Cluster randomized crossover trial to evaluate point-of-care testing and treatment of sexually transmitted infections to improve birth outcomes in high-burden, low-income settings

Short Title:	*WANTAIM*: Women And Newborn Trial of Antenatal Interventions and Management
Trial Sponsor:	Papua New Guinea Institute of Medical Research
Funding:	DfID/MRC/Wellcome Trust Joint Global Health Trials Grant (MR/N006089/1) National Health & Medical Research Council Australia Grant (1084429) Swiss National Science Foundation Grant (IZ07Z0_160909/1)
Population:	4600 antenatal women and their newborns in Papua New Guinea.
Trial Design:	Cluster randomised crossover trial. The unit of randomisation is a primary health care clinic and its catchment communities. Each participating cluster will be randomised to participate in either the intervention or the control arm of the trial in the first phase of the study, and following a short washout period, will then crossover to participate in the alternative trial arm in the second phase of the study.
Research Sites:	Ten geographically distinct clusters in three provinces (East New Britain, Madang and Milne Bay Provinces).
Study Duration:	Four years
Subject Duration:	Each pregnant woman will be enrolled at their first antenatal clinic visit and followed up until one week after birth (approx. 5-6 months per participant). Primary outcome data will be censored at 72 hours postpartum. A subset of 2000 mothers and their newborns will be followed up until 4-6 weeks postpartum.
Aim:	To measure the effectiveness, health system implementation requirements, cost-effectiveness and acceptability of antenatal point-of-care testing and immediate treatment of sexually transmitted infections (STI) to improve birth outcomes in high-burden, low-income settings.

Primary Research Objective:

1. Evaluate whether point-of-care testing and immediate treatment of curable STIs in pregnancy leads to a reduction in preterm birth and low birth weight compared with standard antenatal care.

Secondary Research Objectives:

1. Evaluate whether point-of-care STI testing and treatment in pregnancy leads to an increase in mean birth weight compared with standard antenatal care;
2. Evaluate whether point-of-care STI testing and treatment in pregnancy leads to a reduction in premature rupture of membranes compared with standard antenatal care;
3. Evaluate whether point-of-care testing in pregnancy increases the diagnosis and treatment of STIs compared with symptom-based 'syndromic' management;
4. Evaluate the cost-effectiveness of point-of-care STI testing and treatment in pregnancy compared with standard antenatal care;
5. Evaluate the health system implementation requirements of point-of-care STI testing and treatment in pregnancy compared with standard antenatal care;
6. Evaluate the acceptability of antenatal point-of-care STI testing and treatment compared with standard care;
7. Evaluate whether point-of-care STI testing and treatment in pregnancy leads to a reduction in neonatal eye infection and/or pneumonia compared with standard antenatal care;
8. Evaluate mother to child transmission of *C. trachomatis* and *N. gonorrhoeae*;
9. Evaluate the performance of the Xpert^{TM} CT/NG Test for the diagnosis of neonatal eye infection and pneumonia using ocular and nasopharyngeal specimens.

Intervention summary

Women participating in the intervention arm of the trial will provide self-collected vaginal specimens for point-of-care testing for the curable sexually transmitted and genital infections chlamydia, gonorrhoea, trichomonas and bacterial vaginosis, and provided with immediate treatment as indicated, at the following time points:

- At enrolment (preferably before 20 weeks gestation);
- One month after trial enrolment (to confirm that infections at enrolment have been cured and to detect incident infections. Women with a positive test result at this visit will be asked to return for repeat testing one month later);
- At 34-36 weeks antenatal follow-up.

The rationale for this intervention schedule is based on:

a) current scientific evidence which suggests that diagnosis and treatment of chlamydia, gonorrhoea, trichomonas and bacterial vaginosis early in pregnancy would have the greatest impact on low birth weight and preterm birth;

b) the lack of scientific evidence on the association between incident chlamydia, gonorrhoea, trichomonas and bacterial vaginosis in later pregnancy and risk of adverse birth outcomes, particularly preterm birth and premature rupture of membranes.

Point of care testing will be conducted using the Cepheid GeneXpert^{TM} platform (chlamydia, gonorrhoea, trichomonas) and the Gryphus Diagnostics BV Blue Test (bacterial vaginosis).

To evaluate whether point-of-care testing in pregnancy increases the diagnosis and treatment of STIs compared with symptom-based syndromic management, residual urinalysis specimens collected at enrolment, after one month and at 34-36 weeks in the control arm of the trial will be retained and tested in batches. This will also enable the research team to provide appropriate antibiotic treatment at the postnatal visit, as indicated.

Standard of clinical care to be offered to trial participants

Overview

Women attending routine antenatal clinics in both the control and intervention arms of the trial will receive standard antenatal care in accordance with PNG national guidelines *(Manual of Standard Management in Obstetrics and Gynaecology for Doctors, Health Extension Officers and Nurses in Papua New Guinea*).

Additional care provided to trial participants

Women in both trial arms will receive additional antenatal and postnatal care as per the trial protocol, and in accordance with study-specific standard operating procedures (SOPs).

Additional antenatal care will include the following:

- An obstetric ultrasound for pregnancy dating purposes at enrolment (first antenatal clinic visit)
- Collection/testing of urine and/or vaginal specimens for sexually transmitted infections
- Additional testing of fingerprick blood specimens for malaria infection

Additional postnatal care will include the following:

- A postnatal follow-up visit conducted by a trained member of the clinical research team. This will be carried out either at the health facility or in the community following birth.
- The visit will include the collection of information required for the trial (e.g. birth weight) and be an opportunity to provide additional care for both mother and newborn infant that would not be available as part of routine standard practice (e.g. provision of birth dose vaccinations)

Specialist referral

In the event that a trial participant or her newborn baby experience an adverse health outcome that cannot be managed by antenatal clinic staff or the clinical research team, a specialist referral will be organized by the clinical research team. In the event of an emergency (e.g. postpartum haemorrhage, neonatal sepsis) the research team will use a project vehicle to assist in urgent hospital transfer.