Point-of-care testing and treatment of sexually transmitted and genital infections to improve birth outcomes in high-burden, low-resource settings (WANTAIM): a pragmatic cluster randomised crossover trial in Papua New Guinea

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Summary

Background ***Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, and bacterial vaginosis have been associated with adverse maternal and perinatal outcomes, but there is conflicting evidence on the benefits of antenatal screening and treatment for these conditions. We aimed to determine the effect of antenatal point-of-care testing and immediate treatment of *C trachomatis*, *N gonorrhoeae*, *T vaginalis*, and bacterial vaginosis on preterm birth, low birthweight, and other adverse maternal and perinatal outcomes compared with current standard of care, which included symptom-based treatment without laboratory confirmation.**

Methods **In this pragmatic cluster randomised crossover trial, we enrolled women (aged ≥16 years) attending an antenatal clinic at 26 weeks' gestation or earlier (confirmed by obstetric ultrasound), living within approximately 1 h drive of a study clinic, and able to provide reliable contact details at ten primary health facilities and their catchment communities (clusters) in Papua New Guinea. Clusters were randomly allocated 1:1 to receive either the intervention or control (standard care) in the first phase of the trial. Following an interval (washout period) of 2–3 months at the end of the first phase, each cluster crossed over to the other group. Randomisation was stratified by province. Individual participants were informed about trial group allocation only after completing informed consent procedures. The primary outcome was a composite of preterm birth (livebirth before 37 weeks' gestation), low birthweight (<2500 g), or both, analysed according to the intention-to-treat population. This study is registered with ISRCTN Registry, ISRCTN37134032, and is completed.**

Findings **Between July 26, 2017, and Aug 30, 2021, 4526 women were enrolled (2210 [63·3%] of 3492 women in the intervention group and 2316 [62·8%] of 3687 in the control group). Primary outcome data were available for 4297 (94·9%) newborn babies of 4526 women. The proportion of preterm birth, low birthweight, or both, in the intervention group, expressed as the mean of crude proportions across clusters, was 18·8% (SD 4·7%) compared with 17·8% in the control group (risk ratio [RR] 1·06, 95% CI 0·78–1·42; p=0·67). There were 1052 serious adverse events reported (566 in the intervention group and 486 in the control group) among 929 trial participants, and no differences by trial group.**

Interpretation **Point-of-care testing and treatment of *C trachomatis, N gonorrhoeae, T vaginalis*, and bacterial vaginosis did not reduce preterm birth or low birthweight compared with standard care. Within the subgroup of women with *N gonorrhoeae*, there was a substantial reduction in the primary outcome.**

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Introduction

There is evidence from observational studies that *Chlamydia trachomatis*,[1] *Neisseria gonorrhoeae*,[2] *Trichomonas vaginalis*,[3,4] and bacterial vaginosis[5,6] in pregnancy are associated with higher likelihoods of preterm birth, low birthweight, and other adverse birth outcomes. In several high-income countries, including the USA,[7] screening in pregnancy for chlamydia and gonorrhoea is recommended, based on indirect evidence from observational studies. However, there is little direct evidence that antenatal screening and treatment of these curable sexually transmitted infections (STI) or bacterial vaginosis has an effect on birth outcomes.[8] This clinical equipoise has led to calls for definitive trials,[7,8] particularly in low-income and

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See **Online** for appendix 1

Research in context

Evidence before this study

Before finalising the protocol of our trial on June 9, 2016, we searched MEDLINE, Embase, and the Cochrane Library on May 1, 2016, using the search terms (separately and in combination) in any field: "preterm birth", "prematurity", low birthweight", "spontaneous abortion", "miscarriage", "premature rupture of membranes", "stillbirth", "neonatal death", "adverse birth outcome", "chlamydia", "gonorrhoea", "trichomonas", "bacterial vaginosis", "sexually transmitted infection", "genital infection", and "reproductive tract infection". We searched for randomised trials, clinical trials, field trials, intervention studies, and pilot studies published between Jan 1, 1948, and May 1, 2016, with no language restrictions, and found no randomised trials assessing the benefits of antenatal screening and treatment for *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, and bacterial vaginosis. We updated our search in February, 2018, and in February, 2019, and reviewed new evidence throughout the trial. A randomised trial (MIST) of treatment for bacterial vaginosis and urinary tract infections in pregnancy did not reduce preterm birth in Bangladesh. Treatment of bacterial vaginosis early in pregnancy did not reduce spontaneous miscarriage, preterm birth, or both, in a randomised trial (PREMEVA) in France. Findings from the MIST and PREMEVA trials were published during the course of our trial and discussed with our Data and Safety Monitoring Board and Trial Steering Committee, who recommended that the trial continue as planned (Dec 20, 2018).

Added value of this study

We found that point-of-care testing and same-day treatment of *C trachomatis, N gonorrhoeae, T vaginalis,* and bacterial vaginosis did not result in lower rates of preterm birth, low birthweight, or both (18·8% *vs* 17·8%, risk ratio 1·06, 95% CI 0·78–1·42), or other adverse maternal and perinatal outcomes compared with standard care in the high-burden, low-resource setting of Papua New Guinea. Among women with *N gonorrhoeae,* there was a 53% reduction in preterm birth, low birthweight, or both (16·2% *vs* 34·2%, 0·47, 0·25–0·88). There were large reductions in the prevalence of all three sexually transmitted infections (STIs) in the intervention group. There was a substantial reduction in *C trachomatis,* but not *N gonorrhoeae* or *T vaginalis,* among women in the control group at 4 weeks post-enrolment and at 34–36 weeks' gestation that could have been due to a combination of factors, including high uptake of sulfadoxine–pyrimethamine for malaria prophylaxis, as postulated in a published trial of intermittent malaria prevention in sub-Saharan Africa.

Implications of all the available evidence

Contrary to the findings of earlier observational studies and current expectations in the field, our findings do not support the introduction of screening and treatment of curable STIs or bacterial vaginosis in pregnancy to improve birth outcomes. The trial findings are relevant to all income settings and economies worldwide. The substantial reduction in preterm birth or low birthweight, or both, seen among women with *N gonorrhoeae,* but not among women with other curable STIs, suggests opportunities for future intervention but requires confirmation before this strategy can be added to existing maternal and child health programmes. Efforts to improve maternal and perinatal health in all income settings should focus on proven interventions until the role and potential effect of STI screening and treatment in pregnancy are confirmed. Our hypothesis that sulfadoxine–pyrimethamine for malaria prophylaxis might have reduced *C trachomatis* is consistent with the findings of another large-scale randomised trial and warrants further investigation.

middle-income countries (LMICs), where both curable STIs among pregnant women and adverse birth outcomes are most common.[8,9] The only option in most LMICs has been syndromic management, which is a symptom-based approach for STIs recommended by WHO when laboratory testing is unavailable, but this approach has been shown to have low sensitivity and specificity.[8,10] New, accurate diagnostic technologies that allow same-day testing and treatment make it possible, for the first time, to investigate the potential effect of this strategy on maternal and perinatal health, thereby addressing a key knowledge gap about health care in pregnancy.[7,9]

Our group previously conducted systematic reviews and meta-analyses[2,3] on trichomoniasis and gonorrhoea and found that *T vaginalis* infection was associated with preterm birth and preterm premature rupture of membranes (low birthweight could not be assessed because no published articles were identified). We also found that *N gonorrhoeae* infection was associated with preterm birth, low birthweight, premature rupture of membranes, and perinatal mortality, and that *N gonorrhoeae* infection was more strongly associated with preterm birth in LMICs than in high-income country (HICs). Other groups that have conducted systematic reviews and meta-analysis on chlamydia and bacterial vaginosis[1,5,6] have found that *C trachomatis* was associated with preterm birth, low birthweight, premature rupture of membranes, stillbirth, miscarriage, and seven other adverse reproductive health outcomes. *C trachomatis* infection was more strongly associated with miscarriage in LMICs than in HIC settings. Bacterial vaginosis was associated with preterm birth and miscarriage in one systematic review,[5] which also found that risk of preterm birth was greater among women found to have bacterial vaginosis at 16–20 weeks of gestation or less. Another review[6] found that bacterial vaginosis was associated with premature rupture of membranes, but not preterm birth or low birthweight, in sub-Saharan Africa. The certainty of the overall evidence for all systematic reviews was low or very low for all outcomes.

The Women and Newborn Trial of Antenatal Interventions and Management (WANTAIM, meaning "together" in Tok-Pisin) study in Papua New Guinea aimed to determine the effect of antenatal point-of-care testing and immediate treatment of *C trachomatis*, *N gonorrhoeae*, *T vaginalis*, and bacterial vaginosis on preterm birth, low birthweight, and other adverse maternal and perinatal outcomes compared with current standard of care.

Methods

Study design

We designed a cluster randomised crossover trial to evaluate a point-of-care testing and treatment intervention as it would be implemented in a real-world antenatal clinic setting.[11–13] The trial was conducted in ten primary health facilities and their catchment communities (clusters) in two provinces (Madang and East New Britain) of Papua New Guinea. The trial protocol and statistical analysis plan have been published elswehere[9] (appendix 1 pp 10, 78).

The protocol was approved by the Papua New Guinea Medical Research Advisory Committee (MRAC.16.24), the Institutional Review Board of the Papua New Guinea Institute of Medical Research (IRB.1608), the Human Research Ethics Committee, the University of New South Wales Sydney (HREC.16708), and the Research Ethics Committee, London School of Hygiene and Tropical Medicine (REC.12009). Individual written informed consent was obtained from all participants. For women who were unable to read or write, an impartial witness was present during consent procedures who signed the consent form to confirm that the participant had understood trial procedures and other information provided.[14] For individuals who were unable to write, a witnessed thumbprint was also provided. The Trial Steering Committee oversaw conduct of the trial. An independent Data and Safety Monitoring Board reviewed outcome data during the trial and approved the statistical analysis plan before unblinding of the data.

Participants

Trial clusters were selected in consultation with provincial health authorities, church health services, health facility staff, and other local stakeholders. Participants were eligible for inclusion if they were aged 16 years or older, attending an antenatal clinic at 26 weeks' gestation or earlier (confirmed by obstetric ultrasound), living within approximately 1 h drive of a study clinic, and were able to provide reliable contact details. Women with severe anaemia (haemoglobin <60 g/L with symptoms) or living with a disability that prevented participation or comprehension were excluded.

Randomisation and masking

The unit of randomisation was a primary health-care facility and its catchment communities. Ten geographically distinct clusters were assigned (1:1) to receive either the intervention or control (standard care) in the first phase of the trial. Following an interval (washout period) of 2–3 months at the end of the first phase, each cluster crossed over to the other group.[9]

Randomisation was stratified by province. Within each province, key health and community representatives were invited to a pre-initiation trial event. The Chief Investigator (AJBV) placed identical sealed opaque envelopes containing each possible cluster allocation sequence for that province in a traditional woven string bag (called a *bilum*). A senior independent stakeholder selected one envelope and revealed the allocation to the audience.

We minimised the risk of selection bias that could have arisen if women enrolled in larger centres differed systematically than from those at smaller clinical centres by providing resources and logistics to optimise accrual across all sites. We minimised attrition bias in the ascertainment of trial outcomes by using established community-based strategies to optimise clinical follow-up. To minimise performance bias, we used the same procedures for routine antenatal care in all facilities.[15] Detection bias was minimised by blinding assessments wherever possible. Trial investigators did not ascertain primary outcomes. Preterm birth is an objective outcome defined by gestational age assessed at enrolment and date of birth. Birthweight was measured on digital scales by clinical staff at participating health facilities who were blinded to trial allocation.

Individual participants were informed about the trial group only after completing informed consent procedures. Trial investigators were blinded to participants' outcomes until the trial database was locked. Statistical analyses were blinded.

Procedures

Women in both trial groups received antenatal care according to Papua New Guinea national guidelines,[15] including a clinical interview and examination, HIV and syphilis counselling and testing, haemoglobin estimation, urinalysis for protein and glucose, a rapid diagnostic test for malaria (if clinically indicated), sulfadoxine-pyrimethamine for malaria prevention, iron and folate supplementation, and tetanus toxoid immunisation. In addition to standard care, we conducted an obstetric ultrasound examination at enrolment to confirm eligibility and gestational age. We followed international best practice, which states that if estimated gestation by reported date of last menstrual period and ultrasound examination differ by more than a prespecified number of days (depending on the trimester of pregnancy), then gestational age according to ultrasound examination should be used.[9,16,17] We carried out a postnatal follow-up visit as soon as possible after birth.

In the intervention group, a same day point-of-care testing and treatment intervention was implemented as

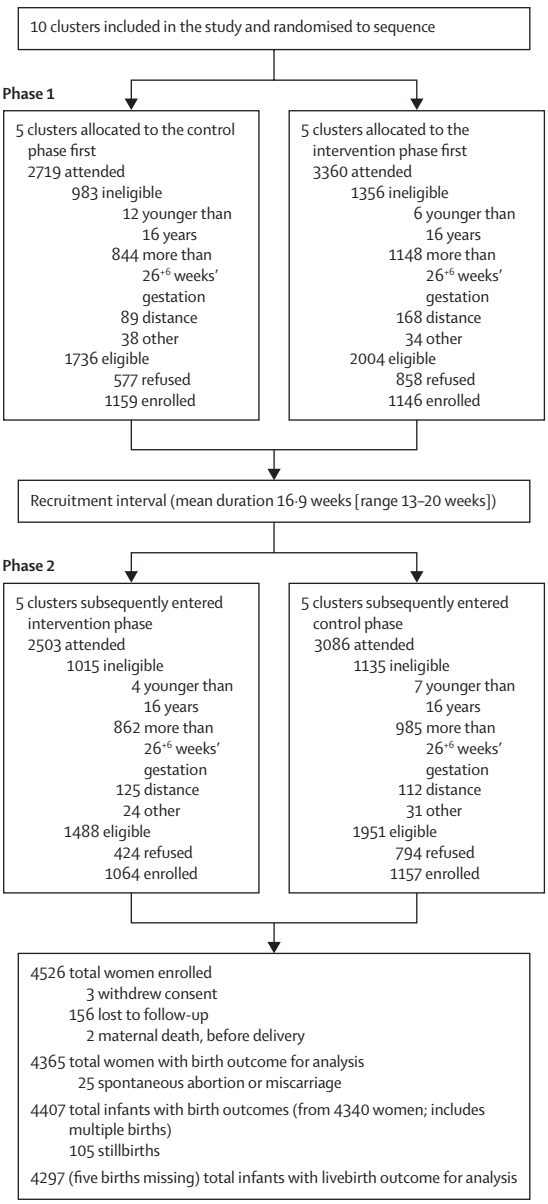

Figure: **Trial profile**

follows: women provided two self-collected vaginal specimens at the clinic, at enrolment, 4 weeks later, and at 34–36 weeks' gestation. One swab was tested for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis* using the GeneXpert platform (Cepheid, Sunnyvale, CA, USA). The other swab was tested for bacterial vaginosis (BVBlue, Gryphus Diagnostics, Knoxville, TN, USA).[18,19] All women with a positive test result were offered same-day directly observed treatment[15,20] and options for male partner treatment.[9]

In the control group, women received symptom-based sexually transmitted infection (STI) syndromic management at all clinic visits. As per Papua New Guinea national guidelines, no vaginal swabs for laboratory testing were taken.[15,20] Residual urinalysis specimens collected at enrolment, 4 weeks later, and at 34–36 weeks' gestation were retained and tested off-site in batches for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis* on the GeneXpert platform. The use of residual urine samples allowed aetiological STI diagnosis in the control group, while keeping procedures as close to standard care as possible. We provided STI treatment and counselling to women and their husband or partner at the study postnatal visit, according to test results.

The treatment regimens for STI treatment and malaria prevention used in the trial were based on published guidelines (appendix 1 p 1).[15,20]

We collected sociodemographic, behavioural, and clinical data using paper-based case record forms and, following onsite accuracy checks and verification, electronically scanned and uploaded them into a database (Oracle; Austin, TX, USA) located on password-protected servers at the University of New South Wales, Sydney, Australia.[9]

Outcomes

The primary outcome was a composite measure of the proportion of women and their newborn babies in each trial group who experienced preterm birth, low birthweight, or both, and were assessed at participating health facilities or in the community according to the place of childbirth. Preterm birth was defined as livebirth before 37 weeks' gestational age, estimated by ultrasound examination at 26 weeks' gestation or earlier, adjusted according to the reported date of the last menstrual period. Low birthweight (<2500 g) was measured within 72 h of birth using electronic medical-grade infant weighing scales calibrated to within 10 g.[9]

Secondary clinical outcomes were mean birthweight, proportion of women who experienced premature rupture of membranes (membrane rupture before onset of labour), and number of curable STIs diagnosed and treated. Other secondary outcomes that were reported separately were intervention acceptability, cost-effectiveness, health system requirements, and neonatal eye infection and pneumonia in a subgroup of 2000 newborn babies followed up at 1–2 weeks and 4–6 weeks postnatally.[9] Serious adverse events recorded throughout the trial were maternal death, hospitalisation, spontaneous abortion or miscarriage, stillbirth, early neonatal death, late neonatal death, congenital anomaly, birth defect, or domestic violence requiring medical attention.[9]

Statistical analysis

Sample size requirements were based on our earlier studies in Papua New Guinea.[21–24] The proportion of pregnancies resulting in preterm birth and low birthweight was estimated to be 15% each, and 18% combined. Published studies[3,25] suggested that effective treatment could reduce this combined proportion by up

	Intervention group (N=2210)	Control group (N=2316)
Age (years)		
Mean	25·5 (5·9)	25·9 (5·7)
Median	25 (21–29)	25 (22–29)
Age group, years		
<20	274 (12·4%)	234 (10·1%)
20–24	784 (35·5%)	842 (36·4%)
25–29	618 (28·0%)	662 (28·6%)
≥30	528 (23·9%)	572 (24·7%)
Missing	6 (<1%)	6 (<1%)
Parity		
P0	929 (42·0%)	893 (38·6%)
P1	482 (21·8%)	542 (23·4%)
P2	353 (16·0%)	378 (16·3%)
P3	227 (10·3%)	252 (10·9%)
P4	121 (5·5%)	134 (5·8%)
P≥5	98 (4·4)	117 (5·1)
Marital status		
Single	110 (4·4%)	88 (3·8%)
Married	2054 (92·9%)	2187 (94·4%)
Separated, divorced, or widowed	28 (1·3%)	30 (1·3%)
Missing	18 (1·0%)	11 (1·0%)
Highest educational level achieved		
Did not attend primary school	150 (6·8%)	174 (7·5%)
Attended primary school only	1065 (48·2%)	1137 (49·1%)
Completed primary school and attended high school	621 (28·1%)	632 (27·3%)
Completed high school and attended tertiary education	374 (16·9%)	373 (16·1%)
Employment (multiple responses permitted)		
Household duties	1861 (84·2%)	1918 (82·8%)
Subsistence farming	1412 (63·9%)	1339 (57·8%)
Market selling	1428 (64·6%)	1382 (59·7%)
Salaried work	204 (9·2%)	226 (9·8%)
Student	56 (2·5%)	64 (2·8%)
Age at sexual debut		
Mean	19·6 (3·2)	19·9 (3·3)
Median	19 (18–21)	19 (18–22)
Number of lifetime sexual partners		
Mean	1·8 (1·6)	1·6 (1·1)
Median	1 (1–2)	1 (1–2)
Number of partners in past 12 months		
1 partner	1342 (60·7%)	1481 (63·9%)
2 partners	502 (22·7%)	486 (21·0%)
≥3 partners	350 (15·8%)	312 (13·5%)
Missing	16 (1·0%)	37 (1·6%)
Vaginal sex in past 4 weeks		
Yes	1436 (65·0%)	1301 (56·2%)
No	770 (34·8%)	1012 (43·7%)
Missing	4 (<1·0%)	3 (<1·0%)

(Table 1 continues in next column)

	Intervention group (N=2210)	Control group (N=2316)
(Continued from previous column)		
Condom use at last vaginal sex		
Yes	59 (2·7%)	70 (3·0%)
No	2144 (97·0%)	2241 (96·8%)
Missing	7 (<1·0%)	5 (<1·0%)
Smoking		
Never smoked	1319 (59·7%)	1452 (62·7%)
Currently smoke	399 (18·1%)	419 (18·1%)
Stopped smoking before or when became pregnant	489 (22·1%)	443 (19·1%)
Missing	3 (<1·0%)	2 (<1·0%)
Alcohol consumption		
Never drank alcohol	1688 (76·4%)	1827 (78·9%)
Currently drink alcohol	64 (2·9%)	89 (3·8%)
Stopped drinking alcohol before or when became pregnant	455 (20·6%)	397 (17·1%)
Missing	3 (<1·0%)	3 (<1·0%)
Betel nut consumption		
Never chewed betel nut	232 (10·5%)	258 (11·1%)
Currently chewing betel nut	1936 (87·6%)	2013 (86·9%)
Stopped chewing betel nut before or when became pregnant	41 (1·8%)	40 (1·7%)
Missing	1 (<1·0%)	5 (<1·0%)
BMI (kg/m²)		
Median	23·0 (21·1–25·1)	22·8 (21·0–24·9)
Mid upper arm circumference (cm)		
Mean	25 (3·2)	25 (3·1)
Median	23 (23–27)	25 (23–27)
Gestation age at enrolment (weeks)		
Mean	19·9 (4·7)	19·5 (5·1)
Median	20 (17–23)	20 (17–23)
Haemoglobin (g/L)		
Mean	92 (16)	93 (17)
Median	93 (81–103)	94 (82–105)
<100 g/L	700/2210 (31·7%)	778/2316 (33·6%)
Malaria (symptomatic women only)		
Negative	125 (5·7%)	132 (5·7%)
Positive	55 (2·5%)	54 (2·3%)
Not indicated	2030 (91·9%)	2129 (92·0%)
Syphilis		
Non-reactive rapid diagnostic test	1857 (84·0%)	1912 (82·6%)
Reactive rapid diagnostic test	311 (14·1%)	383 (16·5%)
Not done or out of stock	42 (1·9%)	21 (1·0%)
HIV		
Negative	2061 (93·3%)	2135 (92·2%)
Positive	12 (1·0%)	5 (<1·0%)
Not done—other*	137 (6·2%)	176 (7·6%)

(Table 1 continues in next column)

	Intervention group (N=2210)	Control group (N=2316)
(Continued from previous column)		
Curable sexually transmitted infections		
Chlamydia trachomatis	533 (24·1%)	506 (21·8%)
Neisseria gonorrhoeae	130 (5·9%)	110 (4·7%)
Trichomonas vaginalis	520 (23·5%)	407 (17·6%)
Bacterial vaginosis (intervention group only)	734 (33·2%)	..
Any of *C trachomatis* or *N gonorrhoeae*	565 (25·6%)	530 (22·9%)
Any of *C trachomatis, N gonorrhoeae, or T vaginalis*	858 (38·8%)	753 (32·5%)
Any of *C trachomatis, N gonorrhoeae, T vaginalis,* or bacterial vaginosis (intervention group only)	1276 (57·7%)	..

Data are n (%), median (IQR), mean (SD), or n/N (%). *Eg, out of stock or counsellor unavailable.

Table 1: **Baseline characteristics of women enrolled into the trial (N=4526)**

to 45% among individuals with an STI, meaning a relative reduction of around 23% if around half of pregnant women have *C trachomatis, N gonorrhoeae, T vaginalis,* or bacterial vaginosis.[21] Assuming α=0·05, β=0·20 (80% power), and intra-cluster correlation coefficient of 0·003, we would require eight clusters of 200 women per phase and 3200 in total. To allow for the risk that a cluster might not complete the trial, and for loss to follow-up for the primary outcome, we planned to enrol 4600 women (ten clusters of 230 women per cluster in each phase).[9]

We adapted statistical methods for a cluster randomised crossover trial in accordance with current best practice[26] and conducted intention-to-treat analysis based on the cluster level summaries. All clusters and all participants with a recorded outcome were included in the primary analysis, and analysed according to the treatment group to which they were randomised. All analyses accounted for clustering, incorporating sources of variation between individuals within each phase, between clusters, and between phases. Briefly, we first considered estimates based on crude averages of cluster-level summaries and referred to them as the observed proportions of events in each cluster. These estimates were calculated by dividing the number of individuals with the outcome of interest within each cluster by the total number of individuals per cluster. We then calculated the mean of these proportions in each study group; these means were used to estimate risk difference and risk ratio to assess the intervention effect, and their 95% CIs were calculated using the cluster means. We used individual-level data and evaluated the effectiveness of the intervention on birthweight as a continuous measurement. We used a linear mixed model after accounting for clustering effects using a random-effect term, and intervention and phase indicators were fitted as fixed effects using a normal distribution and an identity link function. We report effect sizes that were unadjusted for covariates for the primary analysis, as per our published protocol and statistical analysis plan.[9]

The primary outcome was calculated as a proportion with 95% CIs that accounted for clustering. Risk ratios for intervention versus control were calculated (with 95% CIs) incorporating variability between clusters in intervention effects and intrinsic binomial variation in the cluster period proportions. We conducted planned subgroup analyses of the primary outcome among women with *C trachomatis, N gonorrhoeae, T vaginalis,* or any of these STIs at enrolment and, as part of safety reporting, the proportion of women who experienced spontaneous abortion or miscarriage, stillbirth, or early neonatal death. All planned subgroup analyses are listed in our published statistical analysis plan.[9] Prespecified subgroup analyses of the primary outcome among women who tested positive for syphilis will be reported separately. All statistical analyses were done using Stata (version 14.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Between July 26, 2017, and Aug 30, 2021, 11 668 women attended a first antenatal clinic visit, of whom 7179 (61·5%) were eligible, and 4526 of 7179 (63·0%) enrolled (figure). The proportion of eligible women enrolled in the intervention (2210 [63·3%] of 3492 women) and control (2316 [62·8%] of 3687 women) groups were comparable. COVID-19-related disruptions halted enrolment in one trial cluster, resulting in a slightly smaller sample size than planned (4526 [98·4%] of 4600 women). Primary and secondary outcome data collection were completed on March 9, 2022, data entry was completed in all clusters on June 30, 2022, and data validation and statistical analyses were completed on April 20, 2023. Around 90% (4066 of 4526 women) attended a scheduled antenatal follow-up visit at 4 weeks after enrolment, and 78·8% (3565 of 4526 women) attended at 34–36 weeks' gestation, with comparable retention in each group (apprendix 1, p 3). Birth outcome data were available on 4365 (96·4%) of 4526 women enrolled. Primary outcome data were available for 4297 (94·9%) newborn babies of 4526 women enrolled.

There were no substantial differences in baseline sociodemographic characteristics of women in the intervention and control groups (table 1). The proportion of women with *T vaginalis* (23·5% [520 of 2210 women] *vs* 17·6% [407 of 2316 women]) and women with any of *C trachomatis, N gonorrhoeae,* or *T vaginalis* (38·8% [858 women] *vs* 32·5% [753 women]) were higher in the intervention group than the control group at enrolment. The proportion of women with a reactive test for syphilis was higher in the control group than the intervention group (16·5% [383 of 2316] *vs* 14·1% [311 of 2210]).

	Outcomes		Estimated mean difference (based on cluster level summaries)		Estimated risk ratio (based on cluster level summaries)	
	Intervention group P_1	Control group P_0	P_1–P_0 (95% CI)	p value	RR=P_1/P_0 (95% CI)	p value
Number of clusters	10	10	..	..	..	..
% preterm or low birthweight, or both						
Overall proportions	401/2103 (19·1%)	390/2194 (17·8%)	..	..	..	..
Mean of cluster proportions	18·8% (4·7%)	17·8% (6·7%)	1·0% (–4·5 to 6·4)	0·71	1·06 (0·78 to 1·42)	0·67
% preterm						
Overall proportions	178/2103 (8·5%)	168/2194 (7·7%)	..	..	..	..
Mean of cluster proportions	8·2% (3·2%)	7·7% (1·8%)	0·5% (–1·9 to 3·0)	0·65	1·07 (0·79 to 1·45)	0·61
% low birthweight						
Overall proportions	330/2017 (16·4%)	326/2084 (15·6%)	..	..	..	..
Mean of cluster proportions	16·2% (3·2%)	15·9% (7·9%)	0·3% (–5·8 to 6·4)	0·92	1·02 (0·70 to 1·49)	0·90
Mean birthweight (g)*	2960 (58)	2990 (67)	–30	0·46	..	..
% premature rupture of membranes						
Overall proportions	224/2161 (10·4%)	181/2246 (8·1%)	..	..	..	..
Mean of cluster proportions	10·5% (2·8%)	8·0% (3·8%)	2·5% (–1·3 to 5·5)	0·18	1·31 (0·91 to 1·90)	0·19

Data are mean (SD), or n/N (%), unless stated otherwise. *p value from the mixed-effect model for intervention effect (taking into account period effect)=0·485.

Table 2: **Primary and secondary clinical outcomes**

More than half of women in the intervention group (1276 [57·7%] of 2210 women) had any of *C trachomatis, N gonorrhoeae, T vaginalis,* or bacterial vaginosis at enrolment. The number of women with symptomatic, rapid test positive malaria infection at enrolment was the same in each group (2·5% [55 of 2210 women] *vs* 2·3% [54 of 2316 women; table 1).

The proportion of preterm birth, low birthweight, or both among women in the intervention group was 18·8% (SD 4·7%) and, in the control group, it was 17·8% (SD 6·7%; risk ratio [RR] 1·06, 95% CI 0·78–1·42; p=0·67; table 2; appendix 1 p 2 for cluster-specific RRs). There was no group difference in the proportion of preterm birth alone (8·2% *vs* 7·7%; 1·07, 0·79–1·45; p=0·61) or low birthweight alone (16·2% *vs* 15·9%; 1·02, 0·70–1·49; p=0·90).

Mean birthweight was 2960 g in the intervention group and 2990 g in the control group. The proportion of premature rupture of membranes among women in the intervention group was 10·5% (SD 2·8%), and 8·0% (3·8%) in the control group (RR 1·31, 95% CI 0·91–1·90; p=0·19; table 2).

Of 858 women with *C trachomatis, N gonorrhoeae,* or *T vaginalis* in the intervention group at enrolment, 98·6% (846 of 858 women) received same-day treatment. In the control group, of 753 women with at least one of these infections at enrolment (detected retrospectively in stored urine samples), 15·9% (120 of 753 women) received syndromic treatment (appendix 1 p 3). The proportions of women with any of *C trachomatis, N gonorrhoeae,* or *T vaginalis* were 68·0% lower at 4 weeks post-enrolment and 74·5% lower at 34–36 weeks' gestation in the intervention group compared with 20·3% lower at 4 weeks post-enrolment and 28·3% lower at 34–36 weeks' gestation in the control group. The proportion of women with *C trachomatis* in the intervention group was 24·1% (533 of 2210 women) at enrolment and 4·1% (81 of 2000 women) at 4 weeks post-enrolment (83·0% reduction), and in the control arm, it was 21·8% (506 of 2316 women) at enrolment and 9·6% (197 of 2055 women; 56·2% reduction) at 4 weeks post-enrolment. *N gonorrhoeae* and *T vaginalis* were substantially reduced at 4 weeks post-enrolment and 34–36 weeks' gestation in the intervention group only. There were around 50 new cases of any of *C trachomatis, N gonorrhoeae,* or *T vaginalis* in each trial group at 4 weeks post-enrolment and at 34–36 weeks' gestation (appendix 1 p 3). Antibiotic treatment in the 7 days before scheduled visits was uncommon (appendix 1 p 4). Around 90% of women in both the intervention group (2016 [91·2%] of 2210 women) and the control group (1996 [86·2%] of 2316 women) received sulfadoxine–pyrimethamine for malaria prevention at enrolment, around 80% 4 weeks later (1665 [83·3%] of 2000 women and 1634 [79·5%] of 2055 women), and around 60% at 34–36 weeks' gestation (1196 [66·4%] of 1801 women and 1020 [58·3%] of 1749 women; appendix 1, p 4).

The primary outcome was 53% lower among women with *N gonorrhoeae* at enrolment in the intervention group than the control group (16·2% [SD 11·9%] *vs* 34·2% [19·8%]; RR 0·47, 95% CI 0·25–0·88; p=0·0242; table 3). There was no group difference in the primary outcome among women with *C trachomatis* or *T vaginalis* at enrolment.

A total of 1052 serious adverse events were reported among 929 women, none of which were considered related to the intervention or trial procedures (table 4). In the intervention group, 505 women reported a total of

	Outcomes		Estimated mean difference (based on cluster level summaries)		Estimated risk ratio (based on cluster level summaries)	
	Intervention group P_1	Control group P_0	P_1–P_0 (95% CI)	p value	RR=P_1/P_0 (95% CI)	p value
Number of clusters	10	10	..	..	..	..
Among women tested positive for *Neisseria gonorrhoeae*						
Overall proportions	22/121 (18·2%)	33/101 (32·7%)	..	..	..	..
Mean of cluster proportions	16·2% (11·9%)	34·2% (19·8%)	–18·0% (–33·4 to –2·6)	0·0274	0·47 (0·25 to 0·88)	0·0242
Among women tested positive for *Chlamydia trachomatis*						
Overall proportions	98/496 (19·8%)	103/474 (21·7%)	..	..	..	..
Mean of cluster proportions	20·5% (5·0%)	21·7% (8·3%)	–1·2% (–7·6 to 5·2)	0·69	0·94 (0·70 to 1·27)	0·65
Among women tested positive for *Trichomonas vaginalis*						
Overall proportions	96/487 (19·7%)	78/387 (20·2%)	..	..	..	..
Mean of cluster proportions	19·9% (7·7%)	20·3% (7·5%)	0·4% (–6·7 to 7·5)	0·91	1·02 (0·72 to 1·46)	0·88
Among women who tested positive for any of *N gonorrhoeae, C trachomatis, or T vaginalis*						
Overall proportions	163/808 (20·2%)	141/713 (19·8%)	..	..	..	..
Mean of cluster proportions	20·7% (5·9%)	19·8% (7·5%)	0·8% (–5·6 to 7·2)	0·79	1·04 (0·76 to 1·43)	0·75

Data are mean (SD), or n/N (%), unless stated otherwise.

Table 3: **Prespecified subgroup analyses of the primary outcome among women with *Neisseria gonorrhoeae, Chlamydia trachomatis,* or *Trichomonas vaginalis* at baseline**

	Intervention group (N=2210)	Control group (N=2316)	Total (N=4526)
Hospitalisations—maternal*	250 (11·3%)	197 (8·5%)	447 (9·9%)
Hospitalisations—neonatal†	195 (8·8%)	167 (7·2%)	362 (8·0%)
Domestic violence requiring medical attention	2 (<1·0%)	2 (<1·0%)	4 (<1·0%)
Maternal death	5 (<1·0%)	6 (<1·0%)	11 (<1·0%)
Miscarriage‡	7 (<1·0%)	18 (1·0%)	25 (1·0%)
Stillbirth‡	56 (2·5%)	49 (2·1%)	105 (2·3%)
Early neonatal death (<7 days of life)‡	33 (1·5%)	23 (1·0%)	56 (1·2%)
Late neonatal death (>7 days but <28 days of life)	2 (<1·0%)	9 (<1·0%)	11 (<1·0%)
Congenital anomaly or birth defect	16 (1·0%)	15 (1·0%)	31 (1·0%)
Total serious adverse event reported§	566 (25·6%)	486 (21·0%)	1052 (23·2%)

*Proportion of women hospitalised in cluster-adjusted analysis was 10·3% (SD 2·2) in the intervention group versus 8·1% (2·4) in the control group (RR 1·27, 95% CI 1·00–1·61; p=0·111). †Proportion of newborn babies hospitalised in cluster-adjusted analysis was 8·8% (SD 1·4) in the intervention group versus 6·9% (1·9) in the control group (RR 1·28, 95% CI 0·96–1·69; p=0·150). ‡Proportion of pregnancies complicated by miscarriage, stillbirth, or early neonatal death after accounting for variations across the cluster level proportions was 4·1% (SD 1·4) in the intervention group versus 3·3% (1·3) in the control group (RR 1·23, 95% CI 0·87–1·74; p=0·270). §1052 serious adverse events reported among 929 participants.

Table 4: **Safety data**

566 serious adverse events. In the control group, 424 women reported 486 serious adverse events. There was no difference between trial groups in the proportion of maternal or neonatal hospitalisations (table 4), or the proportion experiencing a protocol-defined medically significant serious adverse event (miscarriage, stillbirth, or early neonatal death: 4·1% [SD 1·4%] *vs* 3·3% [1·3%]; RR 1·23, 95% CI 0·87–1·74; p=0·27; table 4; appendix 1 p 5). There was no difference between the trial groups for all adverse maternal and perinatal outcomes combined for preterm birth, low birthweight, premature rupture of membranes, miscarriage, stillbirth, or early neonatal death (28·8% [3·9%] *vs* 26·4% [8·0%]; 1·09, 0·88–1·36; p=0·41; appendix 1 p 5).

In unplanned post-hoc subgroup analyses, there was no difference in the primary outcome among women who enrolled at 20 weeks' gestation or earlier (20·3% [SD 4·3%] in the intervention group *vs* 17·2% [8·3%] in the control group for preterm birth or low birthweight, or both; RR 1·18, 95% CI 0·8–1·7; p=0·35) compared with those who enrolled after 20 weeks' gestation (17·7% [6·7%] *vs* 18·3% [6·5%]; 0·97, 0·7–1·4; p=0·94; appendix 1 p 6). There was no difference in the primary outcome among nulliparous women (24·9% [4·6%] in the intervention group *vs* 24·6% [9·0%] in the control group), or multiparous women (14·6% [5·3%] *vs* 13·9% [6·3%]; appendix 1 p 7).

Discussion

In this cluster randomised crossover trial, point-of-care testing and treatment of *C trachomatis, N gonorrhoeae, T vaginalis,* or bacterial vaginosis during pregnancy did not reduce the primary outcome of preterm birth, low birthweight, or both, compared with the standard of care. In a prespecified subgroup analysis, the primary outcome was more than halved among women with *N gonorrhoeae* at their first antenatal clinic visit in the intervention group compared with women in the control group.

This study was, to our knowledge, the first randomised trial in any setting to investigate whether screening and treatment of curable STIs and bacterial vaginosis translates into a reduction in risk of adverse birth outcomes.[8] The absence of an overall difference in the primary outcome in our trial, in which allocation to the intervention and control groups was randomised, suggests that at least part of the association between these

conditions and adverse birth outcomes found in observational studies could have been due to confounding by unadjusted or unmeasured factors. The reduction in the primary outcome among women treated for *N gonorrhoeae* was consistent with observational studies.[2] It is possible that *N gonorrhoeae* in pregnancy is a stronger risk factor for adverse birth outcomes than other curable STIs or bacterial vaginosis, as could be the case for pelvic inflammatory disease.[27] Systematic reviews of observational studies suggest that the evidence supporting an association between *N gonorrhoeae* and preterm birth, low birthweight, and other adverse birth outcomes[2] could be less heterogeneous than that for *C trachomatis*,[1] *T vaginalis*,[3] or bacterial vaginosis.[6] The certainty of the overall evidence for all systematic reviews was, however, low or very low for all outcomes. Treatment trials have reported findings that also contrast with observational studies. Treatment for bacterial vaginosis and urinary tract infections in pregnancy did not reduce preterm birth in Bangladesh.[28] Treatment of bacterial vaginosis early in pregnancy did not reduce spontaneous miscarriage, preterm birth, or both, in France.[29] The addition of azithromycin to intermittent malaria prevention regimens reduced preterm birth and low birthweight in Malawi[30] but did not confer additional benefits on adverse birth outcomes in two recent trials in four countries in sub-Saharan Africa,[31,32] despite substantial reductions in *C trachomatis* infection observed in one trial (the IMPROVE trial).[32] Two large-scale randomised trials to reduce preterm birth, low birthweight, and other adverse birth outcomes are ongoing and will answer related questions with different study designs: a trial of metronidazole plus sulfadoxine–pyrimethamine for malaria, bacterial vaginosis, and STIs in pregnancy (the ASPIRE trial) in Zambia, and a trial of point-of-care testing and treatment of *N gonorrhoeae, C trachomatis*, and *T vaginalis* in South Africa.[33]

There was a substantial reduction in *C trachomatis,* but not *N gonorrhoeae* or *T vaginalis* among women in the control group at 4 weeks post-enrolment and at 34–36 weeks' gestation, which could have been due to a combination of factors. High uptake of sulfadoxine–pyrimethamine for malaria prevention at enrolment and antenatal follow-up could have played a role[34] because sulphonamide antibiotics are known to have some activity against *Chlamydia* spp.[35] In the IMPROVE trial,[32] *C trachomatis* was reduced from 14% at enrolment to 2% at full term among women randomised to the sulfadoxine–pyrimethamine group, to 10% in the dihydroartemisinin–piperaquine group, and to 7% in the dihydroartemisinin–piperaquine plus azithromycin group. Repeated doses of sulfadoxine–pyrimethamine during the antenatal period for malaria prevention could have had a greater effect on chlamydia infection than a single dose of azithromycin administered at enrolment, particularly when risk of re-infection was considered high due to incomplete or lack of partner contact tracing and treatment.[32] In addition to sulfadoxine–pyrimethamine exposure in our trial, 16·2% (82 of 506 women) with *C trachomatis* at enrolment, 12·2% (24 of 197 women) at 4 weeks post-enrolment, and 7·8% (9 of 116 women) at 34–36 weeks' gestation received azithromycin by syndromic management. Antibiotic exposure between study visits was uncommon and unlikely to have contributed. Spontaneous clearance of untreated genital *C trachomatis*[36–38] might have contributed, but clearance has also been reported for other curable STIs,[39–41] so it is unclear why we might have observed this effect for *C trachomatis* only. Findings from trials of STI point-of-care testing and treatment in high-burden countries where malaria is not endemic and sulfadoxine–pyrimethamine is not provided as part of routine antenatal care, such as South Africa, will be particularly valuable in helping to resolve these issues.[33]

Our trial had several strengths. The trial was conducted according to published protocols[9] and international standards and guidelines,[15] with rigorous trial monitoring and scientific oversight,[12] and achieved almost complete follow-up among over 4500 pregnant women and their babies. The crossover design provided both statistical efficiency and an opportunity for all clusters to receive the intervention at some point during the trial. The point-of-care intervention was highly effective in detecting and treating STIs compared with syndromic management under standard antenatal care, with 98·6% (846 of 858 women) versus 15·9% (120 of 753 women) of STIs successfully treated at enrolment, and substantial and sustained reductions in STIs during clinical follow-up in the intervention group. The trial was carried out in a high-burden LMIC setting in which both the prevalence of curable STIs or bacterial vaginosis, or both, in pregnancy and rates of preterm birth, low birthweight, and other adverse outcomes were high.

For more on the **ASPIRE trial** see https://clinicaltrials.gov/ct2/show/NCT04189744

The trial also had limitations. The first antenatal visit, at a median of 20 weeks' gestation, might have been too late to prevent adverse birth outcomes. Observational studies suggest that the risk of preterm birth and other adverse outcomes associated with bacterial vaginosis and possibly other curable STIs might be higher following exposure early in pregnancy (less than 16–20 weeks' gestation) than in the second or third trimester.[5,42,43] In post-hoc subgroup analyses however, we found no difference in the primary outcome among women who enrolled at 20 weeks' gestation compared with those who enrolled after 20 week's gestation (appendix 1 p 6). The prevalence of *N gonorrhoeae* (around 5% [240 of 4526 women]) was lower than in our earlier studies (up to 14%),[21,22,24] which might have reduced statistical power for our main primary outcome analysis. For ethical and logistical reasons, we did not test self-collected specimens in the control group for bacterial vaginosis. We cannot therefore confirm that the prevalence of bacterial vaginosis at enrolment was comparable between trial groups, but it is likely, given that other variables were well-balanced. We

cannot, however, examine bacterial vaginosis in subgroup analyses. It also meant that we tested different biological specimens in each trial group, which could have led to an underestimation of STI prevalence in the control group. The sensitivity and specificity of the assays using urine and genital specimens have, however, been shown to be comparable.[44,45]

In conclusion, point-of-care testing and same-day treatment of *C trachomatis, N gonorrhoeae, T vaginalis,* and bacterial vaginosis did not result in lower rates of preterm birth, low birthweight, or other adverse maternal and perinatal outcomes compared with standard care. Among women with *N gonorrhoeae,* there was a substantial reduction in preterm birth, low birthweight, or both. This finding requires confirmation before antenatal testing and treatment of gonorrhoea can be considered for inclusion in STI guidelines or maternal and child health programmes. Efforts to improve maternal and perinatal health in all income settings should focus on proven interventions until the role and potential effect of STI screening and treatment in pregnancy are confirmed.[46–48] These interventions include delivery of an integrated package of quality antenatal care at 12, 20, 26, 30, 34, 36, 38, and 40 weeks' gestation as recommended by WHO and scale-up of evidence-based strategies, including education for smoking cessation, micronutrient and dietary supplementation, screening and treatment of syphilis and asymptomatic bacteriuria, and malaria prevention, as recommended in a recent *Lancet* Series.[48] Our hypothesis that sulfadoxine–pyrimethamine for malaria prophylaxis could have played an important role in reducing *C trachomatis* is consistent with the findings of another large-scale randomised trial[32] and warrants further investigation.

Contributors

AJBV, JMK, NL, LMV, WSP, MAR, SGB, CSEH, SL, DMW, HW, LJR, ML, NB, JWB, GK, DB, SNT, SJR, SMG, RJG, and RWP conceived the study and contributed to the study design. MAR, LMV, AJBV, AM, SGB, LA, and IP-G coordinated clinical implementation, collection of primary and secondary clinical outcome data, and safety reporting. VW led the health economics component of the study, AKH led qualitative research, DMW led laboratory research, CM led health systems research, and NL led the extended neonatal follow-up component. HW provided statistical expertise in the trial design and conducted the primary statistical analysis. All authors contributed to the refinement of the study protocol. AJBV wrote the first draft of the manuscript. All authors contributed to revision of the manuscript and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. HW, MAR, LMV, and NL accessed and verified the underlying data reported in the manuscript.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

See Online for appendix 2

Declaration of interests

The Papua New Guinea Institute of Medical Research (MAR, LMV, AM, LJR, AK-H, JWB, IP-G, ML, LA, PJT, WSP, and AJBV) and the Kirby Institute at the University of New South Wales (MAR, LMV, SGB, HW, AK-H, VW, RJG, JMK, and AJBV) have received subsidised test kits for research from Cepheid (Sunnyvale, CA, USA). All other authors declare no competing interests. All authors declare that neither they or their institutions have received direct funding from industry for this or any other research project.

Data sharing

The study protocol and statistical analysis plan are available in appendix **1** (pp 10, 78). Informed consent and case report forms are available from AJBV upon request. With investigator support, after approval of a proposal and a signed data use agreement, de-identified data from this paper will be available upon reasonable request from AJBV.

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