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### SSS STAR STI CTG 2018 Programmatic Meeting on STIs in Pregnancy & Reproductive Health

**Thursday, April 19, 2018, 8:00 A.M.—4:30 P.M.**

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<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:00 AM</td>
<td><strong>WELCOME BREAKFAST &amp; COFFEE</strong></td>
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<tr>
<td>8:15 AM</td>
<td><strong>Overview of Social &amp; Scientific Systems (SSS) and the STAR STI CTG</strong></td>
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<td>Presenters: Jeffrey Klausner, MD, MPH &amp; Sheldon Morris, MD, MPH</td>
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<tr>
<td>8:30 AM</td>
<td><strong>STIs in Pregnancy &amp; Global Health</strong></td>
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<td>Presenter: Adriane Wynn, MPP, PhD University of California, San Diego (UCSD)</td>
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<td>9:00 AM</td>
<td><strong>Infectious Disease During and After Pregnancy in Low and Middle Income Countries</strong></td>
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<td>Presenter: Professor Nynke van den Broek, PhD, FRCOG, Liverpool School of Tropical Medicine (LSTM)</td>
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<td>9:30 AM</td>
<td><strong>Vaginal Microbiome in Pregnancy</strong></td>
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<td>Presenter: Christina Muzny, MD, MSPH, The University of Alabama at Birmingham (UAB)</td>
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<td>10:00 AM</td>
<td><strong>BREAK</strong></td>
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<td>10:30 AM</td>
<td><strong>Mechanisms for Adverse Impact of Perinatal Infections on Pregnancy Outcomes</strong></td>
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<td>Presenter: Suhas Kallapur, MD, FAAP University of California, Los Angeles (UCLA)</td>
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<td>11:00 AM</td>
<td><strong>Mycoplasm Genitalium in Pregnancy</strong></td>
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<td>Presenter: Craig Cohen, MD, MPH, University of California, San Francisco (UCSF)</td>
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<td>11:30 AM</td>
<td><strong>Gaps in Prevention and Control of Congenital Syphilis in the U.S.</strong></td>
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<td>Presenter: Jennifer Fuld, PhD, Centers for Disease Control &amp; Prevention (CDC)</td>
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<td>12:00 PM</td>
<td><strong>LUNCH</strong></td>
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<td>1:00 PM</td>
<td><strong>Chlamydia, Placental Immunity, and Preterm Birth</strong></td>
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<td>Presenter: Robin Ingalls, MD, Boston University (BU)</td>
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<td>1:30 PM</td>
<td><strong>Clinical Issues with STDs &amp; Pregnancy</strong></td>
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<td>Presenter: Harold Wiesenfeld, MD, University of Pittsburgh</td>
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<td>2:00 PM</td>
<td><strong>Review of the GAPPS Biorepository Program</strong></td>
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<td>Presenter: James A. Litch, MD, DTMH, Global Alliance to Prevent Prematurity and Stillbirth (GAPPS)</td>
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<tr>
<td>2:30 PM</td>
<td><strong>BREAK</strong></td>
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<td>3:00 PM</td>
<td><strong>Break Out Sessions</strong></td>
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<td></td>
<td>a. <strong>Discussion of Clinical Research Priorities</strong></td>
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<td>Moderator – Sheldon Morris, MD, MPH, UCSD</td>
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<td>b. <strong>Discussion of Laboratory Priorities</strong></td>
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<td>Moderator – Sharon Hillier, PhD, University of Pittsburgh</td>
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<td></td>
<td>c. <strong>Discussion of Policy Priorities</strong></td>
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<td></td>
<td>Moderator – Jeffrey Klausner, MD, MPH, UCLA</td>
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<td>3:30 PM</td>
<td><strong>Summary of Break Out Sessions</strong></td>
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<td>A Presenter will be selected by each Break Out Group</td>
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<td>4:15 PM</td>
<td><strong>Discussion of Additional Business &amp; Wrap Up</strong></td>
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<td>Presenter: Jeffrey Klausner, MD, MPH, UCLA &amp; Sheldon Morris, MD, MPH, UCSD</td>
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Overview of the STAR Sexually Transmitted Infections Clinical Trials Group (STAR STI CTG)

The SSS STAR STI CTG is a National Institutes of Health (NIH) sponsored clinical trials group that supports large, randomized clinical trials in the field of prevention, diagnosis, and treatment of STIs. The SSS STAR STI CTG is comprised of domestic and international clinical research sites that include STD and sexual health clinics based in community settings and in health departments. The goal of the STAR STI CTG is to foster, develop, and administer a research program that will contribute to human reproductive health and specifically lead to the prevention and control of sexually transmitted infections.

The STAR STI CTG is tasked with developing and soliciting concept proposals in the areas of:

- Antimicrobial Resistance in STIs
- Prevention of Preterm Birth and Stillbirth
- Diagnostics for STIs
- Neglected and Reemerging Diseases
- Adolescent Health and Vaccines
- Syphilis in Men who Have Sex with Men (MSM)
- Drug-Resistant Gonorrhoeae (GC)
- Pelvic Inflammatory Disease (PID)
- Bacterial Vaginosis (BV)
- Herpes and Chlamydia Vaccines

The funding for the STAR STI CTG is through an indefinite delivery indefinite quantity (IDIQ) contract awarded annually by the Division of Microbiology and Infectious Diseases. SSS collaborated with UCLA to form the STAR STI CTG. Dr. Jeffrey Klausner, UCLA, serves as the Principal Investigator (PI) and Dr. Sheldon Morris, UCSD, serves as the Co-PI of the STAR STI CTG.

Social & Scientific Systems (SSS) serves as the Coordinating Center and Ms. Gwendolyn Maddox, SSS, serves as the Project Director for the STAR STI CTG. The Coordinating Center is responsible for supporting the activities of the STAR STI CTG. The responsibilities include budget development for the project; assisting with the development of SOPs; supporting the development of concept proposals (CPs); coordinating, processing, and supporting the scientific peer review of CPs; providing oversight for the CTG’s clinical trials and research studies; supporting meetings and conference calls; and maintaining the group’s website.
Jeffrey Klausner, MD, MPH

Dr. Klausner is Professor of Medicine and Public Health at the University of California, Los Angeles and serves as the Principal Investigator (PI) for the STAR Sexually Transmitted Infections Clinical Trials Group (STI CTG). Dr. Klausner received his medical degree in research from Cornell University and a master’s degree in public health from Harvard University. He is board certified in internal medicine and infectious diseases and has been conducting human subjects research for more than 20 years. Prof. Klausner has conducted trials using investigational products in the treatment of herpes simplex virus infection and chlamydial urethritis, and in the prevention and treatment of syphilis. In addition to therapeutic trials, he has conducted studies to determine the performance of new diagnostic assays for STDs. Dr. Klausner has more than 425 peer-reviewed publications on the epidemiology, prevention, control, treatment and management of STDs and is the senior editor of the McGraw-Hill textbook Current Diagnosis and Management of STDs. He also serves under joint appointments to Social & Scientific Systems, Inc. (SSS), as Chief Scientist/Medical Officer, Center for Infectious Diseases Research (CIDR).

Adriane Wynn, MPP, PhD

Adriane Wynn is a postdoctoral fellow supported by GloCal and UC San Diego. Her research is focused on improving management of sexually transmitted infections during pregnancy in Southern Africa. She received a PhD in Health Policy and Management from the UCLA Fielding School of Public Health in September 2017. Until recently, she was the Associate Director of the Policy Core at the Center for HIV Identification, Prevention, and Treatment Services. She received an MPP from UCLA in 2012. She has worked for the United States Senate and the California State Legislature.

Professor Nynke van den Broek

Professor van den Broek is a recognized international expert in global maternal and newborn health. At LSTM she established and leads the Centre for Maternal and Newborn Health (http://cmnh.lstmed.ac.uk/). This is currently one of the largest academic groups in Europe with an established and internationally relevant portfolio of work that incorporates priority interventions for reducing maternal and newborn mortality and morbidity. Professor van den Broek has designed and conducted large population-based randomized controlled trials of single interventions for improved maternal and newborn outcomes. She has used this experience to develop complex packages of interventions and to design and conduct operational research programmes in multi-country settings in both Asia and sub Saharan Africa to measure ‘what works where and how’ in real life settings. Impact has been ascertained through the development and application of innovative monitoring and evaluation frameworks. New indicators and methodology to measure quality of care and quality improvement as well as to assess maternal morbidity (or health) inclusive of HIV, TB and Malaria have been developed and used. Professor van den Broek enjoys the challenge of bringing the discipline of good research methodology to the planning and evaluation of complex development programmes that aim to strengthen health systems where this is expected to directly benefit maternal and newborn health. At CMNH Professor van den Broek leads a multi-disciplinary team of 50 academics, postgraduate students and programme management staff who wish to make a difference and develop, conduct and disseminate the highest quality research in the area of global maternal and newborn health.
Christina Muzny, MD, MSPH
Dr. Christina Muzny obtained her medical degree at the Texas A&M University Health Sciences Center College of Medicine. She subsequently completed an internal medicine residency and an infectious diseases fellowship at the University of Mississippi Medical Center prior to joining the infectious diseases faculty at the University of Alabama at Birmingham (UAB) in 2010. Her clinical and research interests focus on HIV and sexually transmitted diseases (specifically vaginal infections) among sexual minority women of color and women with increased numbers of recent sexual partners. Dr. Muzny currently has a K23 career development award from the National Institute of Allergy and Infectious Diseases to study the pathogenesis of bacterial vaginosis among African American women who have sex with women. She is currently an Associate Professor in the Division of Infectious Diseases at UAB, a teaching faculty for the Alabama-North Carolina STD/HIV Prevention Training Center, and an Associate Scientist for the UAB Center for AIDS Research.

Suhas Kallapur, MD, FAAP
Dr. Kallapur is the Chief of Neonatology and Developmental Biology and Professor of Pediatrics at the Mattel Children’s Hospital, David Geffen School of Medicine at UCLA. He received his MBBS and MD degree from the Seth G.S. Medical College, University of Mumbai, was a pediatric resident at Wayne State University and completed his fellowship in Neonatology at Cincinnati Children’s Hospital. He then stayed as a faculty member at Cincinnati Children’s Hospital from 1996-2017. He also currently has an appointment as a Clinical Professor at the University of Western Australia. Dr. Kallapur’s major research interest is in Perinatal infections, Chorioamnionitis, Perinatal immunology, and Lung injury. His NIH-funded research focuses on how inflammation at the maternal-fetal interface triggers preterm labor and causes fetal organ injury responses. He has world-wide collaborations that extend to Australia and with multiple U.S. based universities. He has developed powerful experimental models of intrauterine inflammation/infection that are complemented by studies of human placenta immunology. In addition to the NIH, Dr. Kallapur also received grants from Burroughs Wellcome Trust, March of Dimes and other organizations. His laboratory has trained 24 post docs/fellows/residents/graduate students in his lab. He has published 131 peer-reviewed manuscripts and >30 invited reviews. Two of the post-doctoral fellows from Cincinnati (Pietro Presicce and Monica Cappelliotti) have moved with Dr. Kallapur to set up a Perinatal infection/placenta immunology lab at UCLA.

Craig Cohen, MD, MPH
Craig R. Cohen, MD, MPH is professor of obstetrics, gynecology and reproductive sciences at the University of California San Francisco (UCSF). His research has been at the intersection of HIV and reproductive health including sexually transmitted infections. He has co-led the Kenya Medical Research Institute-UCSF collaboration since its inception in 2003, and worked in Kenya for eight prior years while affiliated with the University of Washington.
Jennifer Fuld, PhD
Dr. Jennifer Fuld is the Chief of the Program Development and Quality Improvement Branch (PDQIB) in the Division of STD Prevention at the CDC. Prior to joining the CDC in late 2016, Dr. Fuld was the Director, Clinical and Translational Science Institute at the NYC Health+ Hospitals and previously served as the Director, Clinical Quality Improvement at the Planned Parenthood Federation of America (PPFA). Additionally, Dr. Fuld has worked at the New York City Department of Health and Mental Hygiene, the New York Academy of Medicine and the National Development and Research Institutes. She holds a PhD in Sociology and has more than 15 years in public health.

Robin Ingalls, MD
Dr. Robin Ingalls is a Professor Medicine and Microbiology at Boston University School of Medicine and Boston Medical Center. Dr. Ingalls received her medical degree from Harvard Medical School, and is trained in Internal Medicine and Infectious Diseases. Dr. Ingalls has a longstanding interest in innate immunity, sexually transmitted infections and reproductive immunology. She has over 20 years of experience modeling Chlamydia trachomatis and Neisseria gonorrhoeae infections in vitro and in vivo, and has expertise in Toll-like receptors, cell signaling, and sepsis. For the past 5 years she has been conducting human studies looking at infections and innate immunity in the placenta, and how they might impact preterm birth and pregnancy outcomes.

Harold Wisenfeld, MD
Harold C. Wiesenfeld, M.D.,C.M. completed his medical degree and residency in Obstetrics and Gynecology at McGill University in Montreal, Canada, following which he pursued fellowship training in Reproductive Infectious Diseases at the University of Pittsburgh. He is currently a Professor of Obstetrics, Gynecology and Reproductive Sciences, and Vice-Chair of Gynecologic Services at the University of Pittsburgh School of Medicine.

Dr. Wiesenfeld is a physician scientist whose research centers on the study of infectious diseases in women and their impact on reproductive health. As Director of the Division of Reproductive Infectious Diseases at the University of Pittsburgh and the Medical Director of the STD/HIV Program at the Allegheny County Health Department, his career is dedicated to the study of reproductive infectious diseases and the care of women with STDs and obstetric and gynecologic infections. His research activities include studies exploring the microbiology, treatment and fertility impact of subclinical and acute pelvic inflammatory disease. Dr. Wiesenfeld’s research portfolio also includes investigations of diagnostics and treatment for STDs and strategies to enhance access to STD screening. He is the Director of the Reproductive Infectious Diseases Fellowship at the University of Pittsburgh.

James Litch, MD, DTMH
Dr. Litch is executive director and chief research officer of Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) and serves as the Principal Investigator (PI) for the GAPPS Biorepository Program founded in 2009 to serve the urgent need for international biological specimens at different points throughout pregnancy to support research on complication in pregnancy including preterm birth and stillbirth. Dr. Litch received his medical degree from the University of Michigan, and Diploma in Tropical Medicine and Hygiene from the Liverpool School of Tropical Medicine.
Medicine. He completed residency training in family medicine with the University of Washington and Seattle Public Health. He served as an Epidemic Intelligence Service Officer at the Centers for Disease Control and Prevention (CDC) during his transition from frontline positions in low income countries that ranged from medical officer in remote district hospitals, to NGO program director, to senior advisor for the Ministry of Health. Dr. Litch’s work in global health began more than 25 years ago, and has held positions with GAPPS, Program for Appropriate Technology in Health (PATH), University of Washington, and Johns Hopkins University/Jhpiego. Dr. Litch leads a range of translational research activities related to perinatal health and stillbirth in South Asia and Africa.

**Sheldon Morris, MD, MPH**

Dr. Morris is an Assistant Professor at the University of California, San Diego (UCSD) and also serves as the Co-PI of the STAR STI CTG. Dr. Morris completed his undergraduate work at the University of British Columbia (UBC) in microbiology and attended the UBC School of Medicine. He received his Masters of Public Health at the Harvard School of Public Health, majoring in Quantitative Methods, followed by a residency in Preventive Medicine at UCSF/UC Berkeley and a fellowship at the State of California Department of Public Health STD Control Branch. He has served on the faculty of the UCSD School of Medicine since 2006 and currently is involved in clinical practice, teaching and research. Dr. Morris currently studies infectious disease epidemiology. The focus of his research is epidemiology, natural history and prevention of STIs and HIV. This includes the occurrence of both bacterial and viral STIs. He has clinical specialties in Family Practice and Preventive Medicine. He teaches in the CREST Program and an associated Masters of Advanced Studies in Clinical Research (MAS-CR) degree program at UCSD.

**Sharon Hillier, PhD**

Dr. Hillier is a Professor of Obstetrics, Gynecology and Reproductive Sciences and of Molecular Genetics and Biochemistry at the University of Pittsburgh School of Medicine. She also serves as the Director of the Center of Excellence in Women’s Health at the Magee-Womens Hospital of the University of Pittsburgh Medical Center and is a Senior Investigator at the Magee-Womens Research Institute. Dr. Hillier’s main research interests focus on the role of normal vaginal bacteria and infections on pregnancy complications and their part in genital infection and susceptibility to human immunodeficiency virus (HIV), the virus that causes AIDS. Dr. Hillier received her undergraduate and doctoral degrees in bacteriology and public health from Washington State University. She is author or co-author of more than 400 articles, book chapters and abstracts in the medical literature, and is president of the Infectious Disease Society for Obstetrics and Gynecology, an affiliate organization of the American College of Obstetricians and Gynecologists. She also is a member of the American Sexually Transmitted Disease Association, the Anaerobe Society of the Americas, and the Joint Indo-United States Working Group on Reproductive Health.
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<td><a href="mailto:EAnyalechi@cdc.gov">EAnyalechi@cdc.gov</a></td>
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<td>UMD</td>
<td><a href="mailto:jravel@som.umaryland.edu">jravel@som.umaryland.edu</a></td>
</tr>
<tr>
<td>Reddy, Uma</td>
<td>NICHD</td>
<td><a href="mailto:uma.reddy@nih.gov">uma.reddy@nih.gov</a></td>
</tr>
<tr>
<td>Rietmeijer, Kees</td>
<td>Rietmeijer Consulting, LLC</td>
<td><a href="mailto:kees@rietmeijer.us">kees@rietmeijer.us</a></td>
</tr>
<tr>
<td>Russo, Denise</td>
<td>NICHD</td>
<td><a href="mailto:drusso1@mail.nih.gov">drusso1@mail.nih.gov</a></td>
</tr>
<tr>
<td>Schoolnik, Gary</td>
<td>Click Diagnostics</td>
<td><a href="mailto:gary.schoolnik@clickdx.com">gary.schoolnik@clickdx.com</a></td>
</tr>
<tr>
<td>Shahkolahi, Akbar</td>
<td>SSS</td>
<td><a href="mailto:ashahkolahi@s-3.com">ashahkolahi@s-3.com</a></td>
</tr>
<tr>
<td>Taylor, Melanie</td>
<td>WHO</td>
<td><a href="mailto:mtaylor@who.int">mtaylor@who.int</a></td>
</tr>
<tr>
<td>Turpin, Delmyra</td>
<td>DMID/NIH</td>
<td><a href="mailto:delmyra.turpin@nih.gov">delmyra.turpin@nih.gov</a></td>
</tr>
<tr>
<td>van den Broek, Nynke</td>
<td>Liverpool School of Tropical Medicine</td>
<td><a href="mailto:nynke.vandenbroek@lstmed.ac.uk">nynke.vandenbroek@lstmed.ac.uk</a></td>
</tr>
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<tr>
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<td>SSS</td>
<td><a href="mailto:twaymer@s-3.com">twaymer@s-3.com</a></td>
</tr>
<tr>
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<td>WHO</td>
<td><a href="mailto:wit@who.int">wit@who.int</a></td>
</tr>
<tr>
<td>Wiesenfeld, Harold</td>
<td>University of Pittsburgh</td>
<td><a href="mailto:wieshc@mail.magee.edu">wieshc@mail.magee.edu</a></td>
</tr>
<tr>
<td>Wolff, Peter</td>
<td>DMID/NIH</td>
<td><a href="mailto:pwolff@niaid.nih.gov">pwolff@niaid.nih.gov</a></td>
</tr>
<tr>
<td>Wright, Michelle</td>
<td>Emory University</td>
<td><a href="mailto:michelle.lynn.wright@emory.edu">michelle.lynn.wright@emory.edu</a></td>
</tr>
<tr>
<td>Wynn, Adriane</td>
<td>UCSD</td>
<td><a href="mailto:adriane.wynn@gmail.com">adriane.wynn@gmail.com</a></td>
</tr>
</tbody>
</table>
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Feasibility of *Chlamydia trachomatis* screening and treatment in pregnant women in Lima, Peru: a prospective study in two large urban hospitals

Jeanne Cabeza, 1 Patricia J García, 2 Eddy Segura, 1 Pedro García, 3 Francisco Escudero, 4 Sayda La Rosa, 2 Segundo León, 5, 6 Jeffrey D Klausner 1

**ABSTRACT**

**Objectives** *Chlamydia trachomatis*, which is asymptomatic in most women, causes significant adverse effects for pregnant women and neonates. No programmes conduct antenatal screening in Latin America. We determined chlamydia prevalence, feasibility and acceptability of chlamydia screening, and adherence to treatment in pregnant women in two urban public hospitals in Lima, Peru.

**Methods** We offered chlamydia screening using self-collected vaginal swabs to pregnant women ≥16 years of age during their first antenatal visit. Chlamydia-infected women were contacted within 14 days and asked to bring partners for counselling and directly observed therapy with oral azithromycin. Unaccompanied women received counselling, directly observed therapy, and azithromycin to take to partners. Test of cure was performed ≥3 weeks after treatment.

**Results** We approached 640 women for the study and enrolled 600 (93.8%). Median age was 27.3 years (range 16–47), median lifetime partners 2.3 (range 1–50), and median gestational age 26.1 weeks (range 4–41). Chlamydia prevalence was 10% (95% CI 7.7% to 12.7%). Of 60 infected patients, 59 (98%) were treated with one dose of azithromycin. Fifty-two of 59 (88%) returned for test of cure, all of whom were treated successfully, with 46 (86%) achieving negative test of cure with one dose of azithromycin, and 6 (12%) after retreatment with a second dose.

**Conclusions** *C. trachomatis* screening and treatment in pregnancy was feasible and highly acceptable in two urban hospitals in Peru. Clinical trials to evaluate efficacy and cost-effectiveness of chlamydia screening, and treatment of pregnant women to prevent adverse pregnancy outcomes in low-resource settings, are warranted.

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Chlamydia trachomatis, the most common sexually transmitted bacterial infection worldwide, can cause significant adverse outcomes in pregnancy, including preterm birth, low birth weight, premature rupture of membranes, stillbirth, and miscarriage, as well as inclusion conjunctivitis and pneumonia in neonates.1 No programmes routinely conduct *C. trachomatis* screening in antenatal care in Latin America, and there are no WHO recommendations for routine *C. trachomatis* screening and treatment in pregnant women. To prepare for a trial of *C. trachomatis* screening and treatment in pregnancy to reduce adverse pregnancy outcomes, we explored the feasibility and acceptability of *C. trachomatis* screening in pregnant women during the first antenatal visit, and determined *C. trachomatis* prevalence and patient and partner outcomes to treatment in Lima, Peru.

**METHODS**

**Study design** We conducted a prospective study in two large urban hospitals in Lima, Peru: Instituto Nacional Materno Perinatal (INMP) and Hospital Nacional Arzobispo Loayza (HNAL). INMP participants were recruited in January 2013; HNAL participants were recruited December 2012–January 2013.

During the recruitment period, all pregnant women attending their first antenatal visit were given a brief explanation by hospital midwives about risks of chlamydia infection during pregnancy and were told about the study. We focused on the first antenatal visit since women routinely have antenatal counselling and HIV/syphilis screening at this time. Women ≥16 years old who were interested in participating were screened for eligibility by research midwives and enrolled after providing informed consent. Consecutive women were recruited at the HNAL. Even-numbered women were recruited at the INMP (odd-numbered patients were recruited to another concurrently running research study). Women not mentally competent to understand informed consent were excluded; minors were required to have consent from parent or guardian to participate. The study protocol was approved by the institutional review or ethical boards at the University of California, Los Angeles Universidad Peruana Cayetano Heredia, and each participating hospital.

Women provided self-collected vaginal swabs for chlamydial testing after being instructed on collection technique by the study midwife, and then completed a face-to-face questionnaire regarding demographic data, reproductive and medical history, and number of sexual partners. Women who tested positive for chlamydial infection were asked to return to the hospital for counselling, and directly observed treatment with 1 g of oral azithromycin. They were given the option of bringing their partner(s) with them for counselling and directly observed concurrent treatment at the hospital, or of delivering 1 g azithromycin to the...
partner at home. Approximately 3 weeks after treatment, infected women were contacted to provide a second self-collected vaginal specimen to perform a test of cure to document clearance of infection.

Testing was free, and we reimbursed women their transportation costs to return for treatment and for test of cure.

Laboratory
Specimens were tested for C. trachomatis infection using the Aptima Combo2 system (Hologic, Gen Probe Incorporated, San Diego, California, USA) at the Universidad Peruana Cayetano Heredia Laboratory of Sexual Health in Lima, Peru.

Data management and statistical analysis
Screening acceptability and C. trachomatis prevalence were calculated with 95% CIs. To test the association between categorical variables and C. trachomatis positivity, we used either χ² or Fisher’s exact tests. All other numerical variables were assessed using the Mann–Whitney test. Individuals with missing data were excluded only from the affected analysis. We conducted all analysis using Stata V12.1 (Stata Corporation, College Station, Texas, USA).

RESULTS
Participation rate
Of 640 pregnant women during the recruitment period who were informed about the study, three were excluded (due to high-risk pregnancy, unaccompanied minor status, or lack of intention to return to hospital). Of the remaining 637 eligible women, 600 (93.8%) enrolled: 333 (55.5%) from INMP and 267 (44.5%) from HNAL. The most common reasons given for not participating were lack of time (n=15), fear of being tested (n=7), and not considering the study important (n=7). Five women did not give any reason, and three wanted to consult with family/friends before enrolling but never enrolled.

Participant characteristics
Table 1 shows participant characteristics.

C. trachomatis prevalence
C. trachomatis was identified in 60 study participants (10.0%; 95% CI 7.7% to 12.7%). Prevalence decreased with age; the youngest women (16–23 years) had the highest prevalence (15.6%), and older women (≥31 years) had the lowest (5.2%). Prevalence was higher for single women than for women who were married or cohabiting, but was unrelated to lifetime number of sex partners, education level, or current vaginal symptoms.

Treatment
Of the 60 C. trachomatis-positive patients, 59 (98.3%) received treatment. Fifty-five of 59 partners (93%) received treatment, 21 of them (36%) at the hospital, concurrently with the women, and 34 (58%) with medication brought home by the women.

Fifty-two (91%) treated women returned for test of cure. Forty-six tested negative (infection cured). Of the six who tested positive, indicating continuing infection, three had received concurrent therapy with their partners, two had brought treatment home, and one denied partner contact after treatment. All six were retreated, and subsequent tests of cure were negative.

DISCUSSION
Chlamydial screening in pregnant women at two large urban hospitals in Lima was feasible and highly acceptable. All women who tested positive for chlamydia and returned for treatment and test of cure were successfully treated.

Our data regarding prevalence were consistent with previous research in Peru and globally, showing that the youngest women are most likely to be infected. It is worth noting that in our study, prevalence was also high (5.1%) among women ≥31 years, an age category not generally included in screening programmes.

The participation rate for screening with self-administered vaginal swabs was high (93.8%), which is consistent with previous studies in high-income countries. Use of self-administered vaginal swabs for nucleic acid amplification testing is a non-invasive diagnostic method that has sensitivity and specificity equivalent to provider-collected samples, an advantage in resource-limited settings where there may be shortages of health personnel. Additionally, vaginal swabs are easier to transport, and are equally or more sensitive and specific for diagnosis of chlamydial infection than urine samples.

One potential disadvantage of such molecular-based testing is the absence of laboratory testing capacity in low and middle-income settings. However, with the advent of HIV/AIDS RNA testing and the widespread introduction of molecular testing for tuberculosis in low-income and middle-income settings, that capacity is rapidly increasing. Since results are not available at point-of-care, another drawback of such testing is the potential loss to follow-up, but as yet there exists no point-of-care testing with adequate sensitivity and specificity for chlamydia screening. C. trachomatis positivity at test of cure was 12%, similar to levels in previous studies of recurrent or persistent infections in women treated for genital chlamydia. No significant resistance of C. trachomatis to azithromycin has been reported in the literature, but pharmacologic treatment failure, defined as persistent infection despite antibiotic use, may result from variations in drug absorption, metabolism, or host immune response. False positive results in the test of cure may occur from persistence of residual DNA from non-viable chlamydia. To avoid this problem, current treatment guidelines recommend waiting at least 3 weeks before repeating nucleic acid amplification testing, although residual DNA may persist for longer periods.

Although women were encouraged to bring partners to the hospital for treatment and counselling, nearly 60% chose to bring medication home to partners. This practice, known as patient-delivered partner therapy, is recommended by the US Centers for Disease Control as an alternative therapy for certain sexually transmitted diseases. This is an important consideration, since several studies in developing countries suggest that reliance on patient referral of partners for therapy is often ineffective. More research is needed on the use of patient-delivered partner therapy for partner treatment in low-resource settings.

Our study had several limitations. Women were recruited only from large public hospitals in Lima, so results might not be generalisable to other settings, such as rural areas and mid-sized cities. The educational level in our sample was somewhat higher than average for metropolitan Lima, and since we have no demographic data on the women who chose not to participate, we cannot rule out the possibility that there may have been a selection bias such that women who are more educated were more likely to participate in the study. Despite these limitations,
A strong association between C. trachomatis and adverse pregnancy outcomes is urgently needed. Treatment in low-income and middle-income countries is feasible and acceptable in two large urban maternity hospitals in Lima, Peru. Partner treatment was also readily accepted. The prevalence of C. trachomatis infection was high. Given the strong associations between C. trachomatis in pregnancy and adverse pregnancy outcomes, a clinical trial to demonstrate the efficacy and cost-effectiveness of C. trachomatis screening and treatment in low-income and middle-income countries is urgently needed.

**Table 1** Characteristics of the study participants, total and stratified by chlamydia tests (CT) lab result (n = 600)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (n=600)</th>
<th>Positive (n=60)</th>
<th>Negative (n=540)</th>
<th>p Value*</th>
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<td>Age in years</td>
<td>27 (21–32)†</td>
<td>23 (20–38)</td>
<td>27 (22–33)</td>
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<td>Age categorised</td>
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<td>1st tertile (16–23)</td>
<td>212 (35.3)</td>
<td>33 (15.6)</td>
<td>179 (84.4)</td>
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<td>2nd tertile (24–30)</td>
<td>196 (32.7)</td>
<td>17 (8.7)</td>
<td>179 (91.3)</td>
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<td>3rd tertile (31–47)</td>
<td>192 (32.0)</td>
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<td>182 (94.8)</td>
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<td>Education</td>
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<td>363 (60.5)</td>
<td>37 (10.2)</td>
<td>326 (89.8)</td>
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<td>Some university/tech</td>
<td>211 (35.2)</td>
<td>19 (9.0)</td>
<td>192 (91.0)</td>
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<td>Partnership status</td>
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<td>Single/separated/divorced</td>
<td>116 (19.3)</td>
<td>20 (17.2)</td>
<td>96 (82.8)</td>
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<td>Married/cohabitating</td>
<td>484 (80.7)</td>
<td>40 (8.3)</td>
<td>444 (91.7)</td>
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<td>Parity</td>
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<td>First pregnancy</td>
<td>218 (36.3)</td>
<td>27 (12.4)</td>
<td>191 (87.6)</td>
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<td>&gt; Second pregnancy</td>
<td>382 (63.7)</td>
<td>33 (8.6)</td>
<td>349 (91.4)</td>
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<td>Gestational age in weeks</td>
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<td>Second trimester (13–27)</td>
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<td>324 (54.0)</td>
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<td>Age at first intercourse</td>
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<td>17 (16–19)</td>
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<td>Lifetime number of partners</td>
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<td>Prior diagnosis of syphilis</td>
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<td>0 (0.0)</td>
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<td>Prior diagnosis of HIV</td>
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<td>STD symptoms (current)‡</td>
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<td>472 (90.1)</td>
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<td>Genital wart</td>
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<td>Genital ulcer</td>
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<td>2 (7.7)</td>
<td>24 (92.3)</td>
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<td>Positive for CT (test used in study)</td>
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<td>60 (100.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Positive for syphilis (chart review)</td>
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<td>8 (100.0)</td>
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<td>Positive for HIV (chart review)</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
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For the total sample column, percentages are displayed along the column. For the stratified analysis, percentages are displayed along the row.

*χ² test except for numeric variables marked with † where Mann-Whitney test was used.
†Median (IQR).
‡Could report more than 1 concurrent symptom.

NA, not applicable.

However, we believe that because our study was carried out in two national hospitals with large antenatal services and because most women in Lima give birth in hospitals, our prevalence estimates, treatment acceptability, and risk factors are similar to those for the larger population of low-risk pregnant women in Lima.

C. trachomatis screening and treatment in pregnancy was feasible and acceptable in two large urban maternity hospitals in Lima, Peru. Partner treatment was also readily accepted. The prevalence of C. trachomatis infection was high. Given the strong associations between C. trachomatis in pregnancy and adverse pregnancy outcomes, a clinical trial to demonstrate the efficacy and cost-effectiveness of C. trachomatis screening and treatment in low-income and middle-income countries is urgently needed.

**Author affiliations**
1Department of Medicine/Division of Infectious Diseases, UCLA Geffen School of Medicine, Los Angeles, California, USA
2Unit of Epidemiology, STD and HIV, School of Public Health, Universidad Peruana Cayetano Heredia, Lima, Peru
3Instituto Nacional Materno Perinatal, Lima, Peru
4Hospital Nacional Arzobispo Loayza, Lima, Peru
5Department of Global Health, University of Washington, Seattle, Washington, USA
6Instituto de Medicina Tropical, Universidad Mayor de San Marcos, Lima, Peru
7Instituto Nacional Materno Perinatal and Bertha Zavaleta Hospital Nacional Arzobispo Loayza, as well as the staff at both hospitals and at Universidad Peruana Cayetano Heredia. Jeanne Cabeza was a research fellow in the University Peruana Cayetano Heredia.
8Instituto Nacional Materno Perinatal and Bertha Zavaleta Hospital Nacional Arzobispo Loayza, as well as the staff at both hospitals and at Universidad Peruana Cayetano Heredia.
9Soledad Rodriguez at the Instituto Nacional Materno Perinatal and Bertha Zavaleta Hospital Nacional Arzobispo Loayza.
10Department of Global Health, University of Washington, Seattle, Washington, USA

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Clinical

Contributors JC had full access to all the data in the study and takes responsibility for the integrity of the data analysis. Study concept and design: JC, PJG, JDK. Study supervision: JC, PJG, PG, FE, JDK. Critical revision of the manuscript for important intellectual content: JC, PJG, JDK, PG, FE. Drafting of the manuscript: JC, PJG, JDK. Administrative technical or material support: ES, SLR, SL. Statistical analysis ES.

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Competing interests None.

Ethics approval UCLA (RB #12-000914), UPCH (#60048), HNAL (105 CIE), and INMP (DG N° 959).

Provenance and peer review Not commissioned; externally peer reviewed.

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Prevalence of Curable Sexually Transmitted Infections in Pregnant Women in Low- and Middle-Income Countries From 2010 to 2015

A Systematic Review

DL Joseph Davey, MPH, PhD,*‡ HI Shull, MD,* JD Billings,* D Wang,‡ K Adachi, MD,* and JD Klausner, MD, MPH*‡

Background: Current literature comparing the prevalence rates of curable sexually transmitted infections (STIs) in pregnant women in various global regions is limited. As a result, antenatal screening practices for curable STIs in pregnant women, specifically Treponema pallidum (syphilis), Neisseria gonorrhoeae (NG), Chlamydia trachomatis (CT), and Trichomonas vaginalis (TV), may vary around the world, differing by country and particular STI.

Methods: We conducted a systematic review of publications on STI prevalence among pregnant women in 30 different low- and middle-income countries. We searched PubMed for studies reporting prevalence of syphilis, CT, NG, and TV in pregnant women. English language studies published between January 1, 2010, and March 1, 2015, were included. The adjusted mean STI prevalence by region was calculated via multivariable linear regression adjusting for health care setting, women's mean age, study sample size, and sensitivity of diagnostic test.

Results: We identified 75 studies that met inclusion criteria, providing 116 point prevalence estimates for curable STIs among 3,489,621 pregnant women. Adjusted mean prevalence for NG ranged from 1.2% (95% confidence interval [CI], 1.0–1.3) in Latin America to 4.0% (95% CI, 3.9–4.1) in Southern Africa; syphilis prevalence ranged from 1.1% (95% CI, 0.5–1.6) in Asia to 6.5% (95% CI, 4.7–6.3) in Southern Africa; CT ranged from 0.8% (95% CI, 0.4–1.1) in Asia to 11.2% (95% CI, 6.0–16.4) in Latin America; and TV ranged from 3.9% (95% CI, 2.2–5.6) in Latin America to 24.6% (95% CI, 17.9–31.4) in Southern Africa.

Conclusions: Although we observed a wide variation in STI burden in pregnancy after adjusting for age, test, and health care setting, further valid comparison may depend on adjustment for access to care and screening practices.

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Definitions of low- and middle-income countries were obtained from the World Bank (http://data.worldbank.org/income-level/LMY). When a study reported more than 1 STI prevalence, we recorded each infection and each sample size separately. Data abstraction was not blinded to authors or publication, but was performed independently. See Supplemental file for a complete list of publications included in the analysis.

We stratified our prevalence estimates by region and adjusted for health care setting (eg, hospital-, clinic-, or community-based study), age of pregnant women in the study, and diagnostic tests used. Prevalence values in the included articles were calculated as the number of pregnant women who were diagnosed with an STI over the total number of pregnant women tested.

For syphilis, tests included venereal disease research laboratory, rapid plasma reagin, Treponema pallidum hemagglutination, Toluidine Red Unheated Serum Test, Treponema pallidum particle agglutination assay, enzyme immunoassay, fluorescent treponemal antibody absorption, and rapid diagnostic test. However, 23 of 54 (43%) studies on syphilis only reported venereal disease research laboratory, rapid plasma reagin, or Treponema pallidum hemagglutination but no second test. For CT and NG, tests included nucleic acid amplification testing (NAAT), enzyme immunoassay, IgG antibody screen, culture, APTIMA combo 2 and microscopy. For TV, tests included polymerase chain reaction, culture, and microscopy. Data for diagnostic test used was extracted from the studied articles. Due to the variance in performance of different diagnostic tests, estimated sensitivities and specificities were collected from the current literature for each reported diagnostic test used.18–22

All studies that satisfied the previously mentioned inclusion criteria were analyzed and those with missing data points for any factors are denoted in the final analysis. Site of data collection was stratified in a stepdown method to 3 subgroups: at a hospital, at an antenatal or community clinic, or as part of a study or community screening program. Studies reporting more than 1 type of location for data collection or crossover within a location, that is, an antenatal clinic within a hospital, were considered to have occurred at the higher-level care center. Studies directly reporting mean or median ages for the women were used for portion of the analysis whereas studies that either stratified age as a categorical variable without reporting mean age or did not report age as a factor were noted as missing in the final analysis.

Statistical Analyses

We stratified results by subregion (East Africa, West Africa, Southern Africa, Latin America, and Asia). Asia included South
Asia, and the Middle East and Pacific Regions, and Latin America included both Central and South America, due to the small number of studies from these regions. We calculated the total number of positive pregnant women per STI per region, the median number with positive diagnoses, the study sample size, the mean age, and the mean sensitivity and specificity for each diagnostic test used (if not counted, then was reported as missing). We developed multivariable linear regression models to estimate adjusted mean prevalence by STI and region, and 95% confidence intervals (CI) for all strata. We adjusted for health care setting (eg, hospital-, clinic-, or community-based study), women’s mean age, study sample size, and STI test sensitivity. The specificity was not included in the final model due to collinearity with sensitivity. We used STATA 13.1 (College Station, TX) for all analyses.23

RESULTS

We identified a total of 376 potentially relevant reports from January 2010 to March 2015. Only 75 studies from 30 low- and middle-income countries met inclusion criteria, providing 116 point prevalence estimates for curable STIs in pregnant women, including a total of 3,489,621 women (Fig. 1). The diagnostic test used was reported in 94.7% of included articles. The greatest number of published studies were from Latin America (n = 23 studies, n = 206,848 pregnant women), followed by East Africa (n = 20 studies, n = 23,413 pregnant women), Asia (n = 18 studies, n = 3,109,314 pregnant women), Southern Africa (n = 15 studies, n = 128,467 pregnant women), and West Africa (n = 6 studies, n = 10,790 pregnant women). The total number of studies is greater than the 75 studies included because some studies had more than 1 country in the analysis. The number of women and numbers of tests per woman varied considerably from a sample size of 12 (in Brazil) to a sample size of over 2 million (in China).

Overall, the region with the highest adjusted mean prevalence of curable STIs among pregnant women was Southern Africa. Our analyses included studies in the following countries: South Africa, Malawi, Madagascar, Zambia, Mozambique, and Zimbabwe. In Southern Africa, TV was the most prevalent STI overall, with a adjusted mean prevalence of 24.6% (95% CI, 17.9–31.4) in 3 studies. Next was syphilis with a prevalence of 6.5% (95% CI, 4.70–8.3) in 8 studies. Neisseria gonorrhoeae and CT were similarly high at 4.6% (95% CI, 4.0–5.2) in 3 studies, and 4.4% (95% CI, 2.3–6.6) in 3 studies, respectively (Fig. 2).

In East Africa, we included studies from the following countries: Kenya, Tanzania, Somalia, Ethiopia, Uganda, and Sudan. Eight studies demonstrated a adjusted mean prevalence of syphilis of 4.6% (95% CI, 3.7–5.6), the second highest prevalence after Southern Africa. The adjusted mean prevalence was similarly high for TV in 3 studies at 6.8% (95% CI, 4.6–9.0). The adjusted mean prevalence of CT in 3 studies was 4.2% (95% CI, 2.8–5.6), followed by NG with a prevalence of 2.3% (95% CI, 2.0–2.5) in 3 studies (Fig. 2).

In West Africa, we included studies from Benin, Democratic Republic of Congo, Nigeria, and Burkina Faso. In these countries, the adjusted mean prevalence of CT was 7.2% (95% CI, 0.0–14.6) in 1 study. The adjusted mean prevalence of syphilis was 4.0% (95% CI, 1.7–6.3) in 4 studies (Fig. 2).

For Latin America, we included studies from Peru, Brazil, Ecuador, Argentina, and Guatemala. The adjusted mean prevalence of TV among pregnant women was 3.9% (95% CI, 1.1–5.6) in the 3 studies included. The adjusted mean prevalence of CT in Latin America was 1.2% (95% CI, 0.3–1.0) in 7 studies, which is higher than the mean prevalence in Southern and East Africa. Syphilis had a mean prevalence of 2.6% (95% CI, 1.2–3.9) in 15 studies. The mean prevalence of NG was very low at 0.3% (95% CI, 0.1–1.9) in 3 studies (Fig. 2).

In Asia, we included studies from China, India, Bangladesh, Papua New Guinea, Turkey, Pakistan, Iran, Myanmar, and Cambodia. The mean prevalence of STIs among pregnant women was lower here than the other regions. Trichomonas vaginalis was most prevalent with a mean prevalence of 13.6% (95% CI, 6.8–20.4) in 1 study, followed by NG at 2.8% (95% CI, 2.4–3.3) in 1 study, and CT at 0.8% (95% CI, 0.4–1.1) in 6 studies. The mean prevalence of syphilis was also lowest in Asia at 1.1% (95% CI, 0.5–1.6) in 13 studies controlling for potential confounders (see Table 1).

DISCUSSION

Our study found that the prevalence of curable STIs among pregnant women was substantial throughout low- and middle-income countries. Importantly, our review found a lack of recent data on STI prevalence among pregnant women in many parts of the world. We also note that the variation in diagnostic tests used and populations tested makes it difficult to compare the prevalence
Our findings are particularly relevant for CT and NG, which are largely asymptomatic infections. However, TV and syphilis, which may present with the symptoms of genital discharge and ulceration, also go undertreated. In the past, it was difficult to determine whether women had CT or NG because the performance of the available tests was poor. Now, with the advent of point-of-care NAATs, the specificity and sensitivity of CT and NG tests are much higher and may be cost-effective to use in resource-limited countries. As a testament to the success that can be had with STI screening, point-of-care rapid syphilis tests are now being integrated into antenatal care around the world, and some countries have even started to use a dual syphilis-IV test, which has shown excellent performance. Our study found that most of the syphilis testing was done with point-of-care tests, whereas none of the other STI tests were point of care.

**LIMITATIONS**

Our study was subject to some limitations. We only used PubMed for the search and may have missed other publications as a result. Although PubMed (Medline) and EMBASE are similar, their coverage of the published literature differs. For example, EMBASE is used more frequently in Europe, and PubMed in the United States. As a result of limiting our search to PubMed, we may have excluded European or abstract citations. Further, the quality of the studies included in this analysis varied considerably, including different sampling strategies, diagnostic tests used, testing strategies, and HIV coinfection rates. We attempted to control for that heterogeneity by adjusting for women’s mean age, study sample size, and sensitivity of diagnostic test; TV, model adjusted for study sample size and health care setting; NG, model adjusted for study sample size.

### TABLE 1. Adjusted Mean STI Prevalence Among Pregnant Women Adjusting for Potential Confounders, 2010–2015 (Stratified by Region)

<table>
<thead>
<tr>
<th>STI by Sub-Region</th>
<th>Adjusted Mean Prevalence, % (95% CI)*</th>
<th>No. Positive (Total in Studies) Tested (%)</th>
<th>Median No. With Positive Diagnosis</th>
<th>Study Sample Size, Range</th>
<th>No. Studies</th>
<th>Women’s Mean age (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eastern Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>4.6 (3.7–5.4)</td>
<td>705</td>
<td>18,043</td>
<td>9</td>
<td>165–5,802</td>
<td>8</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>2.3 (2.0–2.5)</td>
<td>18</td>
<td>826</td>
<td>7</td>
<td>185–441</td>
<td>3</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>4.2 (2.8–5.6)</td>
<td>161</td>
<td>856</td>
<td>19</td>
<td>185–441</td>
<td>3</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>6.8 (4.6–9.0)</td>
<td>416</td>
<td>3,688</td>
<td>21</td>
<td>185–441</td>
<td>3</td>
</tr>
<tr>
<td><strong>West Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>4.0 (1.7–6.3)</td>
<td>787</td>
<td>21,481</td>
<td>23</td>
<td>283–17,669</td>
<td>4</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>7.15 (0.00–14.57)</td>
<td>16</td>
<td>98</td>
<td>16</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td><strong>Southern Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>6.5 (4.7–8.3)</td>
<td>37134</td>
<td>119,962</td>
<td>125</td>
<td>149–95,663</td>
<td>8</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>4.6 (4.0–5.2)</td>
<td>128</td>
<td>1,804</td>
<td>27</td>
<td>145–1459</td>
<td>3</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>4.4 (2.3–6.6)</td>
<td>306</td>
<td>1,840</td>
<td>28</td>
<td>151–1459</td>
<td>3</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>24.6 (17.9–31.4)</td>
<td>606</td>
<td>4,861</td>
<td>38</td>
<td>200–1459</td>
<td>3</td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>2.2 (1.2–3.3)</td>
<td>934</td>
<td>196,689</td>
<td>17</td>
<td>12–162,669</td>
<td>15</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>12 (1.0–13.1)</td>
<td>21</td>
<td>3366</td>
<td>1</td>
<td>63–2017</td>
<td>3</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>11.2 (6.0–16.4)</td>
<td>437</td>
<td>4592</td>
<td>33</td>
<td>63–2071</td>
<td>7</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>3.9 (2.2–5.6)</td>
<td>61</td>
<td>2201</td>
<td>24</td>
<td>289–1315</td>
<td>3</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>1.1 (0.5–1.6)</td>
<td>11,057</td>
<td>3,107,741</td>
<td>35</td>
<td>113–2,077,362</td>
<td>13</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>2.8 (2.4–3.3)</td>
<td>4</td>
<td>113</td>
<td>4</td>
<td>63–2017</td>
<td>3</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>0.8 (0.4–1.1)</td>
<td>100</td>
<td>1,375</td>
<td>8</td>
<td>85–784</td>
<td>6</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>13.6 (6.8–20.4)</td>
<td>6</td>
<td>85</td>
<td>6</td>
<td>85</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: study references are listed in the Appendix.

*Syphilis and CT models adjusted for health care setting (hospital, clinic or community-based study), women’s mean age, study sample size, and sensitivity of diagnostic test; TV, model adjusted for study sample size and health care setting; NG, model adjusted for study sample size.

| Study references: 4, 6, 10, 18, 27, 29, 30, 32, 34, 39, 49, 55, 57, 59, 64, 65, 66, 68, 70, 72. |
| Study references: 8, 9, 18, 23, 52, 53. |
| Study references: 7, 17, 18, 20, 28, 31, 38, 41, 48, 56, 57, 63, 67, 70, 71. |
| Study references: 2, 11, 14, 21, 22, 24, 25, 28, 35, 36, 37, 40, 45, 46, 54, 55, 58, 61, 62, 64, 69, 74, 75. |
| Study references: 1, 3, 5, 12, 13, 15, 16, 19, 26, 33, 42, 43, 44, 47, 50, 51, 60, 73. |

between the different regions. Inconsistencies between research and practice may play a role in why the WHO has not implemented clear screening guidelines and policies for STI screening, other than for syphilis and HIV, in pregnancy. In most high-income countries, NAATs are the diagnostic standard of care for NG and CT due to their wide availability and high sensitivity and specificity. Yet, many other nations have no tests available or rely on tests with lower sensitivities and specificities. Cultures for NG and CT have estimated sensitivities of 41% and 21%, respectively, and are dependent on strong laboratory infrastructure.

Other systematic reviews of STI prevalence in pregnant women have found similarly high rates of STIs. A review article by Chico et al. in 2012 found that the prevalence of syphilis was 3.5%, CT was 6.1% and TV was 17.8% among pregnant women in West and Central Africa. Those rates are similar to the mean prevalences we report, which include 41 additional studies from sub-Saharan Africa and expand the review to include a large proportion of low- and middle-income countries.

Despite persistent high level of STIs among pregnant women, there is still a limited focus on CT, NG, and TV. All of those are curable STIs that are risk factors for adverse birth and neonatal outcomes. Despite the well-known negative outcomes of these curable STIs, our systematic review revealed a serious lack of necessary prevalence data, which impedes an accurate assessment of the STIs among pregnant women in multiple regions worldwide, thereby preventing the timely diagnosis and treatment of pregnant women (and their partners and infants) to prevent known complications.

Our study was subject to some limitations. We only used PubMed for the search and may have missed other publications as a result. Although PubMed (Medline) and EMBASE are similar, their coverage of the published literature differs. For example, EMBASE is used more frequently in Europe, and PubMed in the United States. As a result of limiting our search to PubMed, we may have excluded European or abstract citations. Further, the quality of the studies included in this analysis varied considerably, including different sampling strategies, diagnostic tests used, testing strategies, and HIV coinfection rates. We attempted to control for that heterogeneity by adjusting for women’s mean age.
sensitivity of diagnostic test used (when reported), and number of women included in the sample size. Our estimates though may be underestimated because we excluded studies on sex workers (n = 2) and symptomatic women. Additionally, in countries with limited access to STI care, the prevalence studies often used convenience sampling, which may underestimate the true burden in pregnancy. Also, diagnostic tests with poor sensitivity will tend to underdiagnose true-positive cases and underreport STI prevalence as a result. Conversely, studies not performing treponemal specific testing may overreport syphilis prevalence. The limited number of studies on NG and TV might limit generalizability or precision of the estimates. Where possible, we included more than 2 studies; however, there were instances where more than 1 recent study was not available (eg, CT in West Africa, NG and TV in Asia). We excluded studies that only reported estimates of STI prevalence, but did not present data as to where those estimates came from (eg, surveys, subjective or self-reported estimates), which could have caused underrepresentation of studies from West and Central Africa or Asia. Finally, due to the significant heterogeneity in socioeconomic status within each region, regional prevalence studies may not be representative of population-level burden of STIs among pregnant women.

CONCLUSIONS

Our study highlights the urgent need to collect reliable measures of STI prevalence in low- and middle-income countries, where the burden among pregnant women is greatest. We advocate for strengthening prevalence monitoring as a method of STI surveillance in pregnant women worldwide.11 The sequelae of untreated STIs are well known.10 However, the syndromic approach continues to direct STI management among pregnant women in low- and middle-income countries, which substantially under-detects STI prevalence in pregnant women.12,13 Additional focus is needed to expand the clinical evidence for policy makers on the cost-effectiveness of integrating CT, NG, and TV screening and diagnostics into existing antenatal care programs already focusing on syphilis and HIV. In conclusion, the prevalence of curable STIs is substantial among pregnant women in low- and middle-income countries in all regions, suggesting a large population-level burden of untreated curable infections. Our study revealed a lack of necessary prevalence data among pregnant women in low- and middle-income countries, where the disease burden is greatest. The lack of reliable prevalence data not only impedes an accurate assessment of STIs among pregnant women in multiple regions worldwide, but also prevents the treatment of pregnant women to prevent adverse pregnancy and neonatal health outcomes. Data from systematic and comprehensive screening programs in pregnancy are needed to support the design and implementation of effective prevention and control strategies in low- and middle-income countries.

REFERENCES

15. CDC. Sexually transmitted diseases treatment guidelines. MMWR Recommendation Rep 2015, 64(RR):137.
Appendix 1

Search terms used


AND


AND


AND


Appendix 2

Publications included in analysis


Short Report: Acceptability and Feasibility of Rapid Chlamydial, Gonococcal, and Trichomonal Screening and Treatment in Pregnant Women in Six Low-to-Middle Income Countries

Shannon CL, BA;1 Bristow CC, PhD;2 Hoff NA, PhD;3 Wynn A, PhD;1 Nguyen M, MS;4 Medina-Marino A, PhD;5 Cabeza J, MD MPH;6 Rimoin AW, PhD;1 Klausner JD, MD MPH1

1Division of Infectious Diseases, Department of Medicine, University of California Los Angeles, CA, USA
2 Division of Global Public Health, Department of Medicine, University of California San Diego, La Jolla, CA, USA
3 Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, CA, USA
4Department of Epidemiology, Hanoi Medical University, Hanoi, Vietnam
5 Research Unit, Foundation for Professional Development, Pretoria, South Africa
6 South American Program in HIV Prevention Research, David Geffen School of Medicine, University of California Los Angeles, CA, USA

Corresponding Author:
Chelsea Shannon
10290 Wilshire Blvd, Suite 350, Los Angeles, CA 90024
Phone: (310) 748-9794 Fax: (310) 794-8297
cshannon@mednet.ucla.edu
Conflicts of Interest: None

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Short Summary: Prenatal Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis screening and treatment had high levels of acceptability and feasibility among pregnant women in six low-to-middle income countries around the world.
Abstract

Background: Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV) infections during pregnancy are linked with adverse birth outcomes. However, few countries have prenatal CT, NG, or TV screening programs. In this study, we aimed to evaluate the acceptability and feasibility of CT, NG, and TV screening and treatment among pregnant women across six low-to-middle income countries.

Methods: A total 1,817 pregnant women were screened for CT, NG, and TV in Botswana, the Democratic Republic of Congo (DRC), Haiti, South Africa, and Vietnam. An additional 640 pregnant women were screened for CT in Peru. Screening occurred between December 2012 and October 2017. Acceptability of screening was evaluated at each site as the proportion of eligible women who agreed to participate in screening. Feasibility of treatment was calculated as the proportion of women who tested positive that received treatment.

Results: Acceptability of screening and feasibility of treatment was high across all six sites. Acceptability of screening ranged from 85-99%, and feasibility of treatment ranged from 91-100%.

Discussion: The high acceptability of screening and treatment for CT, NG, and TV among pregnant women supports further research to evaluate the cost-effectiveness of prenatal CT, NG, and TV screening programs.

Keywords: STD screening, STD treatment, acceptability, feasibility, international STDs
Introduction

Every year, there are an estimated 349 million new infections with Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV) globally. In pregnant women, those infections can be linked to serious adverse birth outcomes, including premature labor and birth and low birth weight infants. Furthermore, maternal CT or NG infection during birth can cause mother-to-child CT or NG transmission in 30-70% of cases. Neonatal CT infection can cause chlamydial ophthalmia neonatorum as well as chlamydial pneumonia. Neonatal NG infection can cause gonococcal ophthalmia neonatorum, which, if untreated, may lead to blindness. Finally, maternal infection with CT, NG, or TV may be associated with an increased chance of acquiring HIV infection and an increased likelihood of mother-to-child HIV transmission.

Currently, maternal diagnostic screening for CT, NG, and TV is only done in a limited number of countries. Diagnostic screening typically involves nucleic acid amplification tests that are expensive and take multiple days to receive results. Due to the limited access to laboratory testing and the lack of cost-effectiveness data, the World Health Organization (WHO) only recommends symptom-based management of CT, NG, and TV. However, as most of those infections are asymptomatic, the syndromic management approach leaves many sexually transmitted diseases (STDs) undiagnosed and untreated, and thus may contribute to a large number of attributable adverse birth outcomes. A recent study in Australia showed that prenatal CT screening and treatment reduced the risk of adverse birth outcomes on a population level.
Many rapid diagnostic tests for CT, NG, and TV are in development or newly available. Such tests will increase the accessibility of prenatal STD screening globally by increasing access to testing. However, STD screening is often viewed as stigmatizing, and specimen collection through pelvic examination or self-collected vaginal swabs might be considered invasive. As rapid diagnostic tests become more readily available, it is critical to evaluate the acceptability and feasibility of prenatal screening programs for CT, NG, and TV. Understanding the acceptability and feasibility is a key step in informing the development of policy recommendations.

The World Health Organization (WHO) defines acceptability as the extent to which an intervention is considered to be reasonable among those receiving, delivering, or affected by the intervention. Feasibility is defined as the likelihood that an intervention can be properly carried out or implemented in a given context. Studies have shown prenatal syphilis screening to be acceptable and feasible. A study done in Australia used qualitative methods to assess acceptability of rapid CT and NG testing among primary care providers in remote settings. The study found high acceptability of testing among primary care providers delivering the intervention. In this study, we aimed to evaluate the acceptability and feasibility of prenatal CT, NG, and TV screening and treatment among pregnant women in low-to-middle income countries. To do this, we compiled acceptability and feasibility data from CT, NG, and TV screening and treatment projects conducted by our study team in 6 different low-to-middle income countries.
Materials and Methods

Over the past 5 years, we have conducted STD screening studies among pregnant women in six distinct settings. A total of 1,817 pregnant women were recruited for CT, NG, and TV screening at prenatal clinics in Botswana, the Democratic Republic of Congo (DRC), Haiti, South Africa, and Vietnam. Additionally, 640 pregnant women were recruited for CT screening at prenatal clinics in Peru. In Haiti, screening occurred at the Haitian Study Group for Kaposi’s Sarcoma and Opportunistic Infections (GHESKIO) clinics in Port-au-Prince from October 2015 to January 2016. In Peru, screening took place from December 2012-January 2013 at the Instituto Nacional Materno Perinatal (INMP) and Hospital Nacional Arzobispo Loayza (HNAL). In Vietnam, women were screened at the Ha Dong Hospital in Hanoi from September to December 2016. In Botswana, screening occurred at the maternal and child health clinic in Princess Marina Hospital, Gaborone from July 2015 to March 2016. In DRC, women were screened at the Kintanu, Ngeba, Ngamba, and Lemfu clinics in the Kisantu Health Zone, Bas Congo Province from October 2016 to March 2017. In South Africa, screening took place at two clinics in the Soshanguve Township and one clinic in the Mamelodi Township in Tshwane District from September 2016 to October 2017.

In Botswana, DRC, Haiti, South Africa, and Vietnam, eligible women were pregnant, age 18 years or older, and less than 35 weeks pregnant. Eligible women in Peru were age 16 years or older and less than 41 weeks pregnant. Samples were obtained via self-collected vaginal swabs in Botswana, Haiti, Peru, South Africa, and Vietnam. In DRC, samples were collected by the physician during the prenatal visit. Testing in Botswana, DRC, Haiti, South Africa, and Vietnam was conducted using the GeneXpert CT/NG and TV tests (Cepheid, Sunnyvale, California). In
Peru, testing was done using the Aptima Combo2® system (Hologic, San Diego, California). Study protocols were approved by in-country institutional review boards / research ethics committees and the University of California Los Angeles, as well as local health departments and participating hospitals.

Women that tested positive for an STD were treated with 1 gm of oral azithromycin for CT infection, with 250 mg injection of ceftriaxone plus 1 gram of oral azithromycin for NG infection, or with 2 gms of oral metronidazole for TV infection. However, in DRC, women with NG infection were treated with 1 gram of oral azithromycin without ceftriaxone, per local recommendations. For HIV-infected participants, the dosage of metronidazole was 400 mg orally twice daily for 7 days. Patients were asked to return to clinic in three to six weeks for a test of cure. Women typically received same day treatment in South Africa and Botswana, while patients returned to the clinic for treatment in Haiti, DRC, Peru, and Vietnam. Women who tested positive for CT, NG, or TV were given antibiotics to bring to their partner or asked to bring their partner in for treatment.

We assessed acceptability of screening by measuring the uptake of screening among eligible pregnant women. We measured feasibility of treatment by measuring the proportion of pregnant women who tested positive that received treatment. We calculated 95% confidence intervals for acceptability of screening and feasibility of treatment using the binomial method. We calculated percent acceptability overall weighted by the sample size. We also used a full Bayesian method for bivariate random-effects meta-analysis to calculate pooled estimates of acceptability of screening and feasibility of treatment with SAS (v9.4, Cary, NC) PROC
MCMC. By using quantitative metrics, we were able to compare results between countries and determine overall acceptability and feasibility of prenatal CT, NG, and TV screening and treatment among the six sample populations.

Results

Acceptability of CT, NG, and TV screening among pregnant women was consistently high, with values ranging from 85-99%. Feasibility of treatment was also high, ranging from 91-100%. Specific values for the acceptability of screening and feasibility of treatment are shown in the table.

Discussion

Prenatal CT, NG, and TV screening and treatment was acceptable and feasible among pregnant women across all six study populations. Despite the stigma associated with STD testing, nearly all pregnant women were willing to participate in screening, and nearly all who tested positive successfully received treatment. The high acceptability of screening and treatment among pregnant women, in conjunction with previously found high acceptability among primary care providers, indicates an overall high acceptability of prenatal screening programs for CT, NG, and TV among various populations. Furthermore, the successful treatment of prenatal STDs across multiple settings indicates the feasibility of identifying and treating prenatal STDs in countries that traditionally rely on syndromic management. Those findings should be used to inform the development of screening policies for STDs in pregnancy.
We evaluated acceptability and feasibility of CT, NG, and TV screening and treatment using quantitative measures: uptake of screening and the proportion of women who tested positive that received treatment. By using those measures, we were able to quantitatively compare results by country, specimen collection method, and treatment practice. We were also able to avoid response biases that can occur with interviews or surveys.

Despite such advantages, our method of evaluation had a few limitations. Most notably, we have limited information on specific reasons for accepting or declining screening or treatment. In the Botswana, Peru, and DRC studies, the primary reason for non-acceptance of screening was lack of time. It was rare that testing was refused due to screening methods.\textsuperscript{20, 21} However, without qualitative measures at every site, we cannot infer why different sites had varying levels of acceptability and feasibility, and we cannot determine how acceptability and feasibility might be improved. Notably, acceptability of screening was lowest in DRC, which was the only site that used physician-collected samples instead of self-collected samples. Additionally, feasibility of treatment was slightly higher at sites that provided same-day treatment than sites that did not, likely due to the fact that patients did not have to return to clinic to receive treatment.

Another limitation stems from the fact that, while each country had very similar protocols, there were differences from site to site, ranging from differences in staff to differences in clinic set up. It is possible that such differences may have influenced acceptability and feasibility rates from site to site. However, those differences also reflect the reality of

\textsuperscript{20, 21}
implementing STD screening and treatment programs in diverse real world settings, and support
the generalizability of our findings.

Finally, data were only collected from one or two clinical settings per country. The
results do not reflect the acceptability rates of entire regions or countries, and may not reflect all
socioeconomic or demographic groups.

Moving forward, well-powered trials to evaluate the effectiveness of prenatal CT, NG,
and TV screening programs to prevent adverse birth outcomes are urgently needed. It is also
essential to evaluate other aspects of feasibility, such as outcomes of partner treatment, cure
rates, and rates of re-infection. Ultimately, program sustainability will depend on updating WHO
guidelines and adoption on the country level.

Understanding the acceptability and feasibility of prenatal STD screening in low-to-
middle income country settings is an important step towards implementing such programs. The
high acceptability of screening and feasibility of treatment suggest that women are willing to
provide self-collected vaginal swabs, undergo screening, and receive treatment. Given the
increasing accessibility of rapid diagnostic STD tests and the high acceptability and feasibility of
screening and treatment, the data support further programmatic evaluation of prenatal CT, NG,
and TV screening programs.
References


Table Legend: The table shows the acceptability of screening and feasibility of treatment of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* infections among pregnant women in Botswana, Democratic Republic of Congo, Haiti, Peru, South Africa, and Vietnam.
**Table**: Acceptability of Screening and Feasibility of Treatment of *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) Infections Among Pregnant Women in 6 Low-to-Middle Income Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Eligible Women</th>
<th>Number of Women who Agreed to Screening</th>
<th>Acceptability of Screening* (%)</th>
<th>Number of Women with CT, NG, or TV Infection</th>
<th>Number of Women who Received Treatment</th>
<th>Feasibility of Treatment* (%)</th>
<th>Specimen Collection Method</th>
<th>Treatment Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>225</td>
<td>200</td>
<td>88.9% (95% CI: 84.0, 92.7)</td>
<td>30</td>
<td>30</td>
<td>100.0% (95% CI: 88.4, 100.0)</td>
<td>Self-collected</td>
<td>Same-day treatment</td>
</tr>
<tr>
<td>Democratic Republic of Congo</td>
<td>432</td>
<td>368</td>
<td>85.2% (95% CI: 81.5, 88.4)</td>
<td>66</td>
<td>64</td>
<td>97.0% (95% CI: 89.5, 99.6)</td>
<td>Provider-collected</td>
<td>Return to clinic for treatment</td>
</tr>
<tr>
<td>Haiti</td>
<td>322</td>
<td>300</td>
<td>93.2% (95% CI: 89.8, 95.7)</td>
<td>133</td>
<td>122</td>
<td>91.7% (95% CI: 85.7, 95.8)</td>
<td>Self-collected</td>
<td>Return to clinic for treatment</td>
</tr>
<tr>
<td>Peru</td>
<td>640</td>
<td>600</td>
<td>93.8% (95% CI: 91.6, 95.5)</td>
<td>60</td>
<td>59</td>
<td>98.3% (95% CI: 91.1, 100.0)</td>
<td>Self-collected</td>
<td>Return to clinic for treatment</td>
</tr>
<tr>
<td>South Africa</td>
<td>442</td>
<td>430</td>
<td>97.3% (95% CI: 95.3, 98.6)</td>
<td>174</td>
<td>174</td>
<td>100.0% (95% CI: 97.9, 100.0)</td>
<td>Self-collected</td>
<td>Same-day treatment</td>
</tr>
<tr>
<td>Vietnam</td>
<td>403</td>
<td>400</td>
<td>99.3% (95% CI: 97.8, 99.8)</td>
<td>33</td>
<td>31</td>
<td>93.9% (95% CI: 79.8, 99.3)</td>
<td>Self-collected</td>
<td>Return to clinic for treatment</td>
</tr>
<tr>
<td>Pooled (random effects model)**</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>94.2% (95% CI: 86.2, 98.3)</td>
<td></td>
<td></td>
<td>97.9% (95% CI: 92.6, 99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (weighted)</td>
<td></td>
<td></td>
<td>93.3% (95% CI: 92.2%, 94.2%)</td>
<td></td>
<td></td>
<td>96.77% (95% CI: 94.8%, 98.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Acceptability of screening was calculated as the proportion of uptake of screening among eligible women. Feasibility of treatment was calculated as the proportion of women who tested positive for an STI that received treatment. 95% confidence intervals were calculated using the binomial method.

** Random Effects Model run using SAS PROC MCMC
Lost opportunity to save newborn lives: variable national antenatal screening policies for Neisseria gonorrhoeae and Chlamydia trachomatis

Alexandra Medline1, Dvora Joseph Davey2,3 and Jeffrey D Klausner2

Abstract
Unfavorable pregnancy outcomes caused by Chlamydia trachomatis or Neisseria gonorrhoeae infection are well known. The first step in addressing antenatal C. trachomatis and N. gonorrhoeae infection is a national policy to screen all pregnant women for C. trachomatis and N. gonorrhoeae, regardless of symptoms. The aim of this study was to inform policy makers on the presence of antenatal screening recommendations for C. trachomatis and N. gonorrhoeae infection. We conducted a three-part study from June 2015 to February 2016. We analyzed English and French language information online on Ministry of Health websites regarding C. trachomatis and N. gonorrhoeae antenatal screening. We referenced both primary official country and regional policy documents. We contacted the Ministry of Health directly if the information on the national antenatal screening was outdated or unavailable. In parallel, we sent a survey to the regional representative from the World Health Organization to help collect country-level data. Fourteen countries have current policies for antenatal screening of C. trachomatis and/or N. gonorrhoeae infection: Australia, the Bahamas, Bulgaria, Canada, Estonia, Japan, Germany, Latvia, New Zealand, Democratic People’s Republic of Korea, Romania, Sweden, the United Kingdom, and the United States. Australia, New Zealand, and Latvia and the United States restricted antenatal screening to women ≤25 years old and those of higher risk. Several countries responded that they had policies to treat pregnant women with symptoms. This is the currently recommended WHO guideline but is not the same as universal screening. North Korea had policies in place which were not implemented due to lack of personnel and/or supplies. National level policies to support routine screening for C. trachomatis and N. gonorrhoeae infection to prevent adverse pregnancy and newborn outcomes are uncommon.

Keywords
Chlamydia (Chlamydia trachomatis), gonorrhea (Neisseria gonorrhoeae), prevention, screening, women

Date received: 28 March 2016; accepted: 24 June 2016

Introduction
Sexually transmitted infections (STIs) are a significant public health concern with more than one million people acquiring an STI every day worldwide.1,2 The most common sexually transmitted bacterial infection is Chlamydia Trachomatis (CT) with an estimated 131 million new cases each year.1,3 CT and Neisseria Gonorrhoeae (NG) infections are often asymptomatic, especially in women.4 The syndromic approach to CT and NG management currently recommended by the World Health Organization (WHO) may therefore be ineffective.4,5 This approach uses the identification of symptoms and signs that are recognizable and consistent

1Columbia University Mailman School of Public Health, New York, NY, USA
2David Geffen School of Medicine, UCLA, Program in Global Health, Division of Infectious Disease, Los Angeles, CA, USA
3Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, USA

Corresponding author:
Alexandra Medline, Columbia University Mailman School of Public Health, 722 W 168th St, New York, NY 10032, USA.
Email: aem2254@columbia.edu
such as vaginal discharge and lower abdominal pain as a basis for CT and NG treatment. However, only 5–30% of women with laboratory-confirmed CT and NG infection develop symptoms. An alternative approach that screens all pregnant women regardless of symptoms might be beneficial when considering the extensive adverse pregnancy and newborn health outcomes that are linked to both CT and NG.

Unfavorable pregnancy outcomes caused by CT and NG infection include spontaneous abortion, stillbirth, prematurity, low birth weight, and post-partum endometritis. These adverse outcomes may be particularly perilous for newborns in resource-constrained areas of the developing world. Screening may be very important for early eradication of infection which may reduce preterm birth by reducing exposure to these pathogens during pregnancy.

Untreated CT can also increase the likelihood of HIV transmission from a mother to her infant. In addition, perinatal transmission of CT or NG can cause neonatal ophthalmia neonatorum (conjunctivitis) and pneumonia. Worldwide, up to 4000 newborn babies become blind every year because of eye infections attributable to untreated maternal CT and NG infections. Effective means of preventing conjunctivitis and newborn blindness include screening all pregnant women for both CT and NG infection, and subsequently treating pregnant women and their partners for these infections.

Universal antenatal screening refers to testing all pregnant women for CT and NG infection regardless of symptoms, age, and other risk factors. Studies in several regions have demonstrated the acceptability and feasibility of antenatal screening for CT and NG infection including Australia, Africa, Europe, Latin America, and the Middle East. Another study demonstrated that antenatal CT screening of women aged 16–25 years was cost effective in Australia, even with a low estimated prevalence of 3%. Nonetheless, screening recommendations for STIs in pregnancy while strongly supported by evidence for infections like human immunodeficiency virus and syphilis are less strong and made with less certain evidence for other curable STIs like CT and NG. For example, according to the U.S Preventative Services Task Force, there is adequate certainty that there will be a ‘moderate to substantial’ net benefit from screening pregnant women who are at increased risk of infection (i.e. high-risk sexual behavior or age <25 years). However, for women who are not at an increased risk, evidence is considered insufficient and the net benefit of screening is considered to be small.

The aim of our study was to provide additional evidence on the frequency and distribution of CT and NG screening policies in different countries worldwide to add to current literature on this topic. Our study supports updated national, regional, and global recommendations of policies for antenatal CT and NG screening and treatment.

**Methods**

We conducted a three-part study from June of 2015 to February 2016. First, we analyzed available data online on select English-language Ministry of Health websites regarding STI screening for pregnant women. Google was used as our primary search engine. Specific terms that were used in our online search included ‘antenatal Ministry of Health guidelines,’ ‘STI screening recommendations,’ ‘chlamydia antenatal screening,’ ‘gonorrhea antenatal screening,’ ‘STI management,’ and ‘antenatal visit recommendations.’ These terms were searched for each respective country. Official documentation from this search included documents from MOH or other government official websites that provided information on screening policies. Primary source documents other than MOH documents were accepted such as those provided from national health protection bodies such as the European Center for Disease Prevention and Control. We identified 28 countries’ policies on antenatal CT or NG screening online.

Second, we contacted the country’s Minister of Health when official screening recommendations for a country were not available online. If data were available online, the country MOH was not contacted unless online information was ambiguous in order to receive secondary confirmation of results. Ministries of Health were contacted to ascertain whether they had a national CT and/or NG antenatal screening policy in place. Contact was via email in English, French, or Spanish.

Third, we contacted the reproductive health representative for each WHO region and requested assistance in collecting country-level data on screening practices among pregnant women for both CT and NG. WHO regions include Africa (47 countries), the Americas (35 countries), the Eastern Mediterranean (21 countries), Europe (53 countries), South-East Asia (11 countries), and the Western Pacific (27 countries).

This survey included the following four questions:

1. Is there a government policy to provide routine chlamydia screening for pregnant women in the country? (Yes/No)
2. If Yes, [are there] certain criteria for screening? (Please list criteria, e.g. <25 years old, high risk, etc.)
3. Is there a government policy to provide routine gonorrhea screening for pregnant women in the country? (Yes/No)
4. If Yes, [are there] certain criteria for screening? (Please list criteria, e.g. <25 years old, high risk, etc.)
Results

Of all 196 countries worldwide, we identified primary Ministry of Health or other primary sources of data on antenatal CT or NG screening policies for 28 countries (see online supplemental material). For the first round of surveys, we contacted an additional 98 country Ministries of Health, from which we received responses from 16 countries. Five of the 16 responses recommended other sources for screening policy information. For the second round of surveys with the WHO regional offices, we received 20 country responses from WHO representatives, which included three additional countries that have national recommendations for antenatal CT or NG screening. In total, we received 64 responses (including primary sourced documents) which provided clear policy data on 57 countries in total. Of those 57 countries, 14 countries reported to have antenatal CT or NG screening policies, 43 countries reported to not have antenatal CT or NG screening policies, while 139 countries remain unknown (Tables 1 and 2).

Our study found that 14 countries have policies for antenatal screening of CT and/or NG infection: Australia, the Bahamas, Bulgaria, Canada, Estonia, Japan, Germany, Latvia, New Zealand, Democratic People’s Republic of Korea, Romania, Sweden, United Kingdom, and the United States (Figure 1). Of those countries, several restrict to either CT or NG antenatal screening to young women <25 years of age, including Australia, the United States, New Zealand, and Latvia. Several countries responded that they have policies to treat pregnant women with

<table>
<thead>
<tr>
<th>Table 1. Policies for national antenatal screening of Chlamydia trachomatis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 43)</td>
</tr>
<tr>
<td>Austria, Bangladesh, Bhutan, Bolivia, Botswana, Cuba, Cyprus, Denmark, Egypt, Guatemala, Guyana, Haiti, Iceland, India, Indonesia, Iran, Iraq, Israel, Kenya, Latvia, Malaysia, Maldives, Mexico, Morocco, Myanmar, Namibia, Nepal, Norway, Panama, Philippines, Poland, Saudi Arabia, Sierra Leone, Singapore, South Africa, South Sudan, Spain, Sri Lanka, Switzerland, Thailand, Timor-Leste, UK, Uganda, Zambia</td>
</tr>
</tbody>
</table>

*Pregnant women <25 years of age and in areas where CT prevalence is high.

*Pregnant women up to the age of 24, pregnant women of ‘social risk group,’ pregnant women with sexually transmitted infection in anamnesis or clinical symptoms.

*Pregnant women <25 years of age and those older if at increased risk.

<table>
<thead>
<tr>
<th>Table 2. Policies for national antenatal screening of Neisseria gonorrhoeae.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 43)</td>
</tr>
<tr>
<td>Austria, Bangladesh, Bhutan, Bolivia, Botswana, Cuba, Cyprus, Denmark, Egypt, Guatemala, Guyana, Haiti, Iceland, India, Indonesia, Iran, Iraq, Israel, Kenya, Latvia, Malaysia, Maldives, Mexico, Morocco, Myanmar, Namibia, Nepal, Norway, Panama, Philippines, Poland, Saudi Arabia, Sierra Leone, Singapore, South Africa, South Sudan, Spain, Sri Lanka, Switzerland, Thailand, Timor-Leste, UK, Uganda, Zambia</td>
</tr>
</tbody>
</table>

*Includes known risk factors or who live in or comes from areas where prevalence is high.

*Includes <25 years of age, where no previous testing has been done in current relationship, in patients with partner change within previous six months or during pregnancy, in the presence of symptoms, and in patients with a history of previous NG infection.

*Sexually active women under 25 years of age and sexually active women aged 25 years and older if at increased risk.
symptoms, consistent with current WHO guidelines for syndromic management. North Korea had screening policies in place which were not implemented due to lack of personnel or supplies.

Discussion

This study informs public health officials of the presence of current national policies on antenatal CT and NG screening by country. Antenatal CT and NG screening policies were found in 14 countries among 57 countries (25%). Antenatal CT and NG screening policies were uncommon. Thirteen countries were found to have antenatal screening policies for CT infection and eight countries were found to have antenatal screening policies for NG infection. Further, having a national policy does not translate into providing testing to all pregnant women. For example, many women are still not tested for CT and NG infection despite screening recommendations in the US\textsuperscript{27,28} and New

Figure 1. (a) Thirteen countries have policies to provide laboratory screening for CT among pregnant women (2015). (b) Eight countries have policies to provide laboratory screening for NG among pregnant women (2015).
Increasing the coverage of antenatal screening for CT and NG infection could greatly improve maternal and infant health outcomes.

Previous studies have confirmed the importance of improving interventions to screen and treat CT and NG in early pregnancy. Other studies demonstrated that routine antenatal CT and NG screening is the most effective intervention to prevent eye infections and pneumonia among newborns. Previous studies have also indicated that antenatal CT screening can be both cost effective and highly acceptable in various global settings, especially in areas with high CT prevalence.

Recent research has shown a persistent high prevalence of antenatal CT in different settings worldwide, especially in low- and middle-income countries in sub-Saharan Africa and Pacific Island countries. Screening pregnant women for CT has been recommended as a result of studies analyzing antenatal CT prevalence in different settings. Antenatal CT prevalence studies worldwide have demonstrated high prevalence within specific populations in Botswana (8%), Cameroon (38.4% in HIV-infected patients and 7.1% in HIV-uninfected patients), China (10.1%), Kenya (6%), Mozambique (8%), Papua New Guinea (11.1%), Peru (10%), Saudi Arabia (10.5%), South Africa (17.8%), and Tanzania (11.4%).

Integrating antenatal CT and NG screening can help identify curable infections among pregnant women and sequelae among newborns. With the advent of highly sensitive and specific nucleic acid and protein testing platforms, implementation of routine screening during antenatal care in resource limited countries is warranted. Clinical trials, such as the one ongoing in Papua New Guinea, are recommended to evaluate context-specific cost–benefit of CT and NG routine screening during antenatal care in various settings.

One limitation to our study included the large proportion of MOH and WHO representatives who did not provide responses. One hundred and thirty-nine countries were left unknown. The unknown policy status of a large number of countries may be due to both language and internet limitations on the part of the research group. Also, many countries remain unknown due to absence or inaccuracy of MOH contact information. Due to various challenges faced in collecting the aforementioned data, including lack of MOH contact information, language barriers, and lack of responsiveness by WHO and MOHs, we may have excluded countries with antenatal CT or NG screening policies. However, we hypothesize that the response rate was highest among countries with antenatal CT or NG screening policies. We included results for 57 countries for which we received information on antenatal CT or NG policies.

Another limitation was the discrepancy between official online documents compared to email responses received from Ministries of Health. In all cases, the Ministry of Health responses took priority over other sources. Furthermore, if CT or NG screening was not listed on primary source documents as a part of routine prenatal care, we concluded that there was no national policy for screening for these infections. However, we understand that this may be a result of a specific country deciding against screening after consideration of the evidence of that specific country or region. We also recognize that having a policy does not mean that the screening is necessarily done. Further studies should verify where screening is actually available.

**Conclusion**

Universal antenatal CT or NG screening policies were uncommon. Some regions (Middle East, Central and South America) did not have any country with antenatal CT or NG screening policies, despite persistently high antenatal CT and NG prevalence. There is a need for a response from international agencies to build a more robust and comprehensive database of programs to increase routine CT and NG in antenatal care. There is also a need to increase the evidence base on the impact and cost–benefit of routine screening and treatment for CT and NG infections in pregnant women in various settings. Considering the high prevalence of CT and NG, and the negative maternal and newborn sequelae of these infections, we recommend further implementation science to demonstrate the feasibility, acceptability, and cost–benefit of integrating screening for CT and NG into existing antenatal programs. CT and NG screening might be important in prevention of adverse maternal and newborn sequelae. Our study found that CT and NG policies supporting antenatal screening vary by region and in many countries no screening policies exist. We therefore recommend that countries consider national policies on CT and NG screening in pregnancy and make these publicly available.

**Declaration of conflicting interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis screening and treatment of pregnant women in Port-au-Prince, Haiti

Claire C Bristow1, Patricia Mathelier2, Oksana Ocheretina3,4, Daphne Benoit4, Jean W Pape3,4, Adriane Wynn5 and Jeffrey D Klausner2,5

Abstract
In Haiti, routine screening for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), and Trichomonas vaginalis (TV) among pregnant women is not conducted; yet these sexually transmitted infections (STIs) are associated with adverse birth and newborn health outcomes. We aimed to assess the acceptability and feasibility of screening and the prevalence of STIs among pregnant women in Port-au-Prince, Haiti. Pregnant women of at least 18 years of age who attend Haitian Study Group for Kaposi's sarcoma and Opportunistic Infections (GHESKIO) clinics in Port-au-Prince, Haiti provided self-collected vaginal swab specimens. Laboratory testing was done with Xpert\textsuperscript{TM} CT/NG and Xpert\textsuperscript{TM} TV. The results of this study showed that of the 322 pregnant women who visited GHESKIO for their regular scheduled appointments, 300 (93.2%) consented for CT, NG, and TV testing. Of those, 107 women (35.7%) tested positive for at least one STI. There were 42 (14.7%) cases of CT, 8 (2.8%) NG, and 83 (29.0%) TV infections. Most infections were treated – 122 of 133 (91.7%). In summary, we found that it was highly acceptable and feasible to implement CT, NG, and TV screening among pregnant women in Port-au-Prince, Haiti. We found high prevalence of STIs among pregnant women, which suggest that STI screening in this population may be warranted.

Keywords
Sexually transmitted infections, Haiti, STI diagnostics, STI screening, pregnancy

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Introduction
Sexually transmitted infections (STIs) cause a significant global health burden, and cervico-vaginal infections are related to many adverse health outcomes. Although curable, sexually transmitted Trichomonas vaginalis (TV), Chlamydia trachomatis (CT), and Neisseria gonorrhoeae (NG) were responsible for over 350 million new infections worldwide in 2012.\textsuperscript{1} A medical history alone is insufficient for the accurate diagnosis of genitourinary tract infections.\textsuperscript{2} Many STIs can be asymptomatic and can only be diagnosed with screening tests.\textsuperscript{3} Therefore, although the current World Health Organization guidelines recommend syndromic management for STI diagnosis in low- and middle-income countries,\textsuperscript{4} syndromic management is unlikely to enhance STI control.\textsuperscript{5} The early identification and subsequent treatment of STIs and other genital infections among index patients and their partners are paramount to achieving an effective reduction in the disease burden.

\textsuperscript{1}Division of Global Public Health, Department of Medicine, University of California San Diego, La Jolla, CA, USA
\textsuperscript{2}Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA
\textsuperscript{3}Department of Medicine, Weill Cornell Medical College, NY, USA
\textsuperscript{4}Les Centres GHESKIO, Port-au-Prince, Haiti
\textsuperscript{5}Department of Health Policy, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA, USA

Corresponding author:
Claire C Bristow, Division of Global Public Health, University of California San Diego, 9500 Gilman Drive 0507, La Jolla, CA 92037-0507, USA.
Email: cbristow@ucsd.edu
The immunologic response triggered by lower genital tract infections with CT and NG leads to significant inflammation of the cervico-endometrial tissue. Due to infection and the associated chronic inflammatory response, several important sequelae may result from these infections, including pelvic inflammatory disease, ectopic pregnancy, and infertility. TV infection has been associated with a more than 2.7-fold increase in the risk of HIV acquisition, a 1.3-fold increase in preterm labor and a 4.7-fold increase in pelvic inflammatory disease. STIs such as CT, NG and TV during pregnancy may be associated with increased rates of adverse pregnancy outcomes including neonatal and infant death, preterm birth, low birth weight, and spontaneous abortion.

In Haiti, certain adverse birth outcomes remain high, including neonatal mortality, which was estimated at 14.1/100 live births in 2012, and preterm birth was estimated at 25/1000 live births in 2012. Improvements in STI diagnosis and treatment may play a role in reducing the high rates of these adverse pregnancy outcomes. The objective of this study was to assess the acceptability and feasibility of the screening of genital CT, NG and TV infections in Haiti, two reports estimated that 40% of women in rural areas who were receiving antenatal care and 47% of women in urban areas who were receiving antenatal care had at least one STI. In Haiti, certain adverse birth outcomes remain high, including neonatal mortality, which was estimated at 25/1000 live births in 2012, and preterm birth was estimated at 14.1/100 live births in 2010. Improvements in STI diagnosis and treatment may play a role in reducing the high rates of these adverse pregnancy outcomes. The objective of this study was to assess the acceptability and feasibility of the screening of genital CT, NG and TV infections. Acceptability was measured by the percentage of patients who consented for participation among those offered testing.

Testing was conducted by study personnel using the FDA-cleared Xpert® CT/NG and Xpert® TV assays (Cepheid, Sunnyvale, CA). The high sensitivity of nucleic acid amplification tests for CT, NG and TV makes them suitable as screening tests particularly because non-invasive specimens like urine and self-collected vaginal swabs can be used. Nucleic acid amplification tests do not require viable organisms and provide convenient specimen processing, allowing use in diverse settings. Several studies have evaluated the utility and performance of self-collected specimens for CT and NG testing. The Xpert® CT/NG and TV assays have test performance equal to other FDA-approved nucleic acid amplification tests in central clinical laboratories. Laboratory testing was done within 72 hours at the GHESKIO central laboratory.

The women returned to GHESKIO within seven days from specimen collection to receive their test results, and free treatment was provided to those who tested positive. Women who tested positive for CT, NG or TV were given 1 dose (1 g) of azithromycin, ceftriaxone 250 mg injection and 1 g of azithromycin, or 1 dose (2 g) of metronidazole, respectively. They were also counseled on how to prevent infection. Feasibility was measured by the percentage of infections that were treated. Women with positive tests were asked to return no earlier than three weeks after treatment for test-of-cure. Women were counseled to bring their partners or refer their partners with a patient referral card to GHESKIO for onsite treatment. Partner-delivered therapy was provided to some women for treatment of CT and TV infections.

Data were collected electronically in secure databases and were analyzed using SAS v9.4 (Cary, NC, USA). Ethical approval was provided by Weill Cornell Medical College, New York, General Institutional Review Board protocol number 15032016010. Ethical approval was also given by the GHESKIO Institutional Review Board.

Results
A total of 322 pregnant women presenting to GHESKIO were screened for participation over a four-month study period. Of the 322 pregnant women who visited GHESKIO for their regular scheduled appointments, 300 (93.2%) participated in the study and were tested for CT, NG and TV. Of those, 286 (95.3%) returned to receive their test results. There were 107 women (35.7%) who tested positive for at least one STI (Figure 1). There were 42 women (14.0%) who tested positive for CT. Of the women who tested positive for CT, 39 (92.9%) were treated. For NG, eight women (2.7%) tested positive, and six (75.0%) returned and received treatment. And lastly, for TV, 83 women (27.7%) tested positive. Of those

Methods
All pregnant women over the age of 18 years who visited the Haitian Study Group for Kaposi’s sarcoma and Opportunistic Infections (GHESKIO) antenatal clinic in Port-au-Prince, Haiti between 26 October 2015 and 14 January 2016 were offered screening for cervicovaginal CT, NG, and TV infections. GHESKIO is a non-profit organization that works in partnership with the Haitian Government to provide integrated primary care services, including HIV counseling, AIDS care, antenatal care, and management of tuberculosis and STIs. Participants who gave informed consent provided self-collected vaginal swab specimens after verbal instructions provided by GHESKIO healthcare employees. Patients were not offered any incentives for screening. Acceptability was measured by the percentage of patients who consented for participation among those offered testing.
83 women, 77 (92.8%) received treatment. Of all of the participants, four were co-infected with all infections tested: NG, CT and TV. Additionally, of the women who tested positive initially, there were 13 partner referrals to GHESKIO who came for treatment.

Among the 107 women who tested positive for at least one STI, 83 (77.6%) returned for a test-of-cure. Sixty-two TV-infected women returned for the test-of-cure, of whom 28 (45.2%) tested positive for TV. Five NG-infected women returned for test-of-cure, of whom one (20.0%) was positive. Thirty-two CT-infected women returned for test-of-cure, of whom three (9.4%) tested positive for CT. Those women were retreated.

**Discussion**

We provided screening for genital CT, NG, and TV infections for 300 pregnant women in routine antenatal care in Port-au-Prince, Haiti. We found that STI screening in antenatal care was acceptable with most, over 90%, of antenatal patients consenting to STI testing at their antenatal visit. Screening led to the identification of prevalent CT, NG and TV infections; and over a third of participants tested positive for at least one of the three STIs tested. We found high STI prevalence among this population with almost 15% testing positive for CT, an infection known to be associated with serious adverse outcomes in pregnancy.10,12 NG infections were identified in over 2% of participants. TV infection was the most prevalent STI identified in this study with over a quarter of participants testing positive. Infection with TV, a motile protozoan, is the most common, non-viral STI worldwide.1 Of those infections identified, a very high proportion, over 90%, were treated making screening during antenatal care an effective way to both identify and treat STIs in pregnancy. Some participants with STIs did not return for treatment even after follow-up phone calls were made.

Test-of-cure visits were conducted approximately three weeks after treatment. Some participants continued to test positive even after following adequate treatment. Most striking is that almost half of those treated for TV had a positive TV test-of-cure result. Molecular tests detect nucleic acid from organisms whether they are alive or not. However, that means that treated individuals may continue to test positive using a molecular test after treatment beyond the period of infectivity. In addition, there is emerging evidence of metronidazole-resistant TV globally22 and this could be another explanation for the high positive TV rates at the test-of-cure; however, we were unable to explore these possibilities in the present study. Further research is needed to determine the time to organism clearance to inform appropriate timing for test-of-cure; however, some evidence suggests that nucleic acid-based tests for NG infection will be negative at 7 to 14 days after treatment23 and over 85% of women will be negative for TV and CT nucleic acid after 21 days of treatment.24 We were unable to determine if the high positivity rate for TV at test of cure was due to the Xpert® TV assay detecting nucleic acid from dead TV organisms, treatment failure or reinfection.

Many nucleic acid amplification tests have been optimized for use with several specimen types including non-invasive specimens like urine and patient self-collected specimens (such as vaginal and rectal swabs).21 An additional advantage of nucleic acid amplification tests is the advent of multiplex assays, such as the Xpert® CT/NG assay used in this study that simultaneously detected multiple targets to diagnose multiple pathogens. Those factors make the nucleic acid amplification tests ideal for a range of settings.
This study was not without limitations. Participants were those visiting Gheskio centres, a non-governmental clinical setting in Port-au-Prince, Haiti and therefore may not be representative of participants in other settings. Additionally, the moderate sample size and short duration of this study did not provide sufficient power and observation time to look at the impact of testing on pregnancy outcomes or to provide highly precise estimates of prevalence. Despite those limitations, our intervention was able to identify the prevalent CT, NG and TV infections that would have likely gone untreated in the absence of testing.

Screening for STIs in pregnancy provides an opportunity to improve health outcomes of women and infants. This study is comparable to similar pilot studies in Botswana and Peru that have demonstrated the acceptability and feasibility of clinic-based screening for STIs among pregnant women.

STI testing and treatment in antenatal care are acceptable, feasible and have led to the treatment of prevalent infections at Gheskio centers in Port-au-Prince, Haiti. Further, the high prevalence of STIs found in our sample provides support for efforts to increase screening and treatment in order to reduce the disease burden of STIs and subsequent adverse health outcomes among pregnant women and infants.

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Authors’ contributions

CCB provided oversight of the study, conducted the analysis, and wrote the manuscript. PM assisted with study implementation, data collection, data analysis. OO oversaw the study and laboratory-based processes. JWP, DB and JDK oversaw and conceived of the study. AW assisted with the data analysis and provided critical review. All co-authors provided review of the manuscript.

Declaration of conflicting interests

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Mycoplasma genitalium Infection and Female Reproductive Tract Disease: A Meta-analysis

Rebecca Lis, Ali Rowhani-Rahbar, and Lisa E. Manhart
Departments of Epidemiology and Global Health, Center for AIDS and STD, University of Washington School of Public Health, Seattle

To determine the association between Mycoplasma genitalium infection and female reproductive tract syndromes through meta-analysis, English-language, peer-reviewed studies were identified via PubMed, Embase, Biois, Cochrane Library, and reference review. Two reviewers independently extracted data. Random-effects models were employed to calculate summary estimates, between-study heterogeneity was evaluated using $I^2$ statistics, publication bias was assessed via funnel plots and the Begg and Egger tests, and methodologic quality was rated.

Mycoplasma genitalium infection was significantly associated with increased risk of cervicitis (pooled odds ratio [OR], 1.66 [95% confidence interval {CI}, 1.35–2.04]), pelvic inflammatory disease (pooled OR, 2.14 [95% CI, 1.31–3.49]), preterm birth (pooled OR, 1.89 [95% CI, 1.25–2.85]), and spontaneous abortion (pooled OR, 1.82 [95% CI, 1.10–3.03]). Risk of infertility was similarly elevated (pooled OR, 2.43 [95% CI, .93–6.34]). In subanalyses accounting for coinfections, all associations were stronger and statistically significant.

Testing of high-risk symptomatic women for M. genitalium may be warranted.

Keywords. Mycoplasma genitalium; cervicitis; pelvic inflammatory disease; pregnancy outcomes; female infertility.

Mycoplasma genitalium has been considered an emerging sexually transmitted infection (STI) for the past 5–10 years, and its association with nongonococcal urethritis in men is well established, with a pooled odds ratio (OR) of 5.5 (95% confidence interval [CI], 4.3–7.0) [1]. However, associations with female cervicitis, pelvic inflammatory disease (PID), infertility, and preterm delivery have been inconsistent [1]; fewer studies have been conducted in women, and sample sizes have been small. Although several reviews of the association of M. genitalium with female genital tract disease have been published, none has quantitatively evaluated the full spectrum of female reproductive tract syndromes [1, 2], and uncertainty over the public health importance of this organism remains. In many settings, M. genitalium responds poorly to standard therapies [3, 4], and evidence that it plays a role in reproductive tract disease would have substantial implications for current treatment recommendations.

To comprehensively evaluate the role of M. genitalium infection in women, we conducted meta-analyses of studies published since 1980 on the association with cervicitis, PID, adverse pregnancy outcomes, and female infertility, assessing each separately. We evaluated heterogeneity among studies, potential publication bias, and study quality. Where the number of studies allowed, we evaluated whether associations varied by geographic region, method of detecting M. genitalium, and definition of the outcome, through stratified analyses. Subanalyses evaluated studies that accounted for coinfections with other known pathogens.

METHODS

Data Sources and Searches
We searched the literature to identify studies published from 1 January 1980 through 25 June 2014 by using
computerized databases (PubMed, Embase, Biosis, Cochrane Library) and scrutinizing references of identified articles. The following search terms were employed in Medical Subject Heading terms and all fields (See Supplementary Appendix A for full search details): (1) mycoplasma genitalium AND cervicitis, (2) mycoplasma genitalium AND infertility, (3) mycoplasma genitalium AND (pregnancy OR pregnancy complications OR pregnancy outcomes), (4) mycoplasma genitalium AND (pelvic inflammatory disease OR PID OR pelvic infection).

Study Selection
Using preestablished criteria, studies were included if they (1) reported data from an original peer-reviewed study; (2) employed a cross-sectional, cohort, or case-control design; (3) provided adequate description of the assay used; (4) defined the outcome with sufficient detail to evaluate comparability with other studies; (5) reported sufficient data to determine the association with reproductive tract syndromes; and (6) were published in English. Studies were excluded if they reported on the development of laboratory assays, studied genomics, constituted case series or animal studies, had no comparison group, or reported only prevalence. Clinical guidelines, editorials, and letters were also excluded, as well as conference abstracts given their preliminary nature and limited information about study design. For studies from overlapping populations, the study with the largest sample size and most complete analysis was selected. Databases were queried throughout the meta-analysis to ensure complete coverage of current literature.

Data Extraction and Quality Assessment
Using a standardized form, 2 reviewers (R. L. and L. E. M.) simultaneously extracted the following data items: author, year, study location, study design, study population, sample size, detection method for M. genitalium, outcome definition, crude effect estimate, and adjusted effect estimate (if available). If crude effect estimates were not presented, they were calculated by the investigative team. If estimates could not be calculated from available data, authors were contacted for additional information. If estimates were provided for multiple definitions of the outcome, objective definitions (eg, polymorphonuclear leukocyte [PMN] counts, laparoscopy) were prioritized over clinical diagnoses. If multiple objective definitions were presented, estimates based on the most rigorous definition (eg, highest PMN counts) were selected. Discrepancies were discussed between the 2 reviewers to reach consensus.

To evaluate the quality of included studies, we adopted the Cochrane Collaboration’s domain-based approach for randomized controlled trials [5]. Although numerous rating scales have been developed to evaluate the quality of observational studies, most score individual components and combine them to create an overall score. This involves inherent weighting of components, some of which may not directly affect the validity of the study [6]. Therefore, we individually assessed the following domains of potential bias: source population, method of participant selection, rigor of the exposure measurement, rigor of the outcome measure, control for confounding, and whether the reported data were from a primary analysis. We assigned a rating of poor, fair, or good for each of these criteria based on expert knowledge of the topic area and study methods. We then assigned studies an overall quality rating of “good” if no more than 2 of the above criteria were deemed fair; “fair” if ≥3 of the criteria were deemed fair; and “poor” if ≥2 of the criteria were deemed poor (see Supplementary Appendix B for a summary of the full rating scheme). Quality ratings were tied to a specific outcome and do not necessarily reflect the intrinsic quality of the study: in some cases, the same study received different quality ratings when it was included in >1 analysis.

Data Synthesis and Analysis
Data were aggregated across studies for each syndrome to determine an overall summary OR using random-effects models. Studies with a zero cell were included by adding 0.5 to all cell counts to permit calculation of an effect estimate and 95% CI [7]. All models were executed first using crude estimates only and subsequently using adjusted estimates where provided. In all cases, these models did not differ materially, and we present data from the model incorporating the adjusted estimate where provided and crude estimates for studies where adjusted estimates were not provided. Subanalyses restricted to studies that accounted for coinfections (ie, Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis) were conducted for each outcome.

We used the I² statistic to assess heterogeneity: <25% was deemed low and >75% was deemed considerable [8]. Funnel plots were created to visually assess possible publication bias. We also performed the Begg adjusted rank correlation test, a numerical analogue to the funnel plot [9], and the Egger regression asymmetry test to account for the potentially lower power of the Begg test [10]. All analyses were conducted using Stata software version 13.1. Institutional review board approval was not required for these analyses of the published literature, and there was no external funding.

RESULTS
The systematic search for studies of M. genitalium and female reproductive tract syndromes returned 1080 titles. Of these, 311 evaluated cervicitis, 292 studied PID, 174 summarized adverse pregnancy outcomes, and 203 assessed infertility.

M. genitalium and Cervicitis
After excluding duplicate citations, 174 potentially eligible studies were identified (Supplementary Appendix Figure 1). Of these, 151 were excluded after review of title, abstract, and...
publication language. Upon full text review, 3 additional studies were excluded [11–13]. The 20 included studies evaluating the association between cervicitis and M. genitalium are summarized in Supplementary Appendix Table 1. Only 9 studies provided adjusted effect estimates [14–22]. Most used in-house polymerase chain reaction (PCR) assays to detect M. genitalium, although 2 studies employed the APTIMA transcription-mediated amplification (TMA) assay [21, 23] (Hologic, San Diego, California) and 1 study used both TMA and PCR [18]. Most studies employed an objective definition of cervicitis (≥10 to ≥30 PMNs in cervical exudates) with or without clinical criteria, but 6 studies relied solely on a clinical definition [15, 16, 18, 21, 23, 24]. Quality ratings were "good" for 9 [14, 15, 17–19, 22, 24–26] and "fair" for 11 [16, 20, 21, 23, 27–33] studies (Supplementary Appendix Table 5).

In the meta-analysis of cervicitis, M. genitalium infection was associated with a significantly increased risk of cervicitis, with a pooled OR of 1.66 (95% CI, 1.35–2.04) (Figure 1). There was moderate between-study heterogeneity (I² = 56.6% [95% CI, 28.4%–73.6%]), but no significant publication bias (Begg P = .299; Egger P = .54) (Supplementary Appendix Figure 2). In stratified analyses, there was no substantial difference in the pooled effect estimate or the I² statistic by geographic location of the study, study design, type of assay, or definition of cervicitis (data not shown). In subanalyses of studies that accounted for coinfections [14–21], the pooled OR was 1.99 (95% CI, 1.39–2.84) with moderate between-study heterogeneity (I² = 70.7% [95% CI, 39.4%–85.9%]).

M. genitalium and PID

After excluding duplicate citations, 175 potentially eligible studies were identified (Supplementary Appendix Table 3). One hundred fifty-eight references were excluded based on title and abstract review, and an additional 7 studies were excluded following full text review [34–40], resulting in 10 studies with data on the association between M. genitalium and PID (Supplementary Appendix Table 2). Adjusted effect estimates were presented for only 4 studies [20, 41–43]. Seven studies detected M. genitalium infection using PCR, 2 studies used serology [41, 44], and 1 combined PCR and serology [45]. The majority employed clinical diagnoses of PID, whereas 4 studies used objective definitions of endometritis [42, 46] and salpingitis [44, 45] determined by biopsy or laparoscopy (with or without clinical diagnoses). Quality of the studies was rated "good" for 4 studies [24, 42, 43, 46] and "fair" for 6 [20, 41, 44, 45, 47, 48] (Supplementary Appendix Table 5).

Figure 1. Forest plot of the association between Mycoplasma genitalium and cervicitis. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.
In the meta-analysis of PID, *M. genitalium* infection was associated with significantly increased risk of PID, with a pooled OR of 2.14 (95% CI, 1.31–3.49) (Figure 2). There was moderate between-study heterogeneity ($I^2 = 51.3\%$ [95% CI, 0%–76.3%]) but no significant publication bias (Begg $P = .98$; Egger $P = .055$) (Supplementary Appendix Figure 4). Excluding studies that used serology, the pooled OR was 2.73 (95% CI, 1.60–4.66) (Supplementary Appendix Figure 5) with moderate between-study heterogeneity ($I^2 = 42.2\%$ [95% CI, 0%–74.4%]). Among studies that accounted for coinfections [20, 41–43], the pooled OR was 2.53 (95% CI, 1.03–6.26) with moderate between-study heterogeneity ($I^2 = 73.0\%$ [95% CI, 24.0%–90.4%]).

**M. genitalium and Adverse Pregnancy Outcomes**

After excluding duplicate citations, there were 95 potentially eligible references (Supplementary Appendix Figure 6), 82 of which were excluded after review of title, abstract, or publication language. Four additional studies were excluded following full text review [49–52]. Although 10 studies met inclusion criteria (Supplementary Appendix Table 3), only 9 were included in the meta-analysis; 1 study assessing ectopic pregnancy was evaluated separately [41]. Six studies presented information on preterm birth [53–58], 3 presented data on spontaneous abortion [14, 38, 59], and 2 presented data on the association between *M. genitalium* and stillbirth [56, 59]. All adverse pregnancy outcomes were defined clinically, and only 3 studies reported adjusted effect estimates [38, 54, 59]. One study used TMA [54] to detect *M. genitalium*, whereas all others used PCR. Eight studies were assigned “good” quality ratings [38, 41, 54–59], and 2 were designated “fair” [14, 53] (Supplementary Appendix Table 5).

In the meta-analysis of preterm birth, *M. genitalium* infection was significantly associated with increased risk of preterm birth, with a pooled OR of 1.89 (95% CI, 1.25–2.85) (Figure 3). Between-study heterogeneity was low ($I^2 = 0.0\%$ [95% CI, 0%–44.5%]), and there was no significant publication bias (Begg $P = .85$; Egger $P = .74$) (Supplementary Appendix Figure 7). Among studies accounting for coinfections [54, 58], the pooled OR was 2.33 (95% CI, 1.08–5.01), and between-study heterogeneity remained low ($I^2 = 0.0\%$ [95% CI, 0%–0%]).

In the meta-analysis of spontaneous abortion, *M. genitalium* infection was significantly associated with increased risk of spontaneous abortion, with a pooled OR of 1.82 (95% CI, 1.10–3.03) (Figure 4). There was low between-study heterogeneity ($I^2 = 0.0\%$ [95% CI, 0%–82.2%]) and no significant publication bias (Begg $P = .60$; Egger $P = .26$) (Supplementary Appendix Figure 8). Only 1 study adjusted for coinfections [59], precluding subanalysis.

A single case-control study on ectopic pregnancy [41] used serology and reported no association (OR, 1.0 [95% CI, 0.5–2.0]). The 2 studies with data on stillbirth used PCR and demonstrated no statistically significant associations, with ORs of 1.07 (95% CI, 0.42–2.42) [56] and 1.36 (95% CI, 0.76–2.45) [59], but were too few to pool.
After excluding duplicate citations, 112 potentially eligible studies were identified (Supplementary Appendix Figure 9). One hundred two references were excluded based on title and abstract, and an additional 3 studies were excluded following full text review [34, 60, 61], resulting in 5 studies evaluating the association between *M. genitalium* and female infertility (Supplementary Appendix Table 4). Adjusted effect estimates were reported in 3 studies [42, 62, 63]. Most studies evaluated women attending fertility clinics, comparing confirmed tubal factor infertility to other causes of infertility identified through laparoscopy, culdoscopy, or hysterosalpingography [62–65].

**Figure 3.** Forest plot of the association between *Mycoplasma genitalium* and preterm birth. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

**M. genitalium and Female Infertility**

After excluding duplicate citations, 112 potentially eligible studies were identified (Supplementary Appendix Figure 9). One hundred two references were excluded based on title and abstract, and an additional 3 studies were excluded following full text review [34, 60, 61], resulting in 5 studies evaluating the association between *M. genitalium* and female infertility (Supplementary Appendix Table 4). Adjusted effect estimates were reported in 3 studies [42, 62, 63]. Most studies evaluated women attending fertility clinics, comparing confirmed tubal factor infertility to other causes of infertility identified through laparoscopy, culdoscopy, or hysterosalpingography [62–65].

**Figure 4.** Forest plot of the association between *Mycoplasma genitalium* and spontaneous abortion. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.
single study evaluated women with clinically diagnosed PID and defined infertility by self-report [42]. Another compared women with infertility from all causes (including male infertility) to women with proven fertility [65]. Three studies used serology [62–64] and 2 used PCR [42, 65]. “Good” quality ratings were assigned to 3 studies [42, 62, 63], and 2 were designated as “fair” [64, 65] (Supplementary Appendix Table 5).

In the meta-analysis of infertility, the pooled OR was 2.43 (95% CI, 0.93–6.34) (Figure 5). There was considerable between-study heterogeneity ($I^2 = 80.2\% [95\% CI, 53.5\%–91.6\%])$, but no significant publication bias (Begg $P = .52$; Egger $P = .70$) (Supplementary Appendix Figure 10). Among studies accounting for coinfections [42, 62, 63], the pooled OR was 3.27 (95% CI, 1.25–8.57), with considerable between-study heterogeneity ($I^2 = 75.9\% [95\% CI, 20.8\%–92.7\%]$).

**DISCUSSION**

These meta-analyses of the published literature on the association between *M. genitalium* and female reproductive tract disease produced remarkably consistent findings, demonstrating an approximately 2-fold increase in risk for cervicitis, PID, spontaneous abortion, preterm birth, and infertility. With the exception of analyses of infertility, these pooled estimates were all statistically significant. Subanalyses of studies that accounted for other known pathogens demonstrated greater pooled estimates for all 5 syndromes, all of which were statistically significant, providing strong evidence of an association.

Only the association between *M. genitalium* and cervicitis had been previously assessed in meta-analysis, and our pooled estimate of 1.7 was similar to the initial pooled estimate of 2.2 (95% CI, 1.6–2.9), also from random-effects modeling [1]. This similarity was despite our exclusion of 2 studies in the earlier meta-analysis [43, 66] and the addition of 8 new studies [16, 19–22, 24, 27, 32]. The consistency of results across definitions of cervicitis and methods of detection further suggests that *M. genitalium* plays a role in cervicitis. Despite this association, cervicitis is typically asymptomatic, and diagnosis and treatment are recommended primarily to interrupt transmission and to prevent pathogens from ascending to the upper reproductive tract and causing PID [67].

PID causes significant morbidity and, left untreated, can result in infertility, ectopic pregnancy, and chronic pelvic pain [68]. Costs associated with acute PID episodes range from approximately $700 to $8480 per episode for outpatient and inpatient care, respectively [69], and indirect costs related to sequelae are far higher, highlighting the need for rapid and appropriate treatment. Our finding of a significant association between *M. genitalium* and PID has implications for currently recommended therapies [70], which specify the use of antibiotics with poor efficacy against *M. genitalium*. Observations from the PID Evaluation And Clinical Health trial, where 56% of *M. genitalium*-infected women with PID experienced persistent endometritis after standard therapy [42], highlight the inadequacy of these regimens. Nevertheless, the proportion of PID cases due to *M. genitalium* remains unknown, and forthcoming

**Figure 5.** Forest plot of the association between *Mycoplasma genitalium* and female infertility. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.
updates to the Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines recommend that standard antimicrobial therapy not be altered unless PID persists and M. genitalium is identified [70].

Preterm delivery of an infant has numerous causes [71], and infectious agents contribute only a small proportion. Therefore, it was remarkable that we observed a 2-fold increase in risk for preterm birth and spontaneous abortion associated with M. genitalium infection, greater than the risk associated with T. vaginalis in a recent meta-analysis (pooled relative risk, 1.42 [95% CI, 1.15–1.75]) [72]. Nevertheless, the prevalence of this organism in low-risk populations is generally low (approximately 2.0%) [2, 73], suggesting that universal testing of pregnant women for M. genitalium is not warranted. Screening high-risk pregnant women (eg, women with multiple partners or previous STIs) may be warranted, but further studies to determine if treating M. genitalium reduces risk for preterm birth will be required prior to instituting recommendations.

Infertility affects approximately 11% of women aged 15–44 in the United States [74], and identifying preventable causes is a priority. Although the nearly 2.5-fold increased risk of infertility associated with M. genitalium was the sole estimate that was not statistically significant, it was also the sole analysis with substantial heterogeneity. The stronger and statistically significant summary OR in subanalyses accounting for other known pathogens suggests a causal link with infertility. However, more sensitive and specific seroassays and longitudinal studies will be required before the association between M. genitalium and infertility can be definitively determined.

Treatment of M. genitalium infections is challenging and hampered by the lack of a US Food and Drug Administration (FDA)-approved assay and low cure rates after syndromic therapy. Eradication of M. genitalium after doxycycline occurs in only approximately 30% of cases, cell wall–mediated antibiotics are ineffective, and azithromycin resistance is increasing [4, 75, 76]. Moxifloxacin is recommended in cases of azithromycin failure [70], but should be used judiciously. Ideally, targeted testing of high-risk symptomatic women would guide therapy, but until recently only in-house PCR and research-use-only assays have been available in the United States. However, the Aptima TMA assay for M. genitalium is highly sensitive and specific [77, 78] and is now commercially available as analyte-specific reagents [79], and a clinical trial is planned to support a 510(k) application to the FDA (D. Getman, written personal communication).

A major strength of these meta-analyses was our ability to summarize studies with varying exposure and outcome measurements. Despite this variety, heterogeneity was moderate to low in all but 1 analysis. The pooled ORs from subanalyses of studies that accounted for other pathogens were of greater magnitude and all were statistically significant, lending further confidence to the conclusion that M. genitalium is causally related.

Nevertheless, there were also limitations. The number of studies on stillbirth and ectopic pregnancy was too small to draw conclusions. We used random-effects rather than fixed-effects models, erring on the side of more conservative analyses. In an inclusive approach, we retained nearly all studies in the primary analyses, potentially diluting effect estimates. Our exclusion of conference abstracts and non-English-language studies omitted some of the evidence, and 2 recent conference abstracts reported 2-fold [80] to 4-fold [81] higher risks for PID in women with M. genitalium; our pooled estimate may be particularly conservative.

These meta-analyses demonstrate an approximately 2-fold increased risk of cervicitis, preterm birth, spontaneous abortion, PID, and infertility in women infected with M. genitalium, providing strong evidence in support of a causal role. The severity and high costs associated with these conditions, as well as the limitations of syndromic therapies for M. genitalium infection, suggest that targeted testing of high-risk symptomatic women may be warranted. The increasing availability of diagnostic tests for M. genitalium will make this possible.

### Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

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#### Author contributions


### References


Mycoplasma genitalium in Women: Current Knowledge and Research Priorities for This Recently Emerged Pathogen

Harold C. Wiesenfeld1 and Lisa E. Manhart2

1Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, and Magee-Womens Research Institute, Pittsburgh, Pennsylvania; 2Departments of Epidemiology and Global Health, Center for AIDS and STD, University of Washington, Seattle

Health consequences of sexually transmitted diseases disproportionately affect women, making it important to determine whether newly emerged pathogens cause sequelae. Although the pathogenic role of Mycoplasma genitalium in male urethritis is clear, fewer studies have been conducted among women to determine its pathogenic role in the female reproductive tract. Pelvic inflammatory disease (PID) is an important cause of infertility and ectopic pregnancy, and Chlamydia trachomatis and Neisseria gonorrhoeae are recognized microbial causes. Emerging data demonstrate an association between M. genitalium and PID, and limited data suggest associations with infertility and preterm birth, yet the attributable risk for female genital tract infections remains to be defined. Further investigations are needed to better define the impact of M. genitalium on women’s reproductive health. Importantly, prospective studies evaluating whether screening programs and targeted treatment of M. genitalium improve reproductive outcomes in women are necessary to guide public health policy for this emerging pathogen.

Keywords: Mycoplasma genitalium; cervicitis; pelvic inflammatory disease; infertility; preterm birth.

Mycoplasma genitalium was first detected in 2 men with nongonococcal urethritis [1], and subsequent studies linking M. genitalium with male urethritis have been remarkably consistent. Today, M. genitalium is widely accepted as a cause of male urethritis [2], and key issues related to M. genitalium infection in men are summarized in the article by Horner and Martin in this issue [3]. Sexual transmission between men and women is highlighted by studies demonstrating concordance of M. genitalium infection status in sex partners (summarized in [4]) and by multilocus genotyping demonstrating identical genotypes in 87% of concurrently infected sex partners [5]. Despite this, many fewer studies of M. genitalium have been conducted in women, data documenting morbidity are less consistent than in men, and associations with female reproductive tract disease syndromes are of lower magnitude. Nevertheless, because women are at risk of the most significant adverse consequences of reproductive tract infections [6], decisions to invest in disease control programs are often based on the strength of the evidence in women.

A recent meta-analysis summarized the literature on M. genitalium infection in women and reported an approximately 2-fold increased risk of cervicitis, pelvic inflammatory disease, preterm delivery, spontaneous abortion, and infertility that was statistically significant for all but infertility [7]. Nevertheless, questions remain over the importance of M. genitalium and female reproductive tract disease syndromes. Although the evidence for disease associations between M. genitalium and female clinical syndromes has grown substantially in the last decade, it remains imperfect. Given the time and resources required to design and conduct the epidemiologic studies needed to complete that evidence base, identifying key gaps in our knowledge and prioritizing the most important questions are critical. Therefore, we undertook a critical evaluation of the evidence with the goal of summarizing the strength of the evidence base and identifying priorities for future research. We began with the literature identified after a comprehensive search of the literature for a recent meta-analysis, on which one of us was a coauthor [7]. We then searched PubMed for papers published between 25 June 2014 (the last date of the search for the meta-analysis) and 31 December 2016 using a single search term: Mycoplasma genitalium.

Lower Genital Tract Infection

Cervicitis was initially described >30 years ago as “the ignored counterpart of urethritis in men” [8], most likely because the 2 syndromes share known etiologies. However, cervicitis differs from male urethritis in that low-grade signs of infection more often go unnoticed, in part due to the need for a speculum exam to observe these. The clinical diagnosis is also subjective and often inaccurate, and this is evident in studies of M. genitalium and cervicitis. Definitions of cervicitis ranged widely across these studies, and include visible mucopurulent cervical...
discharge [9]; objective evidence of inflammation, defined as ≥10, ≥20, or ≥30 polymorphonuclear leukocytes per high-power field (PMN/HPF) [10–12] (with or without mucopurulent discharge); easily induced cervical bleeding [13]; and more PMNs than epithelial cells [14].

Individual studies evaluating the association of M. genitalium and cervicitis have produced mixed results with respect to statistical significance, but nearly all (n = 18/21) have demonstrated an increase in risk. Effect sizes in most studies are relatively modest, however, suggesting that fairly large sample sizes are needed to detect a statistically significant effect. Despite the heterogeneity across studies, M. genitalium was significantly associated with a 70% increase in risk of cervicitis (odds ratio [OR] = 1.7; 95% CI = 1.35–2.04) per a recent meta-analysis [7] (Figure 1).

Notwithstanding this evidence from meta-analysis, nearly all studies of cervicitis have been cross-sectional in nature. Prospective studies demonstrating that cervicitis followed the acquisition of M. genitalium would provide more definitive evidence, but these studies are challenging to conduct. However, in vitro and animal models help elucidate mechanisms for pathogenesis in the lower reproductive tract. Mycoplasma genitalium is capable of infecting mucosal cells in the marmoset female genital tract and a prolonged inflammatory response resulted in the lower genital tract after inoculation [15]. Acute M. genitalium infection of endocervical cells causes destruction of microvilli and an increase in secretory vesicle formation [16]. Mycoplasma genitalium infection of endocervical cells in vitro also elicited a proinflammatory cytokine and chemokine response with secretion of interleukin 6, interleukin 7, interleukin 8, monocyte chemotactic protein 1, and granulocyte-macrophage colony stimulating factor [17]. Proinflammatory cytokine levels are high in women with chronic M. genitalium infection, raising speculation that, similar to untreated chlamydial infections, persistent M. genitalium infection may be deleterious to the female reproductive tract due to resultant chronic inflammation [18]. However, if M. genitalium infection in the lower genital tract is frequently asymptomatic, additional epidemiologic studies of M. genitalium and clinical cervicitis are unlikely to yield further explanatory data. Efforts focused on gaining a better understanding of the pathogenesis of M. genitalium and immune activation in the lower genital tract may be more informative.

Despite the detection of M. genitalium in vaginal specimens, an association with vaginitis has not been demonstrated. As such, positive nucleic acid amplification test (NAAT) results from vaginal specimens likely reflect detection of bacterial DNA from cervical infections. Furthermore, no data suggest that M. genitalium is associated with specific organisms that can cause vaginitis, such as Trichomonas vaginalis and Candida albicans. In contrast, evidence of a relationship with bacterial vaginosis (BV) is inconsistent, with some studies showing decreased risk of BV in women with M. genitalium [19–21], 1 showing increased risk [12], and several showing no association [22–24]. A recent longitudinal study suggested that susceptibility to M. genitalium may be enhanced in the presence of BV [25] in a manner similar to that described for Neisseria gonorrhoeae and Chlamydia trachomatis. Mycoplasma genitalium alone, however, does not appear to be a cause of vaginitis.

Studies from Sweden and Norway have demonstrated a relationship between M. genitalium and female urethritis, although the magnitude varies based on how urethritis is defined. When defined as clinical symptoms of dysuria or urgency, M. genitalium was associated with a statistically significant 3-fold increase in risk [26], whereas the risk was 2-fold higher when urethritis was defined as ≥4 PMN/HPF on microscopic examination of a methylene blue–stained urethral smear [27, 28]. These studies suggest that M. genitalium can cause female urethritis, but the body of evidence is small.

Pelvic Inflammatory Disease
Pelvic inflammatory disease (PID) is typically a polymicrobial syndrome of the female upper genital tract, including endometritis, salpingitis, pelvic peritonitis, and tuboovarian abscess, and is an important cause of infertility in women. Historically, PID was considered to be primarily caused by either Chlamydia trachomatis or Neisseria gonorrhoeae. However, the majority of women with PID are not infected with either of these 2 STD pathogens; rather, anaerobic and facultative organisms are more frequently isolated from the upper genital tract in women with acute PID [29].

A slowly growing body of literature is examining whether there is an association between Mycoplasma genitalium and

![Figure 1](https://academic.oup.com/jid/article-abstract/216/suppl_2/S389/4040973)
PID. Early studies examining *M. genitalium* serologic responses had conflicting results, partly due to insufficiently sensitive and specific serologic assays and potentially reflecting current uncertainty over the role of serologic testing in the detection of PID and/or its consequences. Among 31 patients with acute PID, approximately 40% had increasing titers of *M. genitalium* antibodies as measured by microimmunofluorescence, consistent with a recent *M. genitalium* infection as the etiologic agent [30]. However, Jurstrand et al demonstrated similar rates of seropositivity to *M. genitalium* in women with acute PID and in pregnant women, consistent with no association [31].

The development of nucleic acid amplification testing (NAAT) in research settings enabled further investigation, demonstrating that *M. genitalium* can be detected in the upper genital tract of women with acute PID. Among women at a Kenyan STD clinic presenting with acute pelvic pain, *M. genitalium* was identified by polymerase chain reaction (PCR) in the endometrium in 12% (n = 7/58) of women with histologic endometritis, whereas it was not present in the endometrium of women without endometritis [32]. Moreover, the prevalence of *M. genitalium* in the endometrium in women with endometritis was similar to that of *N. gonorrhoeae* (10%) and *C. trachomatis* (7%). Simms et al identified *M. genitalium* by PCR on cervical swabs in 13% (n = 6/45) of women clinically diagnosed with acute PID, whereas none of the 37 control women tested positive [33]. In a United States–based PID treatment trial, 15% of women were infected with *M. genitalium*, and infection was associated with histologic endometritis [34]. Results from such studies using NAAT constitute the bulk of the evidence summarized in the meta-analysis, which yielded a 2-fold increase in risk of PID across studies [7] (Figure 1).

Most women with infertility due to fallopian tube damage do not have a history of acute PID but are more commonly seropositive for *C. trachomatis* or *N. gonorrhoeae* than women without infertility [35]. Similarly, an association between *M. genitalium* seropositivity and tubal factor infertility has been observed, independent of past chlamydial infection [36]. These observations suggest that subclinical or unrecognized infections, which may be more common than acute PID, may cause reproductive harm [37]. Subclinical PID (histologic endometritis in the absence of signs or symptoms of acute PID) is often present in women with uncomplicated chlamydial or gonococcal cervicitis or bacterial vaginosis [38]. Among 558 women at an urban STD clinic who did not have acute PID, subclinical PID was identified in 22 of 43 (51%) women infected with *M. genitalium*, similar to the rate of 47% in those testing positive for *C. trachomatis*. When controlling for chlamydia, gonorrhea, and bacterial vaginosis, cervical *M. genitalium* infection was independently associated with subclinical PID (adjusted odds ratio [aOR] = 2.4; 95% confidence interval [CI] = 1.2–4.6), [39]. Similar to acute PID, a prospective study has demonstrated that women with subclinical PID are at risk for infertility [40]. The role and extent of *M. genitalium* in subclinical disease, as well as acute pelvic infection, warrant further study.

Although most studies support an association between *Mycoplasma genitalium* and acute PID, the importance of antimicrobial eradication of this organism has not been determined. Doxycycline and azithromycin are often used as components of antimicrobial therapy for PID, yet the efficacy of doxycycline to treat *M. genitalium* cervicitis is poor, and resistance to macrolides is an emerging concern [41]. Standard treatment consisting of cefoxitin and doxycycline failed to eradicate *M. genitalium* in 41% of women with acute PID [34]. Although short-term treatment failures (defined as histologic evidence of endometritis and pelvic pain) were more common in women with *M. genitalium* in this study, the clinical efficacy of PID regimens that include Centers for Disease Control and Prevention–recommended regimens is high [42]. For these reasons, studies of both the short-term clinical efficacy and long-term reproductive outcomes of PID regimens in women with *M. genitalium* are urgently needed.

Screening and treatment of women with *Chlamydia trachomatis* has been associated with a reduced incidence of PID [43]. A similar relationship with *M. genitalium* would corroborate its pathogenic role in PID. Oakeshott et al performed a secondary analysis of a trial of chlamydia screening to prevent PID, testing stored samples for *M. genitalium* [19]. Women infected with *M. genitalium* had a 2-fold higher incidence of PID over 12 months compared with uninfected women, a difference that did not achieve statistical significance (3.9% vs 1.7%; relative risk = 3.95; 95% CI = 0.8–10.0; P = .14). These results, coupled with the low prevalence of *M. genitalium* (3.3%) in their cohort, led the authors to conclude that *M. genitalium* was not a major causative agent of PID. However, the study population consisted of relatively low-risk women, and PID was initially identified by self-reported symptoms up to 1 year after the *M. genitalium* infection was detected, reducing the sensitivity of the study.

Further studies of *M. genitalium* screening, particularly in communities where *M. genitalium* is prevalent, are necessary to understand the true risk of PID among infected women.

**Sequelae of Upper Genital Tract Infection: Infertility and Ectopic Pregnancy**

Approximately 25% of infertility is due to tubal occlusion and is often referred to as tubal factor infertility (TFI). This is known to occur after upper tract infection with *C. trachomatis* or *N. gonorrhoeae* [44, 45], and the risk of infertility increases with additional episodes of chlamydial infection [46]. In vitro and animal studies are exploring the effect of *M. genitalium* infection on the fallopian tube mucosa. Microscopic evidence of ciliary damage was demonstrated in human fallopian tube explants infected with *M. genitalium*, albeit the damage was more moderate than that seen with *C. trachomatis* or *N. gonorrhoeae* infection [47] (Figure 2). A pig-tailed macaque model...
has been explored to characterize ascension of *M. genitalium* and its pathogenesis in upper genital tract infection [48]. When studied in a model using auto-transplanted salpingal pockets implanted in the animal’s anterior abdominal wall, *M. genitalium* was present for up to 2 weeks [49]. However, when examined for ascending infection after cervical inoculation, none of the 6 primates with persistent lower genital tract infection had evidence of *M. genitalium* infection in the fallopian tubes. Although *M. genitalium* can cause upper genital tract inflammation, additional studies are needed to further elucidate the pathogenesis of *M. genitalium* in the female reproductive tract. Studies should include animal models and should investigate whether recurrent *M. genitalium* infections are associated with a higher risk of sequelae in the same manner as recurrent chlamydial infections.

Epidemiologic studies of infertility are difficult to conduct, in part due to the multifactorial etiology, and in part because the relative importance of a current versus a prior infection is unknown. If damage occurs soon after active infection, detecting the organism may demonstrate associations. If the greatest risk occurs after damage caused by an immune response to infection, detecting circulating antibody by serology may reveal associations. Both direct detection and serology have been used to assess the relationship between *M. genitalium* and infertility, but there are no consistent trends in results based on type of assay. Although epidemiologic data are somewhat mixed, on balance they suggest that the risk of infertility is elevated in women who have experienced *M. genitalium* infections. Serologic studies have produced conflicting results, due in part to suboptimal sensitivity and specificity of current serologic assays. Additionally, the characterization of the immune response to urogenital infection with *M. genitalium* and the significance of serologic assays are not well defined. The earliest serologic study using a first-generation seroassy observed a nonsignificant decrease in risk [50], but 2 subsequent serologic studies that adjusted for antibodies to *C. trachomatis* reported statistically significant 4.5–5.5-fold increased risks of infertility [36, 51]. In contrast, the most recent serologic study among women in Sweden, which also adjusted for the presence of antibodies to chlamydia, found no significant association with TFI and *M. genitalium* [52]. Results from studies using NAAT to detect the organism in the reproductive tract have been similarly mixed. The largest study, which tested endometrial specimens from US women with clinically diagnosed PID, reported a modest and nonsignificant 40% increase in the risk of infertility after adjusting for chlamydia, gonorrhea, and infertility at baseline [34]. In contrast, a case–control study in Poland detected *M. genitalium* by NAAT testing of cervical and peritoneal specimens and showed a 5-fold increase in risk of infertility, although investigators did not adjust for chlamydia or gonococcal infection [53]. Despite the heterogeneity in studies of infertility, in meta-analysis, the approximately 2-fold increase in risk approached statistical significance (OR = 2.4; 95% CI = 0.93–6.34; Figure 1) and increased when restricted to studies that accounted for chlamydia and gonococcal infection (OR = 3.3; 95% CI = 1.23–8.57) [7].

Interpreting studies of *M. genitalium* and infertility is complicated by the populations studied and the methods used to determine infertility. Comparison groups of women at high risk of infertility for other reasons may mask any effect of *M. genitalium*. For example, in the most recent Swedish serologic study, women with TFI were compared with women with other causes of infertility, yet *M. genitalium* was strongly associated with any cause of infertility. The comparison with fertile women, which may have yielded different results, was not reported [52]. Similarly in the large study of US women, all women had clinically diagnosed PID, and all were at elevated risk of infertility, which may have muted any effect of *M. genitalium* [34].

Ectopic pregnancy can result from damaged cilia and has been strongly linked to upper tract infection with *N. gonorrhoeae* and *C. trachomatis* [35]. The ciliary damage observed in fallopian tube tissue suggests that this can also occur with *M. genitalium* infection (Figure 2) [47], but there is a paucity of epidemiologic studies; only 2 studies appear in the published literature and each used different diagnostic methods to detect associations.
M. genitalium. When serum specimens from 82 Swedish women with ectopic pregnancies and 246 healthy pregnant women screened for rubella were tested for the presence of M. genitalium antibodies, the association was modest, not statistically significant, and disappeared after adjustment for C. trachomatis (aOR = 1.0; 95% CI = 0.5–2.0) [31]. In contrast, when NAAT testing for M. genitalium was performed on tubal tissue from 84 hospitalized Saudi women with ectopic pregnancies undergoing salpingectomy and 51 women undergoing hysterectomy or tubal ligation, detection of M. genitalium was significantly associated with ectopic pregnancy, even after adjustment for other pathogens (aOR = 2.3; 95% CI = 1.1–8.6) [54]. Elucidating the role of M. genitalium in both infertility and ectopic pregnancy requires a better understanding of the etiologically relevant time period from infection to adverse outcome, more accurate definitions of infertility and ectopic pregnancy, a thorough characterization of the immune response to urogenital M. genitalium infection, and better serologic assays.

Adverse Pregnancy Outcomes

Preterm delivery, defined as delivery of an infant before 37 weeks of gestation, occurs in approximately 13% of US women [55]. The etiology of preterm delivery is multifactorial, with infectious etiologies accounting for 25–30% of these deliveries [56]. Studies of preterm birth and M. genitalium have included a mix of case-control and cohort studies, yet many had small numbers of women with preterm delivery or M. genitalium infection or both, limiting statistical power. In 2 studies, the prevalence of M. genitalium was <1%, and M. genitalium was not detected in any of the women with preterm birth [57, 58]. Individual studies have reported an increased risk of preterm delivery, ranging from a nonsignificant 30% increase among low-risk women attending a community health center [59] to a 2.5-fold increase in risk among Peruvian women presenting with spontaneous labor in a maternity hospital [60]. Although the nearly 2-fold increased risk of preterm delivery in meta-analysis (OR = 1.9; 95% CI = 1.25–2.85) (Figure 1) is lower than the 5–6-fold increase in risk estimated in meta-analysis (OR = 1.9; 95% CI = 1.04–4.88) among Ugandan women engaged in commercial sex work [20]. Although 2 studies reported inverse relationships, ranging from 0.6 in a large study of West African women to 0.9 among adolescent girls and women attending an emergency department [64, 65], neither of these was statistically significant. Despite this substantial heterogeneity, the meta-analysis demonstrated a statistically significant 80% increase in risk (OR = 1.8; 95% CI = 1.0–3.0) (Figure 1) [7]. Similar to research priorities for preterm delivery, longitudinal studies of high-risk cohorts of women in populations that have a high prevalence of M. genitalium are needed to determine relationships between M. genitalium and spontaneous abortion.

**SUMMARY AND CONCLUSION**

Associations between M. genitalium and most female reproductive tract syndromes have been demonstrated, and, although the statistical significance of study results is not always uniform, a relatively consistent picture across studies has emerged. As with many sexually transmitted pathogens, the strength of the relationships with reproductive tract syndromes is lower in women than in men. Furthermore, the pace of research evaluating the role of M. genitalium in reproductive tract disease syndromes has been slower in women than in men, in part because studies in women are more difficult to conduct, and the sequelae (including PID and infertility) are often challenging to identify. Nevertheless, fairly consistent evidence shows that women with M. genitalium are at increased risk of PID, infertility, and adverse pregnancy outcomes and it is probably an important pathogen. However, additional data will be required before routine screening can be recommended. We have summarized research priorities in Table 1.

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### Table 1. Priorities for Future Research on Mycoplasma Genitalium and Female Reproductive Tract Disease Syndromes

<table>
<thead>
<tr>
<th>Priority</th>
<th>Description</th>
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<tr>
<td>1.</td>
<td>Development of more sensitive and specific serologic assays to facilitate studies of sequelae such as infertility and ectopic pregnancy.</td>
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<td>2.</td>
<td>In vitro and animal studies to further elucidate the pathogenesis of M. genitalium in vaginal, cervical, endometrial, and fallopian tube tissue.</td>
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<td>3.</td>
<td>Identification of the extent of immune activation in the genital tract, as well as predictors and consequences of immune activation.</td>
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<td>4.</td>
<td>Estimation of the attributable risk of M. genitalium infection for adverse reproductive health sequelae in women (eg, pelvic inflammatory disease, spontaneous abortion, preterm delivery, infertility, and ectopic pregnancy).</td>
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<td>5.</td>
<td>Determination of whether screening women for M. genitalium reduces the incidence of adverse sequelae, including pelvic inflammatory disease, spontaneous abortion, preterm delivery, infertility, and ectopic pregnancy.</td>
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*Mycoplasma genitalium* in Women • *JID* 2017:216 (Suppl 2) • S393
Key among these research priorities is identifying the attributable risk for reproductive tract syndromes in women. Determining how often M. genitalium infections result in PID, infertility, and adverse pregnancy outcomes is a necessary prerequisite to determining the public health importance of M. genitalium infection. We currently lack the prospective studies that are necessary to determine this. Prospective studies are also necessary to clearly demonstrate causal relationships, particularly with respect to PID and infertility. Perhaps most important is the lack of clinical trials to determine whether treating M. genitalium infections can prevent adverse sequelae such as PID, infertility, and adverse pregnancy outcomes. Such data will be necessary to accurately judge the extent to which M. genitalium impacts women’s health and the extent to which control programs would be cost effective. Conducting these studies will require a fairly significant investment in time and resources, yet this investment is essential to ensure that healthcare providers have the information they need to make clinical decisions for women seeking reproductive health care and to give public health and regulatory agencies the data needed to determine whether systematic prevention and control programs are needed.

Notes

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References


Comment

Chlamydia trachomatis is one of the most common sexually transmitted infections globally, WHO estimates that there are more than 130 million new cases of chlamydia annually. Because chlamydial infections are often asymptomatic, screening programmes are imperative to control infection and to prevent adverse sequelae. Chlamydial infections are important causes of pelvic inflammatory disease and tubal infertility and can lead to ectopic pregnancies. Additionally, chlamydial infections increase the risk of acquiring HIV infection. Most, but not all, observational studies and meta-analyses have shown that chlamydial infection is associated with adverse obstetric outcomes in pregnancy and increased morbidity and mortality of neonates.

In their Article in The Lancet Infectious Diseases, Joanne Reekie and colleagues report on a large study of chlamydial infection and adverse birth outcomes among reproductive-aged women in the Australian state of Western Australia. They conducted a population-based retrospective cohort study, linking a government registry of women in Western Australia to datasets of laboratory test results, notifiable disease reporting, hospital morbidity, and birth outcomes. The report included birth outcome data on 101,588 women who had singleton births in Western Australia from 2001 to 2012. Of those births, 39,21 (3.9%) were spontaneous preterm births, 9,76 (9.6%) of 101,371 births with available data) were small for gestational age, and 682 (0.7%) were stillbirths.

One strength of the study was that the authors could differentiate between women who were tested for chlamydia before pregnancy and those tested during pregnancy. Within the cohort, 21,267 (20.9%) were tested for chlamydia during their pregnancy, of whom 13,65 (6.4%) tested positive. Of the 19,157 (18.9%) women who were tested before pregnancy, 19,35 (8.3%) tested positive. The authors report that women who were tested before pregnancy, but not during pregnancy, had an increased risk of preterm birth or stillbirth but a reduced risk of having a baby who was small for gestational age. Women who were only tested before pregnancy might represent a higher risk group, which prompted testing (eg, because of symptoms of infection, several sexual partners, or diagnosis of other sexually transmitted infections); this explanation would account for the findings of an increased risk of preterm birth or stillbirth but a reduced risk of having a baby who was small for gestational age. 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tested negative for chlamydia during pregnancy, 2418 (12.2%) women had an infant who was small for gestational age and 864 (4.5%) women had a spontaneous preterm birth. Although a univariate analysis suggested that women with chlamydia have a higher risk for adverse birth outcomes, there was no association in multivariable analyses when controlling for potential confounders. One important limitation of the study was that the authors did not have access to treatment data, which would have strengthened the interpretation of their main findings. Based on a previous clinical audit among the same population, the authors assumed that most cases were treated. With that caveat in mind, the findings suggest that women with chlamydial infections who are screened and treated during pregnancy have the same risk of adverse birth outcomes as women without an infection.

The benefits of antenatal screening and treatment of chlamydial infections have been evaluated in a few prospective studies. Most of those studies support screening and treatment as an effective means to improve pregnancy outcomes. As noted by the authors, there are other observational studies that have not shown an increase in adverse obstetric outcomes associated with chlamydia, although these studies are not without substantial limitations. Cost-effectiveness studies from high-income settings have supported chlamydia screening and treatment programmes for pregnant women. The report by Reekie and colleagues contributes to the evidence that supports the benefits of screening and treatment of chlamydia among pregnant women; however, the effect size and, therefore, cost-effectiveness is not known.

There is an urgent need to further elucidate the necessity of screening and treatment of chlamydia during pregnancy, especially in regions of the world with both a high prevalence of adverse birth outcomes and a high prevalence of chlamydial infections. It is estimated that 99% of stillbirths occur in resource-limited settings and, as a 2016 review noted, there is a high prevalence of chlamydial infections among pregnant women from low-resource settings in sub-Saharan Africa and Asia. Chlamydial screening and treatment programmes during pregnancy will require substantial investments by governments, which can be difficult to prioritise in resource-limited settings, especially given the absence of data on the effect size and cost-effectiveness of these programmes. It is time for large, randomised clinical trials to investigate the effects of chlamydial screening and treatment programmes in pregnant women on adverse birth outcomes and the potential cost-effectiveness of different screening approaches. Findings from those studies will provide crucial evidence to guide policymakers on how to address chlamydial infection in pregnancy and to improve the lives of pregnant women and their children.

Paul C Adamson, *Jeffrey D Klausner
Department of Internal Medicine, School of Medicine, Yale University, New Haven, CT, USA (PCA), and Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA (JDK)
jjklausner@mednet.ucla.edu

Both authors declare no competing interests.

ORIGINAL ARTICLE

Prevalence and treatment outcomes of routine *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* testing during antenatal care, Gaborone, Botswana

Adriane Wynn,1 Doreen Ramogola-Masire,2,3,4 Ponatshego Gaolebale,3 Neo Moshashane,4 Ontiretse Sickboy,4 Sofia Duque,4 Elizabeth Williams,5 Klara Doherty,4 Jeffrey D Klausner,1,6 Chelsea Morroni1,4,7,8

ABSTRACT

**Objectives** *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) are curable, mostly asymptomatic, STIs that cause adverse maternal and perinatal outcomes. Most countries do not test for those infections during antenatal care. We implemented a CT, NG and TV testing and treatment programme in an antenatal clinic in Gaborone, Botswana.

**Methods** We conducted a prospective study in the antenatal clinic at Princess Marina Hospital in Gaborone, Botswana. We offered pregnant women who were 18 years or older and less than 35 weeks of gestation, CT, NG and TV testing using self-collected vaginal swabs. Testing was conducted using a GeneXpert® CT/NG and TV system. Those who tested positive were given directly observed antibiotic therapy and asked to return for a test of cure. We determined the prevalence of infections, uptake of treatment and proportion cured. The relationships between positive STI test and participant characteristics were assessed.

**Results** We enrolled 400 pregnant women. Fifty-four (13.5%) tested positive for CT, NG and/or TV: 31 (8%) for CT, 5 (1.3%) for NG and 21 (5%) for TV. Among those who tested positive, 74% (40) received same-day results (6), 67% (4) were treated.

**Conclusion** The prevalence of CT, NG and/or TV was high, particularly among women with HIV infection. Among women with CT, NG and/or TV infection, those who received delayed results were more likely to be treated than those who received delayed results. More research is needed on the costs and benefits of integrating highly sensitive and specific STI testing into antenatal care in Southern Africa.

BACKGROUND

*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) infections during pregnancy increase the risk of adverse pregnancy and infant outcomes, including preterm birth.1 Coinfection with HIV and CT/NG is associated with an increased risk of mother-to-child transmission of HIV.2 Infection with TV is associated with increased risk for HIV acquisition.3 About 50% of untreated maternal CT and NG infections are transmitted to the neonate during birth.4,5 Both infections can cause ophthalmia neonatorum, and untreated gonococcal eye infections can cause blindness.6 Chlamydial infections are an important cause of neonatal pneumonia as 5%–30% of infants born to mothers with CT infection can develop this condition.7 Infants of mothers infected with TV may contract the infection during delivery, which could result in fever, respiratory problems and urinary tract infections.8,9 Despite serious risks to maternal and infant health, the prevalence and risk factors for these infections in Southern Africa (including Angola, Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe) are not precisely measured.8 A recent systematic review on STI prevalence among pregnant women in low-income and middle-income countries found only 15 studies based in Southern Africa.10 The lack of evidence for the burden of STIs during pregnancy in Southern Africa may be due to the absence of diagnostic testing during antenatal care. A recent study that used both online data and Ministry of Health surveys found that only 14 countries have policies for antenatal screening for CT and/or NG, including: Australia, the Bahamas, Bulgaria, Canada, Estonia, Japan, Germany, Latvia, New Zealand, Democratic People’s Republic of Korea, Romania, Sweden, the UK, and the USA, in 2015.8 Forty-three countries did not have antenatal CT/NG testing policies, and 139 countries’ policies were unknown.9 Most countries identify and manage CT, NG and TV infections using an approach called syndromic management, which was developed for use in countries where laboratory diagnosis was not accessible.10 The approach uses algorithms to classify symptoms (eg, abnormal vaginal discharge) into STI syndromes (eg, vaginal discharge syndrome), which are treated with...
standardised drug regimens. Diagnosis based on symptoms lacks sensitivity because a large proportion of CT, NG and TV infections are asymptomatic. For example, a study that assessed the sensitivity and specificity of diagnostic strategies for identifying CT and/or NG among pregnant women in Botswana found that using symptoms alone (including vaginal discharge and/or lower abdominal pain) had a sensitivity of 21% and specificity of 78%. Romoeren et al found the sensitivity and specificity of abnormal vaginal discharge (other than Candida-like) for diagnosing TV were 61% and 74%, respectively. A recent South African study of 1480 women found that more than 50% of CT and other STIs were asymptomatic. Recent developments in technology have introduced the possibility that antenatal testing for CT, NG and TV infections will become more accessible with highly sensitive, easy to use, rapid tests. For example, several nucleic acid amplification testing-based platforms are in development or newly available for diagnosis of STIs at the point of care. These new testing systems have several benefits that may make them more accessible in low-income and middle-income countries, including multiplex assays that can test for several infections, highly trained laboratory technicians are not required, samples can be self-collected and samples can be processed on site, thus reducing storage and shipping costs.

Botswana has achieved high levels of antenatal care coverage with over 94% of pregnant women receiving at least one visit, and universal screening for HIV and syphilis is integrated into antenatal care. Nevertheless, Botswana faces high rates of adverse birth outcomes, including preterm birth (15/100 live births) and infant mortality (36/1000 live births). The absence of diagnostic testing for curable STIs during pregnancy may represent a missed opportunity to reduce the burden of infection and poor maternal outcomes. Our study implemented an antenatal CT, NG and TV testing and treatment programme in a high-volume antenatal clinic in Gaborone, Botswana, and assessed the uptake of testing and treatment; the prevalence and correlates of CT, NG and TV infections; and the proportion of infections cured.

METHODS
We conducted a prospective study among 400 consecutively enrolled pregnant women in the antenatal clinic in Princess Marina Hospital in Gaborone, Botswana. Pregnant women attending the antenatal clinic between July 2015 and May 2016, who were over age 18 years, less than 35 weeks of gestation (to ensure the possibility of a test of cure after 4 weeks prior to birth) and planning to return to the clinic for a follow-up visit were offered testing for CT, NG and TV infections. With a sample size of 400, a two-sided 95% CI using normal approximation for the assumed prevalence of 13% ranges from 9.9% to 16.7%, which should be narrow enough to give sufficient precision (within half the estimate value on each side) for the estimate of prevalence. Princess Marina Hospital is located in Botswana’s capital city and is the main referral hospital for southern Botswana. Participants who gave written informed consent provided self-collected vaginal swab specimens after receiving verbal instructions from study staff. Samples were collected in the clinic washroom by participants. Following sample collection, study staff reviewed participants’ obstetric records to collect information related to sociodemographic characteristics (eg, age, marital status and education level), obstetric history (eg, prior pregnancies and births) and HIV and syphilis testing and results. Participants also responded to an interviewer-administered questionnaire conducted in English or Setswana (the language spoken by the majority of people in Botswana), which collected behavioural information (eg, condom use) and whether participants had been previously diagnosed and/or treated for an STI during the current pregnancy. We also asked whether participants were experiencing any symptoms that could be related to having an STI, including abnormal vaginal discharge, painful urination and/or lower abdominal pain. We chose these symptoms because they are currently used in Botswana’s syndromic management algorithm to identify STIs. Testing and treatment were free of charge, and participants were not offered incentives for enrollment in the study. Testing was conducted by trained study staff using the US Food and Drug Administration-approved Xpert® CT/NG and Xpert® TV nucleic acid amplification assays (Cepheid, Sunnyvale, California, USA). Xpert® allows for 90 min detection for CT and NG infections and 59 min for TV infection.

The goal of the study was to provide participants with results in person on the same day as testing. If a participant left prior to receipt of results, they were to be called and advised to return to the clinic for treatment if necessary. Those who tested positive for CT, NG and/or TV were offered directly observed treatment. If a participant left prior to receipt of results, they were to be called and advised to return to the clinic for treatment if necessary. Those who tested positive for CT, NG and/or TV were offered directly observed treatment. We followed The US Centres for Disease Control and Prevention (CDC) treatment guidelines, which included directly observed therapy of 1 g oral azithromycin for chlamydial infection, 250 mg intramuscular injection of ceftriaxone and 1 g oral azithromycin for gonococcal infection and 2 g oral metronidazole for trichomonial infection. Participants who were HIV infected were given 400 mg of metronidazole two times per day for 7 days. Participants who tested positive were counselled to tell their partner(s) and abstain from sex for 7 days, given the option of bringing their partner(s) into the study clinic for treatment and provided with a contact sheet with instructions for their partners to receive treatment at a clinic of their choosing. Finally, those who tested positive were encouraged to return to the clinic for a follow-up visit, but no sooner than 4 weeks, for a test of cure. The test of cure is needed to assess persistent infection despite treatment, and the CDC guidelines recommend the test of cure take place 3–4 weeks after treatment completion for pregnant women.

Descriptive statistics were used to characterise sociodemographics and obstetric and medical characteristics of participants. Bivariate comparisons, including z-tests of proportions, Fisher’s exact test, Student’s t-tests and Mann-Whitney U tests were used to examine the relationships between participant characteristics and STI diagnosis. Finally, multivariable logistic regression was used to identify characteristics independently associated with having an STI, adjusting for other factors. Variables were included based on results of stepwise selection for logistic regression analyses, and covariates with a significance level of ≤0.2 were included in the model. Statistical significance of variables in the final model was assessed at the 0.05 level. Stata 13 (StatCorp, College Station, Texas, USA) was used for all analyses.

The institutional review boards at the University of Botswana (URB/IRB/11547), the Botswana Ministry of Health, Health Research Development Committee (PPME 13/18/1 IX(434)) and Princess Marina Hospital (PMH S/79/2(223–3–2016)) approved the study protocol. The University of California, Los Angeles (15–000692), approved analyses using de-identified data.

RESULTS
Between July 2015 and May 2016, we enrolled 400 (86%) of the 466 eligible women recruited (figure 1). Among those who gave
a reason for refusing participation (n=38), the most common reason for refusal was concern about the time it would take to collect the sample (16, 13% (5) said they did not want additional testing and 11% (4) said they were afraid of the results. The remainder gave no reason or said that they needed to think about it. The ages and gestational ages of women who enrolled and those who declined did not differ. (The median age for those who enrolled and refused was 30 years. The median gestational age for both those who enrolled and refused was 26 weeks.) Among those enrolled, we were able to provide results to 99% (399/400) of participants either in person (60%; 240/399) on the same day as testing or by phone (39%; 159/399) on the same day as testing or by phone (39%; 159/399) within a week. As displayed in table 1, the median age of our sample was 30 years, and most women (77%) were unmarried. The HIV prevalence was 2.3%, and among the 319 women with a documented syphilis test, 2 (0.6%) were reactive. Twenty-seven per cent of participants reported never using condoms during the 3 months prior to trying to get pregnant or becoming pregnant, and 47% reported never using condoms during pregnancy. The median number of previous pregnancies was 1 and 65% had a prior birth. Among those who had given birth, 64 (25%) had experienced at least one prior preterm birth. In terms of current symptoms, 41% reported that they were experiencing at least one symptom related to CT, NG and/or TV, including vaginal discharge (27%), lower abdominal pain (22%) and/or painful urination (4%). Symptoms related to herpes simplex virus infections such as genital ulcers (1%) and human papillomavirus infections such as warts (4.5%) were rare. Over 12% had been treated syndromically for an STI (other than HIV) previously during the current pregnancy. Prior treatment did not differ by HIV status. As seen in table 1, we found the prevalence of CT, NG and/or TV, hereafter referred to collectively as STI, to be 13.5% (54/400; 95% CI 10.3% to 17.2%). The prevalence of CT was 7.8% (31/400; 95% CI 4.9% to 10.2%), NG was 1.3% (5/400; 95% CI 0.4% to 2.9%) and TV was 5% (21/400; 95% CI 3.3% to 7.9%). Two participants were dually infected with CT and NG, and one was infected CT and TV. As seen in figure 1, among the women who tested positive for CT, NG and/or TV, 74% received results and treatment in person prior to leaving the clinic on the same day as testing. Eight women were called and provided results on the same day as testing, and among them five were treated within a week and three were treated in less than a month. Six women received delayed results (eg, we were not able to reach them on the same day), and 4 (67%) were treated. In total, 52 (96%) were treated, and 77% were treated on the same day. Further, 41 of the 52 participants treated for CT, NG and/or TV returned for a test of cure. Among the 41 participants, four (9.8%) retested positive, including three with CT and one with TV. Although the reasons for the positive retests were unclear, three women reported that their sex partners were not treated prior to the test of cure. Bivariate comparisons revealed that marital status ($\chi^2$ p value=0.011) and HIV infection status ($\chi^2$ p value=0.002) were significantly associated with having CT, NG and/or TV infection. Unmarried participants were more likely to have an STI (16%) than those who were married (5.6%), and those living with HIV infection were more likely to have an STI (23.3%) than those who were HIV uninfected (10.5%). Among women who had previously given birth, those who experienced a prior preterm birth were more likely to be diagnosed with CT (16%), compared with those with no history of preterm birth (5%). Self-reported STI-related symptoms (abnormal vaginal discharge, lower abdominal pain and/or painful urination) were not associated with a positive CT, NG and/or TV diagnosis ($\chi^2$ p=0.89). Among those diagnosed with an STI, 41% (22/54) reported having a symptom related to CT, NG or TV (28% (15/54) had abnormal vaginal discharge, 17% (9/54) had lower abdominal pain and 4% (2/54) had painful urination). Among those without an STI, 42% reported having a symptom related to CT, NG or TV (27% (92/343) had abnormal vaginal discharge, 23% (79/343) had lower abdominal pain and 4% (14/343) had painful urination). The stepwise regression analysis was performed using eight predictor variables, including participant age, marital status, HIV infection status, education level, condom use before and after pregnancy, prior births and STI-related symptoms (abnormal vaginal discharge, lower abdominal pain and painful urination). Table 2 provides the results from a multivariable logistic regression model with the five independent variables listed in the order in which they were selected by the stepwise procedure. Marital and HIV status were independently and significantly associated

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**Figure 1** Flow of eligible women and participants in a *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) infection testing and treatment study in Gaborone, Botswana.
Epidemiology

Table 1  Characteristics of study participants and associations with CT, NG and TV infection, Gaborone, Botswana (n=400)

<table>
<thead>
<tr>
<th>Total sample (n=400)</th>
<th>STI* (n=54)</th>
<th>CT (n=31)</th>
<th>NG (n=5)</th>
<th>TV (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>p</td>
<td>n (%)</td>
<td>p</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>30 (19–45)</td>
<td>29 (19–43)</td>
<td>28 (19–40)</td>
<td>22 (21–39)</td>
</tr>
<tr>
<td>18–25</td>
<td>95 (23.8)</td>
<td>17 (17.9)</td>
<td>12 (12.6)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>26–35</td>
<td>221 (55.3)</td>
<td>25 (11.3)</td>
<td>14 (6.3)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>84 (21.0)</td>
<td>12 (14.3)</td>
<td>5 (6.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Marital status (n=396)</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>307 (76.8)</td>
<td>49 (16.0)</td>
<td>27 (8.8)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Married</td>
<td>89 (22.3)</td>
<td>5 (5.6)</td>
<td>4 (4.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Education (n=392)</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Junior secondary or less</td>
<td>118 (29.5)</td>
<td>22 (18.6)</td>
<td>9 (7.6)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Senior secondary</td>
<td>114 (28.5)</td>
<td>17 (14.9)</td>
<td>12 (10.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>160 (40.0)</td>
<td>15 (9.4)</td>
<td>10 (6.3)</td>
<td>3 (1.2.5)</td>
</tr>
<tr>
<td>Gestational age weeks (LNMP), median (range)</td>
<td>26 (5–36)</td>
<td>28 (18–35)</td>
<td>28 (8–35)</td>
<td>22 (11–32)</td>
</tr>
<tr>
<td>Prior pregnancies, median (range)</td>
<td>1 (0–10)</td>
<td>1 (0–5)</td>
<td>1 (0–5)</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Prior births, median (range)</td>
<td>1 (0–7)</td>
<td>1 (0–5)</td>
<td>1 (0–5)</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>One or more births</td>
<td>261 (65.3)</td>
<td>37 (14.1)</td>
<td>20 (7.7)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Prior preterm birth</td>
<td>64 (24.5)</td>
<td>12 (18.0)</td>
<td>10 (15.6)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>No prior preterm birth</td>
<td>192 (73.5)</td>
<td>25 (13.0)</td>
<td>10 (5.2)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Current CT/NG/TV symptoms</td>
<td>165 (41.3)</td>
<td>22 (13.0)</td>
<td>10 (6.0)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>107 (26.8)</td>
<td>15 (4.9)</td>
<td>8 (2.8)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>88 (22.0)</td>
<td>9 (10.2)</td>
<td>2 (2.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Painful urination</td>
<td>16 (4.0)</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Treated syndromically during pregnancy</td>
<td>48 (12.0)</td>
<td>8 (16.7)</td>
<td>5 (10.4)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Condom use before pregnancy§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>110 (27.5)</td>
<td>14 (12.7)</td>
<td>8 (7.3)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>185 (46.3)</td>
<td>28 (15.1)</td>
<td>17 (9.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Always</td>
<td>98 (24.5)</td>
<td>12 (12.6)</td>
<td>6 (6.3)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Condom use during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>188 (47.0)</td>
<td>30 (16.0)</td>
<td>16 (8.5)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>83 (20.8)</td>
<td>9 (10.8)</td>
<td>6 (7.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Always</td>
<td>75 (18.0)</td>
<td>12 (16.0)</td>
<td>7 (9.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>HIV infection status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected</td>
<td>90 (22.5)</td>
<td>21 (23.3)</td>
<td>10 (11.1)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Uninfected</td>
<td>305 (76.3)</td>
<td>32 (10.5)</td>
<td>20 (6.6)</td>
<td>3 (1.0)</td>
</tr>
</tbody>
</table>

CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; TV, *Trichomonas vaginalis*; LNMP, last normal menstrual period.

*Diagnosed with CT, NG and/or TV infection.

1p<0.1 and †p≤0.05, which resulted from Student’s t-test, y2 test, Fisher’s exact test or Wilcoxon-Mann-Whitney test. CT, NG and/or TV symptoms include vaginal discharge, lower abdominal pain and painful urination.

§Women were asked about condom use during the 3 months prior to the pregnancy or trying for the pregnancy. Ranges are in brackets. Percentages are in parentheses and may not add up to 100 due to rounding. The denominator for the total sample column is 400. For the remaining columns, the denominators are derived from the row values in the total sample column.

Table 2  Results of a multivariable logistic regression model assessing participant characteristics associated with CT, NG and TV infection (n=376)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Positive for CT, NG and/or TV</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤25 years</td>
<td>1.67 (0.84 to 3.29)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>2.89 (1.09 to 7.67)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>High school education or less</td>
<td>1.69 (0.85 to 3.37)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Never used a condom during current pregnancy</td>
<td>1.59 (0.86 to 2.96)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td>2.72 (1.45 to 5.19)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Independent variables (age, marital status, education level, condom use during pregnancy and HIV infection status) were included based on a stepwise regression model. ORs reflect increased or decreased likelihood of women with this characteristic being diagnosed with CT, NG and/or TV.

CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; TV, *Trichomonas vaginalis*.

with a positive STI diagnosis, after adjustment for age, education and condom use during pregnancy.

DISCUSSION

We provided testing and treatment for three curable STIs to 400 pregnant women at one of the largest antenatal clinics in Gaborone, Botswana. The prevalence of one or more STIs was 13.5%. Being unmarried and HIV infected were significantly associated with testing positive for an STI, and self-reported STI symptoms were not associated with testing positive for an STI. All but one participant received STI test results. Among those who tested positive for an STI, almost three-fourths received results and treatment in person on the same day as testing. However, participants who received delayed results were less likely to be treated.

Our prevalence estimates were high compared with global pooled prevalence estimates among women, and similar to

pooled prevalences among women in the WHO Africa Region, which were estimated at 3.7% (2.7–5.2) for CT, 1.7% (1.1–2.6) for NG and 11.5% (9.0–14.6) for TV.17 Our CT and NG estimates are similar to a 2007 study (using data from 2000 to 2001) among pregnant women in Botswana, which found the prevalence of CT and NG to be 8% and 3%, respectively.11 However, our estimate of TV prevalence was almost four times lower than the 19% identified by Romoren et al.12 These results may be partially explained by differences in our samples. For example, Romoren et al did not exclude those under 18 years of age, and our participants have a median age that is 5 years older. Romoren et al found that age was a predictor of CT, NG and TV infections and the prevalence rates of CT and NG infections were highest among teenagers.11 12 More research is needed to understand whether the difference in TV prevalence estimates was due to sample differences, variation in diagnostics used or a change in the prevalence of TV in Gaborone, Botswana, over time.

Our study has some limitations. First, women were recruited from a single site, Princess Marina Hospital antenatal clinic, which provides antenatal care, and also serves as a referral clinic for women with high-risk pregnancies. For example, 7% were referred for having a history of miscarriages. However, close to a quarter of our sample (17%) reported that their appointment was a routine checkup, and the remainder was referred for a high-risk condition, including high-blood pressure (22%), rhinitis (6%), the need for a caesarian section (3%) and diabetes (3%), which are likely not associated with an STI.11 12 It is encouraging to note that the characteristics of our sample did not differ greatly from the population of women in Botswana. The 2007 Botswana Family Health Survey IV Report, which identifies and surveys a representative sample of the population of Botswana on topics related to family planning awareness and basic maternal and child health indicators, also found that very few women were married (18%), 70% reached at least a secondary level of education and the highest proportion of pregnancies occurred among women between the ages of 30 and 34 years.24 Furthermore, the Botswana AIDS Impact Survey IV Report, which provides HIV incidence and prevalence estimates among the population aged 6 to 64 years, found that the HIV prevalence among pregnant women was 20.5%. The proportion of preterm births among women who had previously given birth (25%) was expected given that Botswana is one of 11 countries with a national preterm birth rate higher than 15%.22 Finally, only 80% of our participants had a documented syphilis test, and it is unclear if this is due to a lack of testing or documentation in obstetric records. Although our estimate of the prevalence of reactive syphilis tests was low, a 2016 study that used clinic antenatal registers estimated the syphilis prevalence to be 1.15% (95% CI 0.89 to 1.41) among pregnant women in Gaborone in 2008.27

In addition, our sample represents women who agreed to participate and may be more likely to include women who believe they are at greater risk for infection. However, this concern is mitigated by the large proportion of women who accepted (86%) out of all those eligible. This study showed it was possible to integrate CT, NG and TV diagnostic testing into antenatal care in Botswana. Results highlighted that, even with a 90 min testing time, it was not possible to provide all participants with results and treatment on the same day as testing. The average wait time at the Princess Marina antenatal clinic was 45 min, and many women were unwilling or unable to wait for results after their appointment concluded. Thus, to maximise the effectiveness of an STI testing and treatment programme, a faster time to result would be useful as would efforts to ensure treatment uptake among those who received delayed results. Because many sub-Saharan African countries have an antenatal care attendance rate of at least 70% and deliver opt-out antenatal HIV testing, antenatal care could provide a framework for CT, NG and TV testing.22 As the costs (eg, capital and supplies) and infrastructure needs (eg, continuous power and reliable shipping) associated with STI testing may be high for some low-income and middle-income countries, more research is needed to compare the costs of testing and treatment with the health benefits associated with curing infections and the subsequent savings to the health system. To conserve resources, subgroups, such as women infected with HIV, may be appropriate to target for STI testing. Our study also found a lack of an association between self-reported STI symptoms, which provides further evidence that syndromic management may not adequately identify STIs in pregnant women. Although syndromic management has the benefit of low costs and resource requirements, it is likely that pregnant women are being unnecessarily exposed to antibiotics, which is particularly concerning given the expansion of drug-resistant NG.28 Furthermore, true infections are likely being missed, which may be contributing to the high rates of adverse birth outcomes in Botswana, including preterm birth.

In conclusion, providing testing and treatment for curable STIs to pregnant women in an antenatal clinic in Gaborone, Botswana, revealed a high STI prevalence. Participant HIV infection and marital status were significantly positively associated with being diagnosed with CT, NG and/or TV, and self-reported STI symptoms were not associated with testing positive. Among participants with an STI, those who received same-day results were more likely to be treated than those who received delayed results. The absence of diagnostic tests for STIs during antenatal care likely represents a missed opportunity to improve pregnancy and birth outcomes in Botswana. As highly sensitive and specific point-of-care testing assays become more widely available, it is important for health ministers and other policy makers to assess the short-term and long-term cost and benefits of offering STI screening during antenatal care.

Key messages

► The prevalence of STIs among pregnant women was high.
► HIV infection and being unmarried were associated with being diagnosed with an STI.
► Self-reported symptoms (eg, abnormal vaginal discharge) were not associated with infection.
► Among those who tested positive, 74% received in person, same-day results and treatment.

Contributors AW managed the study, did the analyses and data collection and wrote the first and final draft. PG was the clinician on the study and approved the final draft. NM, DD, EJ and KD worked on the study, reviewed analyses, wrote sections and edited/approved the final version. DR-M helped conceive the study and data collection protocols, reviewed drafts of the manuscript and edited/approved of the final version. JG was the PI on the study, supported analyses, wrote sections and approved the final draft. CM was the PI on the study, supported analyses, wrote sections and approved the final draft.

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Ethics approval University of Botswana, the Botswana Ministry of Health, Health Research Development Committee, and Princess Marina Hospital approved the...
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study protocol. The University of California, Los Angeles, approved analyses using de-identified data.

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Kevin Beverly, President, at KBeverly@s-3.com
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