A rapid intrapartum test for group B *Streptococcus* to reduce antibiotic usage in mothers with risk factors: the GBS2 cluster RCT

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Declared competing interests of authors: Jane Plumb is the chief executive of Group B Strep Support (Haywards Heath, UK), a charity working to stop group B streptococcal infections in babies. She is the vice chairperson of Women's Network within the Royal College of Obstetricians and Gynaecologists (London, UK). She received support from Cepheid (Maurens-Scopont, France) to attend an academic conference in 2016, from Pfizer Inc. (Pfizer Inc., New York, NY, USA) to attend a summit for vaccine advocacy stakeholders in the USA in 2019 and from i–CONSENT (Valencia, Spain) to attend workshops in London in 2018 and Brussels in 2019, regarding consent for vaccine trials. She was a member of the Department of Health and Social Care Research Prioritisation Expert Group in 2016. Jane Plumb (2019–present) and Jim Gray (2018–2020) are members of the National Institute for Health and Care

Excellence's Guideline Update Committee for Neonatal Infection: Antibiotics for Prevention and Treatment (August 2018, guideline to be published 2021). Jim Gray was a member of the National Institute for Health and Care's Diagnostics Advisory Committee (August–November 2010) that produced *Rapid Tests for Group A Streptococcal Infections in People With a Sore Throat* (DG38) in 2019 (which included an assessment of the Cepheid GeneXpert Xpert® Xpress Strep A test). Jane Daniels, Jane Plumb and Jim Gray are grant holders for Health Technology Assessment (HTA) programme 17/86/06 (GBS3), a cluster randomised trial of routine screening for group B *Streptococcus*. Jane Daniels and Jane Plumb are grant applicants for a study to determine a serocorrelate of immune protection against group B *Streptococcus* (MRC MR/T030925/1). Jane Daniels is a member of the National Institute for Health Research (NIHR) Clinical Trials Unit Standing Advisory Committee (2016–present). Jonathan Deeks was on various NIHR panels between 2008 and 2017 [i.e. the HTA Efficient Study Designs 2 (2015–16), HTA End of Life Care and Add-on Studies (2015–16), HTA Medical Tests Methods Group (2015–17), HTA Primary Care Themed Call Board 2013–14, Pre-Exposure Prophylaxis Impact Review Panel (2017), HTA Funding Committee Policy Group (2011–16) and the HTA Commissioning Committee (2011–16)]. Michael Millar was a member of the NIHR Funding Committee for Antimicrobial Resistance Studies (2014–15), the NIHR Board for Hospital Infections (2006–7), the Economic and Social Research Council Antimicrobial Resistance Board (2016–17) and of the NIHR HTA Diagnostic and Screening panel (2008–15).

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Scientific summary

The GBS2 cluster RCT

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Scientific summary

Background

Group B *Streptococcus* (*Streptococcus agalactiae*) colonises the vagina and/or rectum of at least 20% of women, from where it can be passed to the baby, usually during labour. Administration of intrapartum antibiotic prophylaxis to group B *Streptococcus*-colonised mothers reduces the risk of early-onset group B *Streptococcus* infection, disability and death in the newborn. In the UK, intrapartum antibiotic prophylaxis is offered to all women with risk factors for having a baby with early-onset group B *Streptococcus* disease. However, neonatal infection rates are low, and so most babies and their mothers are therefore unnecessarily exposed to antibiotics.

Aim

To determine whether or not intrapartum antibiotic prophylaxis based on the results of rapid point-of-care intrapartum group B *Streptococcus* tests in women at high risk of having babies with early-onset group B *Streptococcus* disease reduces maternal and neonatal antibiotic exposure, and if the rapid test can accurately detect group B *Streptococcus* colonisation in clinical practice.

Objectives

Primary

- To determine if the use of the rapid intrapartum test for maternal group B *Streptococcus* colonisation reduces maternal and neonatal antibiotic exposure, compared with usual care where intrapartum antibiotic prophylaxis is based on maternal risk factors, in a cluster randomised trial.
- To determine the real-time accuracy of the rapid intrapartum test for group B *Streptococcus* colonisation among women in labour with risk factors for group B *Streptococcus* transmission, compared with the reference standard of selective enrichment culture, in a cross-sectional study nested within the randomised cohort.

Secondary

- To evaluate if the rapid intrapartum test reduces intrapartum antibiotic prophylaxis in the mother for any indication, compared with usual care.
- To evaluate the effect of the rapid test, compared with the usual-care strategy, on neonatal exposure to antibiotics and neonatal morbidity and mortality.
- To evaluate if timely intrapartum antibiotic prophylaxis administration can be achieved with a rapid intrapartum test to ensure adequate antibiotic exposure, by establishing a standard operating procedure for use of the test.
- To evaluate the cost and cost-effectiveness of using the rapid intrapartum test, compared with usual care.
- To evaluate the antibiotic resistance profile of group B *Streptococcus* and the colonisation by other antibiotic-resistant bacteria of the mother from the intrapartum vaginal/rectal swab, and the risk of such colonisation in the baby at 6 weeks of age.
- To evaluate the colonisation rate of antibiotic-resistant bacteria, particularly *Escherichia coli*, meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in vaginal/rectal samples from women.

- To evaluate the extent to which colonisation of specific resistant bacteria or resistance elements in the mother at the time of birth increase the risk of carriage of those specific bacteria or elements by the infant at 6 weeks of postnatal age.
- To gather some information on peripartum risk factors for transmission (e.g. mode of birth, gestational age, antibiotic exposure).

Design

A multicentre, prospective, unblinded, parallel-cluster, randomised controlled trial, with a nested test accuracy study, an economic evaluation and a microbiology substudy.

Methods

Clusters and participants

Twenty UK maternity units were clusters. The units were eligible to participate if they were prepared to accept a policy of rapid test-directed intrapartum antibiotic prophylaxis administration as their standard practice to prevent early-onset group B *Streptococcus* infection for the duration of the trial period. The sites had to recruit women with risk factors specified in the Group B Streptococcus 2 trial, irrespective of the implementation date of the Royal College of Obstetricians and Gynaecologists' guidelines and its current local policy, and should have access to microbiology facilities to perform selective enrichment bacteriological culture to detect group B *Streptococcus*.

Randomisation of clusters was performed at the Birmingham Clinical Trials Unit using a minimisation algorithm programed in a Microsoft Excel® spreadsheet (Microsoft Corporation, Redmond, WA, USA), incorporating the following factors:

- region (Midlands or London and the South East)
- pre-trial intrapartum antibiotic prophylaxis rate (above or below the median)
- the number of vaginal or emergency caesarean births (above or below the median).

Women were eligible for inclusion in the Group B Streptococcus 2 trial if they met one or more of the following criteria:

- a previous baby with early- or late-onset group B *Streptococcus* disease, as reported by the mother and documented in the maternal notes
- group B *Streptococcus* bacteriuria during the current pregnancy, as documented in the maternal notes, regardless of whether or not the group B *Streptococcus* bacteriuria was treated at the time of diagnosis with antibiotics
- group B *Streptococcus* colonisation of the vagina and/or rectum (determined from a vaginal/rectal swab) in the current pregnancy, as documented in the maternal notes
- preterm labour (< 37 weeks' gestation) whether suspected, diagnosed or established and whether in women with intact membranes or women with prelabour rupture of membranes of any duration
- maternal pyrexia (≥ 38 °C) observed at any point in labour, including clinically suspected/confirmed chorioamnionitis.

Women were ineligible if they were aged < 16 years, at < 24 weeks' gestation, in the second stage of labour at admission or considered likely to give birth to their baby imminently, had a planned elective caesarean birth, or their baby was known to have died in utero or had a congenital anomaly incompatible with survival at birth.

Testing strategies assessed

The trial procedures at sites varied according to the strategy randomly allocated to the participating maternity unit. The recommended antibiotic regimen for prevention of group B *Streptococcus* transmission in both types of unit was identical, irrespective of the allocation. Subsequent clinical management of mother and baby was the responsibility of the local health-care team and was not directed by the Group B Streptococcus 2 trial. Usual-care units followed their standard risk-based screening strategy and should have offered intrapartum antibiotic prophylaxis to all women with risk factors.

The units that were randomised to the rapid test received a GeneXpert® Dx IV GBS rapid testing system (Cepheid, Maurens-Scopont, France). Swabs were taken using a double-headed swab. Depending on the stage of labour, the swabs were obtained by either the woman herself or a suitably trained member of the woman's care team. One swab was used immediately for the rapid test and the other was returned to transport tube and sent to the local microbiology laboratory for selective enrichment culture to detect group B *Streptococcus*. For units in London and the south-east of England taking part in the microbiological substudy, an additional single-headed swab was taken and sent to the substudy laboratory. For eligible women in rapid test units, a single swab was taken from the baby's ear canal and cultured to detect the presence of group B *Streptococcus*, as per the mother's swab.

Outcome measures

Owing to the difference in the strategies for testing women and for directing intrapartum antibiotic prophylaxis, it was not possible to blind women or their care team to the randomised allocation. Data were extracted from maternity and neonatal notes by research midwives within each unit who were involved in the implementation of the trial, and therefore it was not possible to blind them to the randomised allocation.

Cluster randomised trial outcomes

Primary outcome

- The proportion of women with risk factors who received intrapartum antibiotic prophylaxis to prevent early-onset group B *Streptococcus* infection.

Secondary outcomes

- The rates of intrapartum maternal antibiotic administration for any indication and for any indication other than caesarean birth, and postpartum maternal antibiotic use for any indication.
- The time of intrapartum antibiotic prophylaxis exposure that was defined as the duration between the start time of the first dose of intrapartum antibiotic prophylaxis and the birth of the baby. (Sufficient exposure was considered as an interval of either > 2 hours or > 4 hours before birth.)
- Neonatal outcomes at any time until discharge from the hospital, including neonatal antibiotic administration for prophylaxis or treatment, suspected neonatal infection, neonatal group B *Streptococcus* colonisation rates and neonatal mortality.
- Serious adverse events.

Test accuracy outcomes

- Measures of test accuracy (i.e. sensitivity and specificity of the GeneXpert GBS rapid test).
- Maternal and neonatal colonisation rates and mother-to-baby group B *Streptococcus* transmission rates.

Process outcomes (for the rapid test units only)

- The proportion of the cartridges on which the tests were not commenced within 15 minutes of inoculation, which is defined as an invalid test.
- The proportion of tests initiated on the Cepheid GeneXpert machine that failed to produce a result within 55 minutes, which is defined as a failed test, or were reported as failed by the system.

Economic outcomes

- Cost per instance of intrapartum antibiotic prophylaxis avoided. Sensitivity analysis 1 included maternal costs using trial data and sensitivity analysis 2 included data on maternal and newborn stay in hospital.

Microbiology substudy outcomes

- Colonisation rates of antibiotic-resistant group B *Streptococcus* and a selected Gram-negative bacteria in swabs taken from the mother during labour, and her baby at 6 weeks of age.

Sample size

The proportion of women receiving intrapartum antibiotic prophylaxis was expected to be 50–75%. With a sample size per unit of 83 women and a minimum of 20 units, the trial would have 90% power to detect a reduction to 63% in rapid test units, assuming an intracluster coefficient of 0.01. This sample would also be capable of showing that the rapid test with estimated sensitivity of 96.4% was greater than a fixed value of 90%. With a power of 90% to demonstrate this sensitivity, 167 cases of maternal group B *Streptococcus* colonisation were required.

Results

The first site opened to recruitment on 26 July 2017 and the trial closed to recruitment on 30 April 2019. Twenty-two maternity units agreed to participate and were randomised to usual-care or rapid test pathways. Following randomisation, two sites, one allocated to each strategy, requested withdrawal from the trial. In total, 722 women (749 babies) in the 10 rapid test units and 906 women (951 babies) participated in 10 usual-care units. The mean age of included women was 29.7 years and 35% were nulliparous. The two most frequently reported risk factors were group B *Streptococcus* detected in their current pregnancy prior to labour (35%) or the women was in preterm labour (41%).

Effectiveness of screening strategies

Maternal outcomes

Overall, 41% (297/716) of women in the rapid test group were given intrapartum antibiotic prophylaxis for group B *Streptococcus* prophylaxis, compared with 36% (328/906) of women in the usual-care group, with no significant differences in the rates of antibiotics prescribed to prevent early-onset group B *Streptococcus* infection (risk ratio 1.16, 95% confidence interval 0.83 to 1.64; risk difference 5%, 95% confidence interval −7% to 18%).

There were no differences between the two groups in the proportion of women who received intrapartum antibiotic prophylaxis for any indication (risk ratio 0.99, 95% confidence interval 0.81 to 1.21; risk difference −0.7%, 95% confidence interval −14% to 12%), intrapartum antibiotic prophylaxis for any indication other than for a caesarean birth (risk ratio 1.01, 95% confidence interval 0.83 to 1.23;

risk difference 7%, 95% confidence interval −11% to 13%) and antibiotic treatment postpartum for any indication (risk ratio 0.92, 95% confidence interval 0.60 to 1.44; risk difference −2%, 95% confidence interval −12% to 8%). There was a significant increase in the proportion of women who received sufficient antibiotic exposure (> 4 hours before birth) with rapid test than usual care (risk ratio 1.32, 95% confidence interval 1.12 to 1.55, risk difference 0.16; 95% confidence interval 0.06 to 0.27) and there were no differences in the rates of women with intrapartum antibiotic prophylaxis exposure > 2 hours between the two strategies.

Neonatal outcomes

Babies live born to women in the rapid test units (33%, 244/737) had a significantly lower risk of receiving antibiotics than those in the usual-care units (44%, 412/946) (risk ratio 0.71, 95% confidence interval 0.54 to 0.95; risk difference −13%, 95% confidence interval −23% to −2%). The predominant reason stated for administration of neonatal antibiotics was for suspected early-onset sepsis, which was significantly lower in babies born to mothers in rapid test units (risk ratio 0.63, 95% confidence interval 0.43 to 0.92).

There were 11 reports of group B *Streptococcus* infection among 561 babies who received antibiotics, (3/187 in the rapid test units and 8/374 in the usual-care units). There were three perinatal deaths in the rapid test units and eight in the usual-care units.

There were no serious adverse events in the mother or baby at any unit.

Accuracy of rapid intrapartum test to diagnose group B *Streptococcus* colonisation in women

Of the cohort of 722 women, 557 (77%) women provided results from the rapid test and 619 (86%) women provided results from the selective enrichment culture test, with 534 (74%) women providing information from both tests. The sensitivity of the rapid test was 86% (95% confidence interval 81% to 91%) and specificity was 89% (95% confidence interval 85% to 92%). The test accuracy values were not statistically different from an expected sensitivity or specificity of 90%.

The maternal colonisation rate was 43% (95% confidence interval 39% to 48%) using selective enrichment culture of all swabs. The neonatal colonisation rate was 11% (95% confidence interval 8% to 14%) among 445 babies in the rapid test units who had a result from selective enrichment culture of a neonatal ear swab.

Process outcomes

In 14% of women recruited in the rapid test units (100/721), the test was invalid or the machine failed to provide a result. In addition, the test was not performed in a further 8% of women (56/710). Among all women who were rapid test positive, intrapartum antibiotic prophylaxis was administered for 79% of women (190/241) for group B *Streptococcus* and 87% of women (210/241) for any indication. Of those who were rapid test negative, in 16% of women (52/316), intrapartum antibiotic prophylaxis was administered for preventing early-onset group B *Streptococcus* infection.

Economic evaluation

The mean cost per woman was £4128 and £4003 in the rapid test units and usual-care units, respectively, after considering the cost of tests, antibiotics and inpatient care of the mother. The rapid test is dominated by usual care, as it is both more costly and also results in a higher proportion of

women receiving intrapartum antibiotic prophylaxis. When neonatal inpatient costs were included in the cost, there was more uncertainty about the costs and an indication of an increase in costs in the usual-care arm.

Microbiological substudy on antibiotic resistance

Of the 39 of 117 maternal samples from which group B *Streptococcus* was isolated, 82.1% (32/39) were tetracycline resistant, 23.1% (9/39) were erythromycin resistant, 17.9% (7/39) were clindamycin resistant and there were no penicillin-resistant isolates. *E. coli* was isolated from 85 (72.6%) of the 117 maternal samples, and found to be resistant to ampicillin in 54.1% (46/85), amoxycillin/clavulanate in 43.5% (37/85), trimethoprim/sulfamethozaxole in 24.7% (21/85), ciprofloxacin in 5.9% (5/85), gentamicin in 4.7% (4/85), demonstrated extended-spectrum β-lactamase in 3.5% (3/85) and 21.2% (18/85) were resistant three of more antibiotic classes. In 63 mother–child pairs, the proportion of babies carrying antibiotic-resistant *E. coli* (multidrug resistant, co-trimoxazole resistant) was higher when there was maternal colonisation with antibiotic resistant *E. coli* or other resistant genes than when there was no colonisation.

Conclusions

The Group B Streptococcus 2 trial found no evidence that the rapid test reduces the rates of maternal intrapartum antibiotic prophylaxis for early-onset group B *Streptococcus* infection, compared with usual care, but has the potential to reduce the administration of antibiotics to babies. The trial showed some evidence of differential ascertainment of participants across rapid test and usual-care units, both with respect to both the number of participants and some of the characteristics of the participants. The rapid test shows reasonable sensitivity and specificity and was within the acceptable limit determined a priori. The rapid test strategy is economically dominated by usual care when only maternal outcomes are considered, but is less expensive than usual care if neonatal hospital stay costs are also included. Babies born to mothers who carry antibiotic-resistant *E. coli* are more likely to also be colonised with the same strains than those born to mothers with antibiotic-susceptible *E. coli*. The trial is limited to women with risk factors for group B *Streptococcus* vertical transmission to the newborn, and the role of rapid test in all pregnant women needs to be evaluated. Given that early-onset infection is relatively rare, a very large randomised trial would be required to determine the impact of either testing strategy relative to usual care. Cost implications beyond the neonatal period would need to be considered and the impact on the neonatal microbiome would need to be explored.

Trial registration

This trial is registered as ISRCTN74746075.

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