Sexually Transmitted Infections in Pregnancy: A Narrative Review of the Global Research Gaps, Challenges, and Opportunities

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Background: Sexually transmitted infections (STI), such as chlamydial, gonorrheal, and trichomonal infections, are prevalent in pregnant women in many countries and are widely reported to be associated with increased risk of poor maternal and neonatal outcomes. Synergistic STI management is frequently used in pregnant women in low- and middle-income countries, yet its low specificity and sensitivity lead to both overtreatment and undertreatment. Etiologic screening for chlamydial, gonorrheal, and/or trichomonal infection in all pregnant women combined with targeted treatment might be an effective intervention. However, the evidence base is insufficient to support the development of global recommendations. We aimed to describe key considerations and knowledge gaps regarding chlamydial, gonorrheal, and trichomonal screening during pregnancy to inform future research needed for developing guidelines for low- and middle-income countries.

Methods: We conducted a narrative review based on PubMed and clinical trials registry searches through January 20, 2020, guidelines review, and expert opinion. We summarized our findings using the frameworks adopted by the World Health Organization for guideline development.

Results: Adverse maternal-child health outcomes of potential interest are wide-ranging and vary by country. No completed randomized controlled trials on etiologic screening and targeted treatment were identified. Evidence from observational studies was limited, and trials of presumptive STI treatment have shown mixed results. Subgroups that might benefit from specific recommendations were identified. Evidence on harms was limited. Cost-effectiveness was influenced by STI prevalence and availability of testing infrastructure and high-accuracy/low-cost tests. Preliminary data suggested high patient acceptability.

Discussion: Preliminary data on harms, acceptability, and feasibility and the availability of emerging test technologies suggest that etiologic STI screening deserves further evaluation as a potential tool to improve maternal and neonatal health outcomes worldwide.

The curable sexually transmitted infections (STIs) Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV) are common in pregnant women in many countries. From the *Public Health NetNds, LLC, Seattle, WA; †Department of Disease Control, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom; ‡Department of Pediatric Newborn Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; §Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; ¶Research Unit, Foundation for Professional Development, East London, South Africa; The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; Obstetrics, Gynecology, and Reproductive Biology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; **Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, United Kingdom; Botswana Harvard AIDS Institute, Gaborone, Botswana; Botswana UPenn Partnership, Gaborone, Botswana; Women’s Health Research University, School of Public Health and Family Medicine, University of Cape Town, South Africa; ††Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Botswana, Gaborone, Botswana; †††Department of Obstetrics and Gynecology, Permanente School of Medicine, University of Pennsylvania, Philadelphia, PA; §§Division of Infectious Diseases, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA; ‡‡University of North Carolina Project-China; and §§§Dermatology Hospital of Southern Medical University, Guangzhou, China; ¶¶¶Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea; †††Kirby Institute, University of New South Wales, Sydney, Australia; §§§Division of Infectious Diseases and Global Public Health, University of California, San Diego, San Diego; ††††Pediatric Infectious Disease, David Geffen School of Medicine, and ‡‡‡‡Division of Infectious Diseases and Department of Epidemiology, University of California, Los Angeles David Geffen School of Medicine and Fielding School of Public Health, Los Angeles, CA

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countries. Regional estimates of STI prevalence among pregnant women vary: NG, 1.2% (Latin America) to 4.6% (Southern Africa); CT, 0.8% (Asia) to 11.2% (Latin America); and TV, 3.9% (Latin America) to 24.6% (Southern Africa). Although it is difficult to fully elucidate their relative impact, multiple studies have found associations between these 3 STIs and increased risk of poor maternal and neonatal outcomes (e.g., miscarriage, stillbirth, preterm birth, low birth weight, and mother-to-child HIV transmission).2,6

Few countries recommend routine screening for chlamydial, gonorrheal, or trichomonal infection in pregnant women.7 The World Health Organization (WHO) recommends screening for HIV infection and syphilis8 but has no specific guidelines for other STIs beyond syndromic management, which limits treatment to symptomatic women.8 The frequently asymptomatic nature of STIs in women is well established,10 and syndromic management fails to identify most infected women. Syndromic management has modest sensitivity (40%–75%) and specificity (54%–76%) for detecting chlamydial and/or gonococcal infection.10 A study of HIV-infected pregnant women in South Africa found that only 24% of women who tested positive for a chlamydial, gonococcal, or trichomonal infection had vaginal symptoms (sensitivity), whereas 47% of those with symptoms were negative for all 3 infections (specificity).11 The poor specificity and sensitivity of syndromic management lead to both overtreatment and undertreatment. Poor antimicrobial stewardship may increase the risk of antibiotic resistance.12

The prevalence of and likely adverse outcomes associated with curable STIs in pregnant women suggest that etiologic STI screening of all pregnant women followed by targeted treatment might be beneficial. However, the evidence base around that intervention is insufficient to support the development of global recommendations. The WHO uses a systematic process for developing guidelines13 based, in part, on the Population, Intervention, Comparator, Outcomes (PICO) and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) frameworks for formulating the question and assessing the benefits, harms, and other relevant factors. This narrative review aimed to describe key considerations and knowledge gaps regarding etiologic STI screening during pregnancy using the PICO and GRADE frameworks. We also aimed to identify key studies in progress that may contribute to addressing these knowledge gaps. Our goal was to inform future research contributing to the evidence needed for developing guidelines, particularly for low- and middle-income countries.

**MATERIALS AND METHODS**

This narrative review drew on focused PubMed literature searches, review of WHO and other agency guidelines, and expert opinion. International public health and clinical experts from academia, government, industry, and community-based organizations met on July 14, 2019, in Vancouver, British Columbia, Canada, to frame the initial inquiry. Presentations and discussion during the meeting were the initial source of information for the review. PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and clinical trials registry (https://clinicaltrials.gov and http://www.isrctn.com) searches conducted through January 20, 2020, were developed iteratively based on initial searches using the terms “pregnancy” and “screening,” and “sexually transmitted infections,” “chlamydia,” “gonorrhea,” or “trichomonas.” PubMed searches initially focused on review articles. Reference lists were examined to identify relevant studies. Randomized controlled trials, observational studies, modeling, and qualitative studies related to STI screening/treatment and presumptive STI treatment were examined. We limited our review to studies where the full-text was available in English. Because this was not a systematic review, literatures searches were not conducted systematically, and identified studies and articles were not assessed using standardized criteria.

We presented findings using the PICO and GRADE Evidence to Decision frameworks for health system/public health decisions14 and for tests in clinical practice and public health.15 The population (pregnant women in low- and middle-income countries), intervention (etiologic screening for CT, NG, and/or TV of all pregnant women followed by treatment and case management of those with positive test results), and comparator (syndromic STI management) were predetermined by the authors to delineate the scope of the project. We examined the following GRADE domains: priority/importance, test accuracy, desirable effects (benefits), undesirable effects (harms), resource requirements/cost-effectiveness, equity, acceptability, and feasibility. We did not formally address the quality of available evidence or develop recommendations.

**Findings**

Formulating the key question using the PICO format and selecting outcomes are critical initial steps in the WHO guideline process.17 (Fig. 1) The population, intervention, and comparator were selected a priori by the authors. The adverse outcomes of potential interest were wide-ranging. In meta-analyses of associations between chlamydial infection and adverse pregnancy outcomes, women with chlamydial infection had increased risk of preterm labor/birth, perinatal mortality, stillbirth, intrauterine fetal demise, and newborn low birth weight/birth size compared with those without chlamydial infection.2,4,5 The strength of those associations was attenuated in adjusted analyses and higher-quality studies. Chlamydial infection was found to increase mother-to-child HIV transmission by almost 50% in one study.1 A meta-analysis of trichomonal infection in pregnancy found that infected women had a 41% increased risk of preterm birth and 51% increase in having small for gestational age newborns compared with those without trichomonal infection.2 We did not identify any meta-analyses on maternal gonococcal infection; however, maternal gonococcal infection has been associated with preterm birth, low birth weight, and neonatal eye infections.5

Outcome definitions varied substantially among studies. Outcomes related to birth size have been examined using (1) mean birth weight,16 (2) low birth weight categorization based in weight (<2500 g)17,18 or chest/head circumference,19 or (3) intrauterine growth restriction categorization based on weight or height (<10th percentile).18 In some studies, gestational age was measured using ultrasound, a highly accurate method,20 whereas others used self-reported date of last menstrual period or fundal height, which is less accurate. Other outcome measures had similarly variable definitions across studies.

**Subgroups**

We identified several patient and population-level subgroups that might benefit from specific recommendations. Pregnant women living with HIV infection may have higher STI prevalence21 and a higher risk of poor birth outcomes22 than those without HIV infection, which may modify the effect of screening interventions. In malaria-endemic areas, sulfadoxine-pyrimethamine for intermittent preventive treatment in pregnant women may have some efficacy against CT and NG and associated adverse birth outcomes.23 As such, local implementation of intermittent preventive treatment of malaria23 could also influence the need for specific recommendations. Geographic heterogeneity in health systems and the distribution of STIs and HIV infection1 might indicate other identifiers of subgroups.

Figure 2 summarizes the GRADE Evidence to Decision domains.
Priority/Importance

Improved maternal-child health is a primary target of the UN Sustainable Development Goals,24 and addressing STIs will contribute to meeting these targets. The high prevalence of STIs in pregnant women in low- and middle-income countries is established,1 and treatments are widely available and easy to administer.25,26 However, the magnitude of the impact of treating STIs in pregnant women on poor maternal-child outcomes has not yet been fully elucidated (see Benefits), a necessary step for establishing this area as a priority for intervention.

Benefits and Desirable Effects

The benefits of etiologic screening and treating curable STIs in pregnancy in low- and middle-income countries, apart from syphilis,9 have not been rigorously examined. We did not identify any completed clinical trials on etiologic gonococcal, chlamydial, or trichomonal screening in pregnant women in low- and middle-income countries. Some observational studies from high-income countries support chlamydial screening for improving pregnancy outcomes, but generalizability to low- and middle-income countries is unclear.21 Multiple authors of reviews and meta-analyses reported that insufficient information on confounders, including timing of infection versus testing/treatment, diagnosis of other infections, and other causes of poor maternal-child health outcomes, complicated the interpretation of the available evidence.4,21,27

Trials of presumptive STI treatment in pregnant women to improve maternal/neonatal outcomes provide information that may help elucidate the potential impact of screening and treatment.16,17,19 A cluster randomized controlled trial among ~4000 pregnant women in Uganda19 found that one-time treatment with azithromycin 1 g, cefixime 400 mg, and metronidazole 2 g, which were effective against NG, CT, TV, chancroid, and bacterial vaginosis, as well as several non-STI pathogens, resulted in a 17% decrease in early neonatal deaths and 47% improvement in birth weight compared with syndromic STI management. No effects on stillbirth, maternal deaths, or preterm delivery were identified. Three randomized trials of intermittent treatment of malaria in pregnancy were relevant. In Malawi,17 pregnant women received sulfadoxine-pyrimethamine 1500 mg/75 mg for malaria prevention and azithromycin 1 g, effective against NG, CT, and a variety of non-STI pathogens, during the second and third trimesters or placebo. The authors found a 34% decrease in preterm delivery and a 36% decrease in low birth weight among those who received azithromycin compared with placebo. No differences in perinatal or neonatal mortality were found. A second trial in Malawi16 that compared presumptive azithromycin 1 g + sulfadoxine-pyrimethamine 1000 mg/50 mg during the second and third trimesters with placebo + sulfadoxine-pyrimethamine found no significant impacts on preterm birth, gestational age at birth, mean birth weight, or perinatal death. In Papua New Guinea, presumptive azithromycin 1 g + sulfadoxine-pyrimethamine 1500 mg/75 mg compared with sulfadoxine-pyrimethamine and chloroquine 450 to 600 mg in ~2000 pregnant women resulted in a 26% lower prevalence of low birth weight and 38% lower risk of preterm delivery.28

Insufficient knowledge of the effects of STIs at different gestational ages on birth outcomes limits our ability to optimize the...
timing of etiologic screening and treatment. Administration of presumptive STI treatment in the aforementioned trials varied from one-time treatment at any point during pregnancy \(^{19}\) to monthly treatment during 14 to 26 weeks' gestation until delivery.\(^{17}\) Even if successfully treated, women can be reinfected during pregnancy if partners are not treated. Unfortunately, the effectiveness of partner management in these settings has not been fully examined. In addition, the physiologic mechanisms by which chlamydial, gonococcal, and trichomonal infection impact birth outcomes are complex and unclear.\(^{21,29}\)

Table 1 shows the status of ongoing studies on the effectiveness of etiologic screening and treatment in pregnancy. Randomized controlled trials are underway in China\(^{30}\) and Papua New Guinea,\(^{29}\) and in the planning stages in Botswana and South Africa. A prospective cohort study was recently completed in Brazil.\(^{31}\) A comparative-effectiveness study is in the planning stages in Ethiopia. Studies in Cameroon,\(^{32}\) Kenya, Tanzania, and Malawi,\(^{33}\) Mali,\(^{34}\) and Zambia\(^{35}\) are examining the impact of presumptive STI treatment, usually coupled with preventive malaria therapy.

### Harm and Undesirable Effects

Evidence of harm from etiologic STI screening and treatment studies in low- and middle-income countries was limited. Publications of large clinical trials on presumptive STI treatment have not reported worse birth outcomes compared with control interventions.\(^{16,17,19,28}\) In a trial of presumptive treatment in Papua New Guinea, numbers of adverse events were similar between in the control and intervention arms.\(^ {28}\) In one trial in the United States, treatment of asymptomatic trichomonal infection in pregnant women was associated with increased preterm birth\(^ {36}\) but the selected intervention (two 2-g doses of metronidazole 48 hours apart at 16–23 and 24–29 weeks gestation) was nonstandard.

Harm attributable to antibiotic use during pregnancy is possible; however, STI treatment guidelines were designed to minimize potential harm.\(^{25,26}\) Although increasing antibiotic use can lead to increased antimicrobial resistance, treatment based on etiological test results rather than syndromic management should reduce overtreatment and decrease selective pressure for antimicrobial resistance. However, the effects on STI antimicrobial resistance have not been studied empirically. The presumptive STI treatment trial in Zambia\(^ {35}\) is investigating antimicrobial resistance in the vaginal microbiome.

Sexually transmitted infections are often stigmatized\(^ {12}\) and have been associated with intimate partner violence\(^ {37}\) and fear of intimate partner violence\(^ {38,39}\). However, many studies have reported very high rates of acceptance of partner notification,\(^ {38,41}\) suggesting that concerns about intimate partner violence and stigma around STIs were not a significant barrier for most women. The trial underway in Papua New Guinea\(^ {29}\) is examining intimate partner violence as an adverse event.

### Test Accuracy

Culture-based STI testing requires trained laboratory staff, specialized specimen transport, and equipment, and has long turn-around times and low sensitivity.\(^ {42,43}\) Consequently, STI diagnostics have moved toward molecular testing in many settings.\(^ {42s}\) Although molecular tests also require specialized equipment, some

| Characteristic                   | Assessment                                                                                                                                                                                                 |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Priority/importance             | Maternal-child health is a high global priority; potential impact of etiologic STI screening on improving outcomes is unknown.                                                                             |
| Desirable effects (benefits)    | No randomized controlled trials identified; insufficient observational data; presumptive sexually transmitted infection (STI) treatment trials have had mixed results.                                      |
| Undesirable effects (harms)     | Evidence of harm is limited; presumptive STI treatment trials have not reported worse birth outcomes; concerns for stigma and intimate partner violence; possible risk of preterm birth associated with treatment of asymptomatic trichomonal infection; absence of evidence regarding antimicrobial resistance. |
| Test accuracy                   | Variable; very high with some molecular tests.                                                                                                                                                            |
| Resource requirements           | Insufficient evidence to assess; accurate tests are high-cost; cost-effectiveness impacted by STI prevalence, availability of testing infrastructure, and cost of diagnostic tests.                               |
| Equity                          | Successful interventions could decrease global inequities in reproductive health and maternal and infant health outcomes.                                                                               |
| Acceptability                   | Limited evidence shows high patient acceptability; no evidence on provider acceptability.                                                                                                               |
| Feasibility                     | Limited evidence shows high feasibility in various settings; however, access to and cost of accurate tests is substantial barrier.                                                                      |

Figure 2. Summary of GRADE Evidence to Decision characteristics for etiologic screening and treatment of chlamydial, gonorrheal, and/or trichomonal infection in pregnant women in low- and middle-resource countries.
### Table 1. Key Characteristics of Known Studies in Progress on Nonsyndromic Management of Chlamydia, Gonorrhea, and/or Trichomonas in Pregnant Women in Low- and Middle-Income Countries

| PI (Country) | Study Name, Status | Study Design and Target Sample Size | Study Population and Inclusion Criteria | Study Groups and Interventions | Outcomes |
|--------------|--------------------|-------------------------------------|------------------------------------------|---------------------------------|----------|
| Lee and Berhane (Ethiopia), ENAT, status: not yet recruiting | Pragmatic comparative effectiveness study 2 × 2 factorial design Target sample size: 3600 | Pregnant women with first ANC visit at study health centers at ≤24 wk of gestation based on last menstrual period and/or fundal height | Health center randomization Group 1: strengthening Ethiopian MOH/WHO-recommended nutrition interventions, including iron, folate, iodized salt, and local com soya blend supplement to women with MUAC <23 cm Group 2 (control): nutrition standard of care Individual randomization All groups: routine screening for HIV, syphilis, malaria Group 1: urine culture and AST, molecular CT/NG testing (GeneXpert*), symptomatic women screened for BV (BVBlue*) and TV (OSOM*) at enrollment using self-collected vaginal swabs; treat per test results; deworming in second and third trimesters. Group 2: standard of care screening urine dipstick; syndromic STI management | Primary Birth weight; birth length Secondary Gestational age at delivery; preterm birth; small-for-gestational age; low birth weight; length for age (at birth and 6 mo); weight for age (at birth and 6 mo); gestational weight gain; maternal anemia; stillbirth; cost-effectiveness |
| Klausner, Morroni, Wynn (Botswana), status: preparation | Cluster randomized controlled crossover trial in 2 antenatal clinics 500 women | Pregnant women aged ≥18 y attending first ANC visit who are asymptomatic for CT/NG | Group 1: molecular CT/NG (GeneXpert) screening using self-collected vaginal swabs at first ANC visit and again after 27 wk of gestation; treat per test results; partner treatment provided when possible Group 2 (control): syndromic STI management | Primary Mother-to-child CT/NG transmission; newborn eye infection; newborn pneumonia Secondary Preterm birth; low birth weight; premature rupture of membranes; maternal STI diagnosed and treated; incremental cost-effectiveness ratios, acceptability among women and health care workers |
| PI (Country) [Reference], Study Name, Status | Study Design and Target Sample Size | Study Population and Inclusion Criteria | Study Groups and Interventions | Outcomes |
|------------------------------------------|-----------------------------------|----------------------------------------|--------------------------------|---------|
| Medina-Marino and Klausner (South Africa), status: not yet recruiting | 3-arm (1:1:1) individually randomized-controlled hybrid-effectiveness trial with economic evaluation 2500 women (834 per arm) | Pregnant women aged ≥18 y attending first ANC visit at public antenatal clinic at <20 wk of gestation by ultrasound | All groups: routine screening for HIV and syphilis Group 1: molecular screening for CT, NG, and TV (GeneXpert) at first ANC visit using nurse-collection vaginal swabs; treat per test results; tests-of-cure at 3 wk of posttreatment Group 2: molecular screening and treatment of CT, NG, and TV (GeneXpert) at first ANC visit using nurse-collection vaginal swabs; repeat screening at 30–34 wk of gestation; treat per test results Group 3 (control): syndromic STI management | Change in maternal STI status between first ANC visit and birth; composite outcome: low birth weight, premature rupture of membranes, preterm birth, stillbirth/spontaneous abortion |
| Tang (China), status: recruiting | Individually randomized controlled trial in hospital-based antenatal clinic 200 women | Pregnant women aged 18–45 y at first ANC visit to hospital-based clinic | Group 1: molecular CT/NG screening (Cobas of urine or vaginal swab on enrollment and during 37–40 wk of gestation; azithromycin 1 g as per test results; test of cure at 1 mo, and 3 mo after treatment as needed; patients offered expedited partner therapy Group 2 (control): syndromic STI management; molecular CT/NG testing (Cobas) during 37–40 wk of gestation | Primary Composite outcome: stillbirth, spontaneous abortion, preterm labor, premature rupture of membranes, small for gestational age, low birth weight, infant death, birth defects, neonatal conjunctivitis Secondary Stillbirth; spontaneous abortion; preterm labor; premature rupture of membranes; infant death; birth defects; neonatal conjunctivitis and pneumonia; screening rate; treatment rate; cure rate; partner treatment; costs of testing and treatment |
| Vallely and Pomat (Papua New Guinea), WANTAIF, status: recruiting | Cluster randomized controlled crossover trial in 10 health centers 4600 women | Women aged ≥16 y attending ANC at ≤26 wk of gestation by ultrasound | All groups: HIV and syphilis screening Group 1: molecular CT/NG and TV (GeneXpert) and BV (BVBlue) screening using self-collected vaginal swabs at 4 wk of postenrollment and 34–36 wk of gestation; treat per test results; partner treatment provided when possible Group 2 (control): syndromic STI management | Primary Composite outcome: preterm birth, low birth weight Secondary Premature rupture of membranes; maternal STI diagnosed and treated; incremental cost-effectiveness ratios; health system implementation requirements; acceptability among women and health care workers; newborn eye infection; newborn pneumonia; mother-to-child STI transmission; test accuracy for neonatal infection |
| Presumptive treatment interventions | HIV-negative pregnant women who have not yet started IPTp‡ |
|------------------------------------|----------------------------------------------------------|
| Chico and Chandramohan (Zambia), 35s | 3-arm individually randomized controlled trial |
| ASPIRE, status: recruiting |
| 5436 pregnant women (1812 per group) | All groups: HIV and syphilis screening; syndromic STI management |

**Group 1:** monthly IPTp-SP‡; metronidazole 2 g at first and second ANC visit

**Group 2:** monthly IPTp-DP‡; metronidazole 2 g at first and second ANC visit

**Group 3** (control): monthly IPTp-SP; placebo at first and second ANC

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| Primary | Composite outcome: spontaneous abortion, stillbirth, small for gestational age, low birth weight, preterm delivery, neonatal mortality |
|---------|------------------------------------------------------------------------------------------|
| Secondary | Individual components of composite outcome; maternal length and stunting; clinical malaria; malaria parasitemia; placental malaria; maternal anemia; congenital anemia; congenital malaria; TV and BV treatment efficacy; GI side effects; maternal NG, CT, TV, and syphilis infection; maternal vaginal microbiota; inflammation markers; AST of cultured isolates from vaginal swabs in symptomatic women; intervention costs; maternal and health care preferences for treatments |

| Primary | Plasmodium falciparum peripheral parasitemia; composite outcome: CT, NG, and syphilis infection |
|---------|------------------------------------------------------------------------------------------|
| Secondary | Birth weight; symptomatic malaria; parasite density; placental malaria; maternal anemia; Group B streptococcus colonization; Mycoplasma genitalium infection; composite adverse birth outcome: low birth weight, miscarriage, preterm delivery, small-for-gestational age, congenital anomaly, early neonatal mortality; maternal adherence |

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Dionne-Odom (Cameroon), 32s

PREMISE, status: recruiting

| Individually randomized controlled trial | HIV-positive pregnant women |
|----------------------------------------|----------------------------|
| 310 pregnant women |

**Group 1:** IPTp with daily trimethoprim-sulfamethoxazole DS; monthly azithromycin 1 g × 3 d

**Group 2** (control): IPTp with daily trimethoprim-sulfamethoxazole DS; monthly placebo × 3 d

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Continued next page
| PI (Country) [Reference], Study Name, Status | Study Design and Target Sample Size | Study Population and Inclusion Criteria | Study Groups and Interventions | Outcomes |
|------------------------------------------|-----------------------------------|----------------------------------------|--------------------------------|----------|
| Kotloff (Mali), status: not yet recruiting | 3-cohort individually randomized controlled trial<br>Cohort 1 (rural) 2 × 2 factorial design with mothers and infants randomized separately (groups 1–4)<br>Cohort 2 (rural infant-only): infants randomized (groups 5 and 6)<br>Cohort 3 (urban): mothers/infants randomized in tandem (groups 7 and 8)<br>99,700 participants | Pregnant women attending ANC visit during 13–37 wk of gestation by fundal height and/or maternal report of quickening<br>Unborn infants enrolled with mothers.<br>Cohort 2 infants enrolled during routine vaccination visits | Group 1 and 7 (cohorts 1 and 3, respectively): maternal oral azithromycin 2 g at 2nd- and 3rd-trimester ANC visits and during delivery; infant oral azithromycin at 6- and 14-wk visits<br>Group 2 (cohort 1): maternal oral azithromycin 2 g at 2nd- and 3rd-trimester ANC visits and during delivery; infant placebo at 6- and 14-wk visits<br>Group 3 (cohort 1): maternal placebo at 2nd- and 3rd-trimester ANC visits and during delivery; infant oral azithromycin at 6- and 14-wk visits<br>Groups 4 and 8 (cohorts 1 and 3, respectively): maternal placebo at 2nd- and 3rd-trimester ANC visits and during delivery; infant placebo at 6- and 14-wk visits<br>Groups 5 and 6 (cohort 2): no maternal intervention; infant oral azithromycin at 6- and 14-wk visits versus placebo | Primary<br>Infant mortality from 6 wk to 6–12 mo of age; composite outcome: stillbirth, infant mortality through 6–12 mo of age; Secondary<br>Gestational age at birth; birth weight; incremental cost-effectiveness ratio |
| ter Kuile and Madanitsa (Kenya, Tanzania, Malawi), status: done recruiting | 3-arm (1:1:1) individually randomized controlled trial<br>4680 pregnant women (1560 per group) | HIV-negative pregnant women 16–28 wk of gestation assessed by ultrasound who have not yet started IPTp | Group 1: monthly IPTp-DP; placebo at first ANC visit<br>Group 2: monthly IPTp-DP; azithromycin 2 g at first ANC visit<br>Group 3 (control): monthly IPTp-SP at ANC | Primary<br>Composite outcome: spontaneous abortion, stillbirth, small for gestational age, low birth weight, preterm delivery, neonatal mortality<br>Secondary<br>Individual components of composite measure; neonatal length and stunting; clinical malaria; malaria parasitemia; placental malaria; maternal anemia; congenital anemia; congenital malaria; TV and BV treatment efficacy; GI side effects; maternal NG, CT, TV, and syphilis infection; maternal vaginal microbiota; inflammation markers; intervention costs |
Cohort: women and partners at ANC visits; partner STI diagnosis; sexually transmitted infections (STIs) treated per test results; referral

Prospective cohort

Pregnant women aged >18 yr with sexual activity at least 3 mo prior to antenatal care visit

Etiologic STI screening and treatment has been shown to be highly acceptable to pregnant women in low- and middle-income countries. Given that pregnant women in low- and middle-income countries suffer from a disproportionate burden of STIs and poor maternal/neonatal outcomes, access to etiologic STI screening could help improve health equity around reproductive health and maternal/neonatal outcomes, although the potential magnitude of the impact global etiologic STI screening on health equity is unclear.

Acceptability

Etiologic STI screening and treatment has been shown to be highly acceptable to pregnant women in low- and middle-income countries. In a combined analysis of 1817 pregnant women from 6 different studies, 93.3% of women approached agreed to be tested. Most participants preferred self-collected vaginal swabs
Feasibility

Feasibility must be considered at both the facility and health system levels. Some etiologic STI tests can be conducted at or near the point of care, allowing for decentralized diagnostic services and enabling same-day testing and treatment in low-resource settings.52s The 6-study combined analysis discussed previously reported high levels of feasibility across study sites (overall 96.7%) defined as the percentage of diagnosed women who received treatment.49s The pilot in Papua New Guinea found that etiologic STI testing and treatment could be successfully implemented with same-day treatment.50s In South Africa, 92% of 172 pregnant women with positive STI test results received same-day treatment.51s Although all of those studies used molecular test platforms that require electricity, the findings suggest that etiologic STI screening and treatment can be operationalized in a variety of settings.

Despite successes in research studies, access to test technologies is a substantial barrier to implementing sustainable etiologic screening globally. The WHO has recommended the GeneXpert platform to diagnose tuberculosis in low- and middle-income countries since 2013.53s As a result, many low- and middle-income countries have some laboratory infrastructure to support molecular testing using GeneXpert,53s which rests on ICT for MDR-TB molecular testing. This approach has not been adopted in most STI molecular testing settings, although the Expedit diagnostic system offers promise for decentralized STI screening and treatment of gonococcal, chlamydial, and/or trichomonal infections on pregnancy outcomes in low- and middle-income countries.54s We found that differences in outcome definitions may contribute to future challenges with evaluating the evidence for operational feasibility of etiologic screening in select clinics (Table 1). In Ethiopia, investigators are examining operational feasibility of etiologic screening in select clinics (Table 1). In Ethiopia, investigators are examining operational feasibility of etiologic screening in select clinics (Table 1).

Feasibility

Feasibility must be considered at both the facility and health system levels. Some etiologic STI tests can be conducted at or near the point of care, allowing for decentralized diagnostic services and enabling same-day testing and treatment in low-resource settings.52s The 6-study combined analysis discussed previously reported high levels of feasibility across study sites (overall 96.7%) defined as the percentage of diagnosed women who received treatment.49s The pilot in Papua New Guinea found that etiologic STI testing and treatment could be successfully implemented with same-day treatment.50s In South Africa, 92% of 172 pregnant women with positive STI test results received same-day treatment.51s Although all of those studies used molecular test platforms that require electricity, the findings suggest that etiologic STI screening and treatment can be operationalized in a variety of settings.

Despite successes in research studies, access to test technologies is a substantial barrier to implementing sustainable etiologic screening globally. The WHO has recommended the GeneXpert platform to diagnose tuberculosis in low- and middle-income countries since 2013.53s As a result, many low- and middle-income countries have some laboratory infrastructure to support molecular testing using GeneXpert,53s which rests on ICT for MDR-TB molecular testing. This approach has not been adopted in most STI molecular testing settings, although the Expedit diagnostic system offers promise for decentralized STI screening and treatment of gonococcal, chlamydial, and/or trichomonal infections on pregnancy outcomes in low- and middle-income countries.54s We found that differences in outcome definitions may contribute to future challenges with evaluating the evidence for operational feasibility of etiologic screening in select clinics (Table 1). In Ethiopia, investigators are examining operational feasibility of etiologic screening in select clinics (Table 1). In Ethiopia, investigators are examining operational feasibility of etiologic screening in select clinics (Table 1). In Ethiopia, investigators are examining operational feasibility of etiologic screening in select clinics (Table 1).
middle-income countries leads to both underdiagnosis and overdiagnosis and treatment. Emerging technologies have created new opportunities for implementing more effective STI screening and treatment approaches, which are now being evaluated in large randomized controlled trials. Research focused on addressing key knowledge gaps identified here will be central to generating a robust evidence base to inform the development of effective and sustainable interventions aimed at reducing the burden and consequences of curable STIs in pregnancy in low- and middle-income countries.

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For further references, please see “Supplemental References,” http://links.lww.com/OLQ/A539.