepsis	II

ROM, rupture of membranes.

In total, serotyping data were available for 14 of the 15 iGBS cases (including the four cases from the feasibility study); the distribution is shown in *Figure 5*. None of the infants whose samples were collected died during the study.

Exploratory objectives

Impact of timing of processing and blood sample storage conditions on immunoglobulin G concentrations

There was an acceptable impact on total IgG concentrations for periods of time from 6 hours up to 1 week between sample collection and spinning time (*Figure 6*). The average time of spinning and freezing samples varied between hospitals but was generally within 1 week of sample receipt (*Table 17*). St. George's Hospital processed all samples from Croydon, Kingston and St. George's Hospitals.

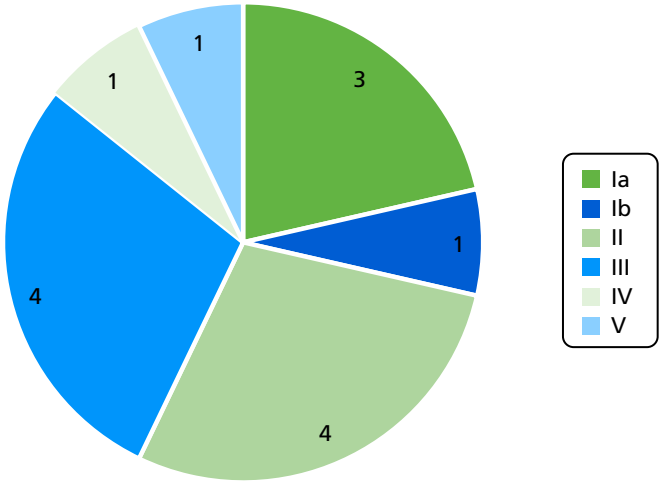

FIGURE 5 Serotype distribution in iGBS cases.

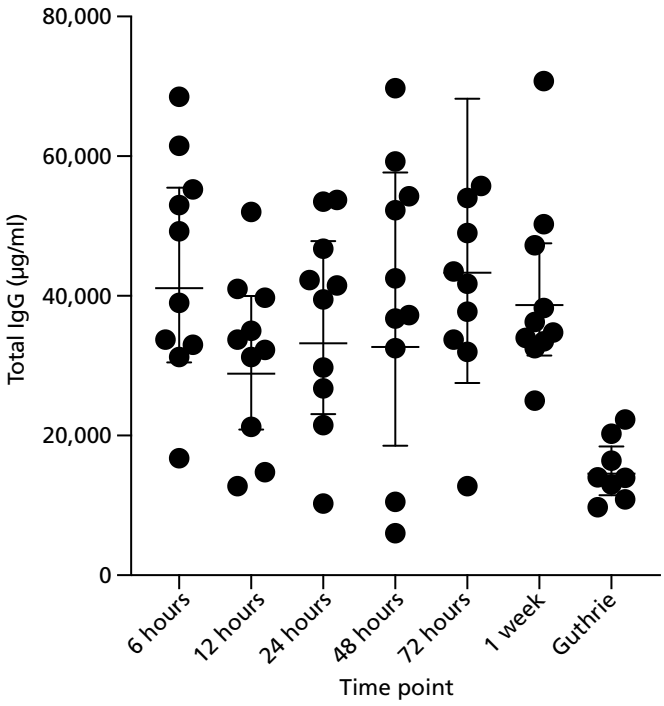

FIGURE 6 Total IgG concentrations by time between sample collection and centrifuging of sample. Guthrie refers to IgG detection from Guthrie cards.

TABLE 17 Description of timing of blood sample processing by hospital

Laboratory	Description	Number of samples	Mean (days)	Standard deviation (days)	Minimum (days)	Maximum (days)	Total (days)
Surrey and Sussex Healthcare NHS Trust	MB collection to spin	23	1.4	1.0	0.0	4.0	23
	MB spin to freeze	23	0.0	0.2	0.0	1.0	
	CB collection to spin	388	1.8	1.2	0.0	7.0	389
	CB spin to freeze	389	0.1	0.6	0.0	4.0	
St George's University Hospitals NHS Foundation Trust	MB collection to spin	349	6.5	6.5	0.0	44.0	366
	MB spin to freeze	366	6.4	6.6	0.0	42.0	
	CB collection to spin	480	7.0	6.7	0.0	44.0	524
	CB spin to freeze	524	7.3	6.7	0.0	42.0	
Poole Hospital NHS Foundation Trust	MB collection to spin	13	4.2	8.1	0.0	31.0	13
	MB spin to freeze	13	0.0	0.0	0.0	0.0	
	CB collection to spin	457	1.5	1.8	0.0	33.0	458
	CB spin to freeze	458	0.0	0.4	0.0	8.0	

CB, cord blood; MB, maternal blood.

Serotype-specific group B streptococcus anticapsular polysaccharide immunoglobulin G concentrations in maternal serum, cord and infant blood in subjects colonised with group B streptococcus at delivery

We were able to identify serotype-specific GBS anti-CPS IgG concentrations in maternal serum and cord blood. Antibody concentrations generally declined between birth and 3 months of age.

The correlation between two different culture techniques for detection of group B streptococcus in rectovaginal swabs: enrichment culture medium versus direct plating using selective agar

The enrichment culture medium was more sensitive than direct plating at identifying GBS from rectovaginal swabs (*Table 18*). A total of 97% (116/120) of positive swabs were identified by enriched culture medium (ECM) plus plating onto selective agar as compared with 75% (90/120) by direct plating onto selective agar ($p < 0.001$, McNemar's test).

TABLE 18 Comparison of enrichment culture medium vs. direct plating for identification of GBS colonisation

	Direct plating onto selective agar positive	Direct plating onto selective agar negative	Number of swabs
ECM positive	86	30	116
ECM negative	4	477	481
Total (*n*)	90	507	597

Feedback from sites

We undertook site visits to all of the participating hospitals on two occasions during the study period. Feedback from the local teams resulted in changes to study design, including recruitment strategies and data and sample collection. Details of feedback from sites can be found in *Appendix 1*.

Chapter 5 Discussion

The ultimate aim of this work was to determine the serocorrelates of protection against the major GBS serotypes causing disease in young infants in order to facilitate GBS vaccine licensure. Given the anticipated size and logistical complexities of the study that would be needed to address this, the aim of this initial feasibility study was to test key operational aspects of the proposed study design.

The feasibility study recruited 1823 women from five hospitals over a period of time, ranging from 3.5 to 6 months. This represented 22% of all women delivering during this period, but 74% of those women who were approached (95% CI 71% to 76%). Once consent was obtained, there was a very high rate of blood sample collection [i.e. 85% (95% CI 83% to 87%) for the three hospitals that were collecting cord samples only]. This is very reassuring because it is cord blood collection from a large number of women nationally (180,000) that is required in the main study. The significance of this group for the large study is that it will form the cohort from which cases are captured (i.e. to determine the antibody levels in the cord blood of babies who go on to develop iGBS at < 3 months of age).

There was notable variation in recruitment across the sites, with one site (Poole Hospital NHS Foundation Trust) achieving a very high (93%) recruitment rate of those approached (32% overall). A number of factors might account for this and our observations at sites and, in particular, the feedback from sites revealed different recruitment strategies and examples of best practice. For example, by following such feedback, we sought and gained ethics approval to allow retrospective consent for cord blood collection, which led to improved recruitment and collection of samples. Engagement of the whole clinical midwife team in the study by enthusiastic research staff was found to be more effective than recruitment by the research staff alone; sending out information sheets to parents prior to approaching them was also shown to result in better recruitment at one site. Such observations (see *Appendix 1*) can now be implemented in a future study.

Other work undertaken during the study has also allowed us to define practical issues around sample collection that can now be applied in a future study. For example, the lack of impact on IgG concentrations for periods of time between blood sample collection and spinning time, ranging from 6 hours to 1 week (substudy), will enable sites to batch samples before spinning to maximise efficiency savings. These results differ from previous guidelines that recommended a maximum of 6 hours between collection and spinning.[31]

The demographics of the recruited women suggest important differences in the populations served by the different hospitals, which is a major consideration when selecting these hospitals for the feasibility study. Croydon Health Services NHS Trust, for example, had a very high proportion of black and Asian mothers (45%) compared with Poole Hospital NHS Foundation Trust (3%). Such factors may also have influenced the success of recruitment in the different sites: Poole Hospital NHS Foundation Trust recruited 93% of those approached (32% overall) whereas Croydon Health Services NHS Trust recruited 49% of those approached (16% overall). This can be explored further by comparing the characteristics of those recruited, by site, with the characteristics of all women at the site, but does also suggest the need for additional strategies (e.g. translation of the patient information sheet into relevant local languages).

In the two hospitals undertaking the substudy (rectovaginal swab, maternal blood and cord blood), the enrolment rate was (understandably) lower: 10–15% of all women delivering during the period of the study. Again, rates of blood sample collection varied by hospital: 34–45% at St George's University Hospitals NHS Foundation Trust versus 79–81% at Kingston Hospital NHS Foundation Trust. A key difference here was the timing of approach and sample collection, with lower rates associated with recruitment in antenatal clinics and higher rates with recruitment in the labour ward, which suggested the latter as the better model for a future study. By contrast, collection rates of vaginorectal swabs were extremely high at both sites, indicating that pregnant women are keen to participate in swabbing studies and are (probably) highly motivated to understand more regarding GBS disease. The significance of this substudy is that it defines the control group needed to address the serocorrelates of protection (i.e. the antibody levels in women who are known to be colonised at delivery and did not receive IAP but whose infants do not develop iGBS in < 3 months).

For those women who consented, collection of the key clinical information needed to interpret antibody concentrations (in controls) was also generally high, although some information, such as ethnicity and infant sex, was collected only in the final 2 months of the study.

Colonisation rates (22%, 95% CI 19% to 26%) and the serotype distribution among colonising isolates are consistent with those found in previous studies.[3] However, as these studies were conducted a number of years ago, this study provides contemporary data that are essential for planning new studies (e.g. GBS3) and for modelling new interventions (e.g. vaccination).

Parents uniformly agreed to being followed up by a telephone call once their baby was 3 months of age, indicating this to be a satisfactory method to follow up babies for later disease (and to ensure that suitable controls are chosen). However, actually telephoning these parents was very labour intensive, which suggested that alternatives, such as data linkage to national databases and networks, may be a more effective method of identifying infants who have not developed iGBS.

During the study period, parental consent and all relevant samples were collected from 15 infants with invasive GBS disease: four cases from the study cohort (of 1823; incidence 2.2/1000 live births) and 11 from national surveillance, which was instituted part-way through the study period. This provides strong reassurance that our system can successfully obtain relevant samples from cases of disease; this is critical in addressing the objectives of the serocorrelates of protection study. It will be imperative that sites are set up in advance of the main study to ensure that samples can be collected while the infant is still in the hospital.

An important substudy was to identify the best laboratory methods for detecting GBS colonisation. Of the 100 microbiology laboratories in the UK, only approximately 20% are currently equipped to undertake ECM analysis of GBS swabs. The majority of UK microbiology laboratories use direct plating onto selective agar in a semiautomated system. We compared direct plating versus incubation in ECM before plating onto selective agar. The latter method identified 97% of the positive GBS swabs compared with 75% using the standard method. These considerations are important as the UK moves towards fewer, more centralised laboratories that require automation to manage the throughput of samples within clinical microbiology. Our results have important implications for sample size calculations in future UK studies, such as the GBS3 trial.

Parents were very keen, in principle, to have blood obtained from their infants over the first 3 months of life. We enrolled 34 infants, born to colonised women, into the antibody kinetics substudy and preliminary data indicate a waning of antibodies between birth and 3 months of life. This will help us understand the relationship between the antibody at the time of iGBS with the antibody in the cord blood of that baby and of the mother. A serocorrelate of protection in the baby will be important in determining protection, but protective antibody at the time of acute disease might overestimate (or underestimate) the true protective level. Our results will therefore enable this interpretation in the main study.

Limitations and recommendations

In summary, this initial feasibility study has been able to assess key operational aspects of the large study that is needed to define the serocorrelates of protection against iGBS.

The main limitation is that we were not able to recruit the (hypothetical) target of 4000 women, mainly because of the short period of the study and insufficient staff dedicated to it. However, we believe that we have recruited a suitable number to allow us to draw conclusions that will now aid the design and co-ordination of the main trial. This includes the clinical data to be collected, how they are recorded, when to approach women in pregnancy and how the issue of cord blood collection can be managed. For example, we believe that an opt-out approach, whereby cord blood sampling would become part of normal routine practice, would help to recruit the large cohort we are aiming for in the serocorrelates study. We propose to assess this in a continuation of this study.

Chapter 6 Next steps

As described and justified earlier, we propose that to define the serocorrelates of protection against the most common serotypes of GBS causing infant disease in the UK will require a case–control study of suitable size.

Sample size calculation

Based on previous correlates of risk reduction studies,[8,20,22] correlates that give risk reductions of 80–90% are feasible and acceptable. An 80% reduction in a case–control study implies an odds ratio of 0.2. The precision around 0.2 for varying case sample sizes and varying proportion of controls with IgG levels above the potential correlate levels ('cuts') is shown in *Appendix 2*.

Cases

Based on the incidence of iGBS from our 2014 national surveillance study (0.9/1000 live births up to 90 days of age),[10] we anticipate being able to collect at least 150 iGBS case samples (EOD and LOD) over 2 years of collection from 180,000 women.

Controls

The number of controls is based on the need for a 3 : 1 ratio of controls to cases (see *Appendix 2*). Of 150 iGBS cases, we would expect approximately 100 cases of serotype III disease and, thus, 300 suitable controls are required to be matched to them (i.e. women colonised with serotype III, who do not receive IAP and whose babies do not develop iGBS). As indicated previously, and confirmed by the results of the feasibility study, with a control group of 5000 women we would expect to recruit approximately 380 healthy term infants born to GBS serotype III-colonised women who have not received IAP.

Possible strategies for completing the case–control study

On discussion with the GBS3 trial team, it is apparent that the most efficient way of recruiting the control group would be by extending the feasibility study rather than by recruiting these women within the GBS3 trial. This is because, in the context of the GBS3 trial, the women who would potentially be eligible to form the control group (i.e. women who are having a swab performed) will (essentially) all go on to receive IAP if they are found to be GBS colonised. By definition, if a woman has received IAP then she would be ineligible to be in the control group as the receipt of IAP will alter the risk of EOD in her baby. It is likely that women in the 'standard of care' arm in GBS3 will be less likely to receive IAP but, as they are not having a swab performed, they would not be eligible as controls. Based on the data from this feasibility study, in which 8.3% of women at the three sites that did not participate in the colonisation substudy happened to have a positive swab obtained before birth (89/1072, excluding missing data), we would need to recruit 12,000 women to identify the 1000 in the 'standard of care' arm who have been opportunistically swabbed and are colonised in order to capture the 380 infants born to mothers colonised with GBS serotype III.

An alternative for generating the control group would be to identify women in GBS3 who have a positive GBS swab result, but (for whatever reason) do not receive IAP. This is not our preferred method, as it seems likely that they will be an unusual (and potentially unrepresentative) group of women. However, more importantly, the GBS3 team have indicated that it will not be possible to identify (at an individual level vs. a unit level) those women who actually receive IAP. Owing to the design of the GBS3 study, it will therefore be impossible to identify these women.

The feasibility study has allowed us to identify best practice in recruiting women to have a rectovaginal swab, cord blood and key clinical information collected. We believe that the control group of 5000 women could therefore be recruited using the five sites that have participated in the feasibility study; all sites have expressed a willingness to do so, subject to sufficient funding to support recruitment.

We have recruited around 600 women with swabs in 4 months from two sites (75 per site per month). We therefore estimate that we will require an additional 12 months at five sites to complete control group recruitment (i.e. 75 women per month per site = 75 × 5 = 375 women per month; 375 women × 12 months = 4500 women), plus 3 months for site set-up (renewal of ethics and local approvals) and to ensure staff coverage within the midwifery teams (total 15 months extension). This would ensure that we achieve our target of 5000 women, of whom we expect 380 to be colonised with GBS serotype III and who would serve as our control group for iGBS III cases, recruited in the main study.

Invasive group B streptococcal disease cases from the proposed main trial (GBS3)

As indicated, cord blood will be required from a cohort of approximately 180,000 women. The feasibility study has indicated that recruitment to a study in which cord blood is to be obtained can be very high when a study midwife has the opportunity to approach a woman to obtain consent (74%, 95% CI 71% to 76%). However, as it was possible to approach only a minority of women during the study period because of the individual consent approach, the overall recruitment rate (22% of all births during the study period, 95% CI 21% to 23%) was much lower. Performing clinical trials for an intrapartum intervention has historically been challenging because of issues related to consent in an 'emergency' setting. Advances in experience and knowledge of delivering high-quality and high-impact research in labour have however recently emerged. A consent pathway developed by the GBS3 trial group[32] now features in the RCOG guidance on intrapartum consent.[33] Recent examples of successful intrapartum emergency studies include deferred or immediate cord clamping in preterm birth,[34] glyceryl trinitrate for retained placenta,[35] tranexamic acid for treatment of post-partum haemorrhage,[36] with further trials under way [e.g. the High Or Low Dose Syntocinon for delay in labour (HOLDS) trial ISRCTN 99841044 (Kenyon S, Taylor R, Hewston R, Johnston T, Hinshaw K, Middleton L, *et al.* Birmingham Women's NHS Foundation Trust, March 2016 to June 2019) and ANODE ISRCTN: 11166984[37]]. Feedback from the participating sites suggests that obtaining cord blood from women in labour using an opt-out strategy would be both realistic and acceptable. We propose testing this strategy more formally through patient groups and by seeking ethics committee advice.

To identify those infants in this cohort in GBS3 who develop iGBS we propose to undertake surveillance via Public Health England and specific paediatric clinical networks (BPAIIG and neonIN). We have successfully identified cases through these networks in the feasibility study and have been able to capture 15 cases of iGBS in a short period of time. This provides confidence in our approach. An additional advantage to extending the feasibility study as proposed above would be to continue to test the feasibility of national surveillance and to embed it as a routine, in preparation for the GBS3 study.

In addition, an extension would allow us to test the hypothesis that antibody concentration at the time of acute disease equates to antibody concentration from cord blood. We have already enrolled 27 babies born to healthy women into our antibody kinetics study (eight colonised with serotype III). However, to ensure that we understand the relationship between antibody in the acute disease phase and in a healthy infant exposed to GBS, we now need to undertake the kinetics study in cases of GBS disease up to 3 months of life. Collecting acute serum from 50 infants with serotype III disease will enable us to interpret antibody in health and disease up to 90 days of life. If infant antibody at the time of acute disease proves to be an accurate reflection of cord blood antibody for that infant, this would make a major difference to the design of the GBS3 trial as it would negate the need for the full 180,000 cord sera samples. This would mean that we would need blood from only 150 cases of iGBS serotype III disease rather than collecting cord blood from 180,000 women. We can resolve this during the extended feasibility study.

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Dr Clara Carreras-Abad (https://orcid.org/0000-0002-9068-3233) was responsible for the day-to-day operation of the study, laboratory work, data analysis and drafting the final report.

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Mr Tom Hall (https://orcid.org/0000-0002-9001-6684) and **Ms Laxmee Ramkhelawon (https://orcid.org/0000-0001-8038-8313)** were responsible for the immunological analysis of serum samples at St George's, University of London.

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Dr Tim Planche (https://orcid.org/0000-0002-0263-0888) contributed to the microbiologic study design and was responsible for all samples analysed at St George's University Hospitals NHS Foundation Trust.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review and agreement of the Steering Committee.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Feedback from sites, looking towards the 'big study'

BOX 1 Feedback from sites, looking towards the 'big study'

Recruiting methods

Feedback

- Retrospective consent has improved recruitment and collection of cord blood.
- Having time to explain the study before consenting increases the enrolment rate.
- Sending the information sheet prior to delivery reduces midwife face-to-face time.
- Main refusal reasons: language barriers, taking part in research, using samples for future research, rectovaginal swabs and taking samples from babies.

Tips

- An opt-out approach, where swabs and blood collection would be part of normal routine, would be well accepted and easier for recruitment.
- Information of the study prior to delivery would be useful: letters, social media.
- A patient information sheet translated to other languages would be helpful, especially Urdu.

Data collection

Feedback

- REDCap, as a tool for case report form, has been well accepted and appreciated. It does not take long to fill it.
- Data may be missing, especially data collected during labour, if research midwives are not present.

Tips

- Collaboration of clinical midwives is essential.

Sample collection

Feedback

- It has been easier to recruit in labour wards in order to collect blood samples.
- Maternal blood is easy to collect from women who need a cannula (caesarean sections, inductions).
- Vaginorectal self-swab collection (with midwife support) helps to increase the consent rate.

Tips

- It is essential to have a team involved on labour wards (cord blood team, midwives, obstetricians, nurses).
- Having staff dedicated exclusively to cord blood collection would be helpful.

BOX 1 Feedback from sites, looking towards the 'big study' (*continued*)

Invasive group B streptococcal disease surveillance

Feedback

- Telephone calls might be time-consuming and not so effective to detect LOD.

Tips

- A national surveillance could be more effective to recruit iGBS cases following the logistics represented in the flow chart (*Figure 7*).

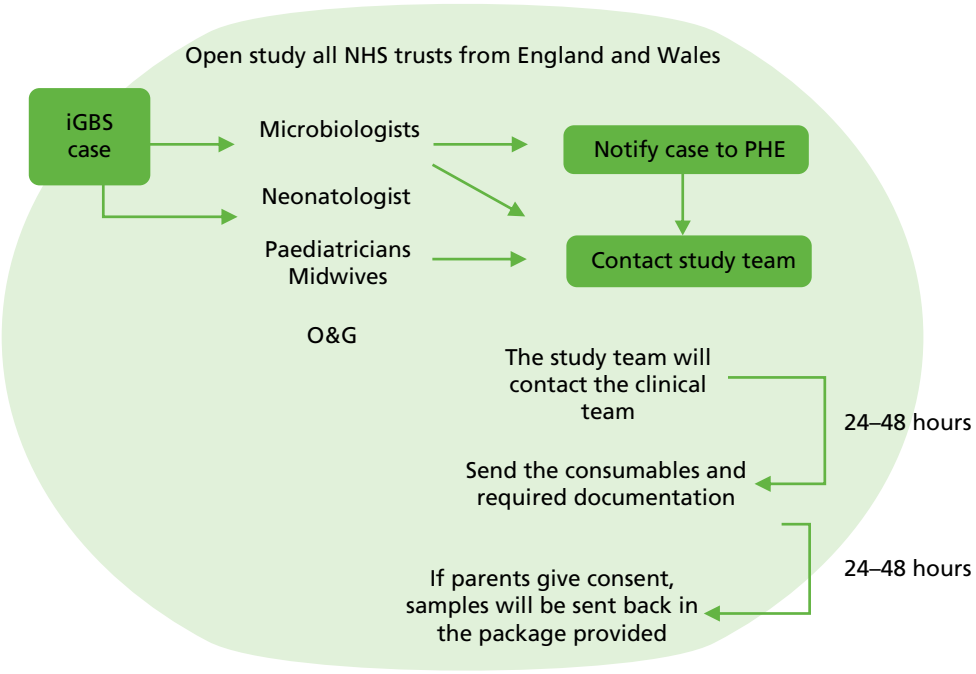

FIGURE 7 The iGBS national surveillance. O&G, obstetrics and gynaecology.

Appendix 2 Precision of correlates of risk reduction for serotype-specific group B streptococcus disease estimates according to different sample sizes

Based on previous GBS CoP studies,[2–4] GBS serocorrelates that give risk reductions of 80–90% are feasible. A reduction of 80% in a case–control study implies an odds ratio of 0.2. The precision around 0.2 for varying case sample sizes and varying proportion of controls with IgG levels above the potential CoP levels ('cuts') is shown above with three controls per case. Thus, if 50% of controls have levels above the cut-off point, with 30 cases the 95% CI around an 80% reduction is 43% to 93%; with 90 cases it is 63% to 89% (bold values in table below).

TABLE 19 Precision of correlates of risk reduction for serotype-specific GBS disease estimates according to different sample sizes

	95% CI		
Controls > 'cut'	*N* = 30 cases and *N* = 90 controls	*N* = 90 cases and *N* = 270 controls	*N* = 150 cases and *N* = 450 controls
70%	0.08 to 0.49	0.12 to 0.33	0.13 to 0.30
50%	**0.07 to 0.57**	**0.11 to 0.37**	0.13 to 0.32
30%	0.05 to 0.81	0.09 to 0.45	0.11 to 0.37

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