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

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Scientific summary

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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.

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This report

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