Mycoplasma genitalium Treatment Failure Registry

SUPPORTING STATEMENT – Section A

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34.

- **Goal of the information collection:** The purpose of this information collection is to determine which second-line antibiotics are in use for *Mycoplasma genitalium* treatment failure and monitor antibiotic resistance patterns for treatment failure cases throughout the United States.
- **Intended use of the resulting data:** The resulting data will be used to inform national treatment recommendations from the CDC for *Mycoplasma genitalium.*
- **Methods of information collection:** Data will be collected using a standardized case report form, which includes quantitative information collection. Data will be transmitted via secure email using a fillable PDF or secure fax using a paper form.
- **The subpopulation to be evaluated:** The information will be collected from healthcare providers who care for patients with sexually transmitted *Mycoplasma genitalium.*
- **How data will be analyzed:** The following analytic tests will be applied to the quantitative data: frequencies and cross-tabulations, correlations, means, medians, ANOVA and logistic regression to explore relationships within the data.

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37. Section A. JUSTIFICATION

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39. 1. Circumstances Making the Collection of Information Necessary

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41. The Centers for Disease Control and Prevention (CDC), Division of STD Prevention (DSTDP) requests a 3-year approval for a new information collection request (ICR) entitled, "Mycoplasma genitalium Treatment Failure Registry." This data collection is intended to determine which second-line antibiotics are in use for *Mycoplasma genitalium* treatment failure and monitor antibiotic resistance patterns for treatment failure cases throughout the United States This information collection is authorized by Section 301 of the Public Health Service Act (42 U.S. Code, Sec. 792[295k] (a)) (**Attachment 1**).

42. *Mycoplasma genitalium* is a sexually transmitted bacterium that was first identified in the early 1980s. According to the National Longitudinal Study of Adolescent Health, *M. genitalium* is more common than gonorrhea but less common than chlamydia. (Manhart 2007, *Am J Public Health,* Mena 2002, *Clin Infect Dis*) *Mycoplasma* and chlamydia coinfections may also occur. (Huppert 2008, *Sex Transm Dis*) *M. genitalium* is strongly associated with urethritis in males, accounting for approximately 15-20% of all cases of non-gonococcal urethritis (NGU) and 30% of persistent or recurrent urethritis (Taylor-Robinson 2011 *Clin Microbiol Rev*). Despite a clear association with urethritis, it is unknown whether *M. genitalium* causes male infertility or upper urogenital tract disease. *M. genitalium* can be detected in the rectum but its relationship with clinical proctitis is also unclear. In females, *M. genitalium* has been associated with 1.6-1.9-fold increased odds of cervicitis, pelvic inflammatory disease, preterm birth, and spontaneous abortion. It may also be associated with tubal factor infertility (Lis 2015, *Clin Infect Dis*)

43. Until recently in the United States, suspected *M. genitalium* was managed on a syndromic basis, as there were previously no FDA-approved tests for clinical diagnostic use. As of 2019, the FDA approved the first nucleic acid amplification testing (NAAT) for *M. genitalium,* (Aptima, Hologic Inc., Marlborough, MA), which will greatly expand access to testing and identification of *M. genitalium* infections. There are no national guidelines for use of *M. genitalium* NAAT for asymptomatic screening. However, the 2020 CDC STD Treatment Guidelines will address use of M. genitalium NAAT testing for patients with genital or urinary symptoms.

44. Previously in the 2015 CDC STD Treatment Guidelines, the recommended treatment for *M. genitalium* was the macrolide antibiotic azithromycin followed by a course of moxifloxacin in cases of azithromycin treatment failure. The cure rate for moxifloxacin was previously thought to be 100%, however, reports of antibiotic resistance or treatment failure have been reported from Australia, Japan, South Africa, Europe, and the US (Murray 2017, *Emerg Infect Dis*; Deguchi 2018, *J Infect Chemother*, Muller 2019, *BMC Infect Dis*, Unemo 2018, *Clin Microbiol Infect*, Glaser 2019 *Int J STD AIDS*). In the United States, there are currently no national guidelines for treatment in cases of moxifloxacin treatment failure, and data are needed to provide evidence for future treatment recommendations.

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46. 2. Purpose and Use of the Information Collection

47. The purpose of the *Mycoplasma genitalium* Treatment Failure Registry is to monitor antibiotic use for cases of *M. genitalium* that fail treatment with first-line therapy. Data will be collected from approximately 100 healthcare providers annually who care for patients with sexually transmitted *Mycoplasma genitalium* infections who experience persistent symptoms and treatment failure after receiving standard therapy. Data from the registry will be analyzed to describe the demographic characteristics of patients with treatment failure, frequency of use of second-line antibiotic therapies, and patterns of antibiotic resistance. Further information can be found in the registry protocol (**Attachment 2**)
48. Providers will be recruited to send cases via an email which will describe the registry and reporting procedures. The recruitment email will be sent via listservs from the eight CDC-funded centers in the National Network of Clinical STD Prevention Training Centers (NNPTC), which are located in WA, CA, CO, MO, MA, AL, NY, MD and train healthcare providers in all 50 states and the US Virgin Islands. (**Attachment 3**)
49.
50. Reporting providers will be asked to submit a two-page case report form (either by fax or email) to CDC DSTDP. (**Attachment 4**) Providers will be reporting on clinical and demographic characteristics of the cases but will not be reporting on any personally identifiable information. (See section 10 of this document for additional information on measures to protect the confidentiality of the patients' information) If desired, reporting providers will also be connected with a clinician in the STD Clinical Consultation Network (www.STDCCN.org, managed by the NNPTC) to provide further guidance on antibiotic management. Reporting providers will be asked to omit any identifiable information during the consultation process to ensure patient confidentiality.
51. If specimens are available, remnant specimens from patients with M. genitalium treatment failure will be sent to the DSTDP laboratory to be tested for genetic mutations associated with antibiotic resistance to macrolides, fluroquinolones, and tetracyclines. Specimen test results will be analyzed in aggregate to determine the prevalence of antibiotic resistance markers.
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53. The purpose of this information collection is to determine which second-line antibiotics are in use for *Mycoplasma genitalium* treatment failure and monitor genetic markers of antibiotic resistance among treatment failure cases throughout the United States.
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55. 3. Use of Improved Information Technology and Burden Reduction

56. A fillable PDF version of the case report form will be used, and respondents may either submit those forms via secure email or print them and send via fax. If completed electronically, the instrument may be completed by computer or tablet. This information collection instrument was designed to collect the minimum information necessary for the purposes of this project.
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58. 4. Efforts to Identify Duplication and Use of Similar Information

59. The information being collected for the registry is unique. *Mycoplasma genitalium* cases are not reportable to CDC, therefore this information collection represents CDC DSTDP's only means to monitor treatment for this infection. There is currently no information available that can substitute for the responses to the data collection instrument.
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61. **5. Impact on Small Businesses or Other Small Entities**
62. This data collection will not involve small businesses or other small entities.
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64. **6. Consequences of Collecting the Information Less Frequently**
65. The Case Report Form (Attachment 4) will be completed one time by clinical providers at the time they encounter a patient with *Mycoplasma genitalium* who fails treatment with the antibiotic regimens recommended by CDC. It is unknown how often these cases will arise, but they are currently rare. Therefore, providers will be expected to complete 1 case report form per year. Less frequent collection of case reports would hinder the ability to evaluate the annual burden of *M. genitalium* treatment failure in the US.
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67. **7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5**
68. This request fully complies with the regulation 5 CFR 1320.5.
69.
70. **8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency**
71. The 60-day federal register notice to solicit public comments was published in the Federal Register Vol. 85, No. 109, pg. 34636 / (June 5, 2020) (**Attachment 5**). No public comments were received.
72.
73. Consultations outside CDC occurred with outside experts at three universities (University of Alabama, Emory University, University of Washington) in 2019 who provided feedback on the data collection instrument. Consultation and review of the instrument also occurred internally within the Division of STD Prevention. Other programs within CDC were not consulted. Following the consultation there was consensus on the final instrument, with no unresolved issues.

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76.
77. **9. Explanation of Any Payment or Gift to Respondents**
78. CDC will not provide payments or gifts to respondents.
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80. **10. Protection of the Privacy and Confidentiality of Information Provided by Respondents**
81. The Privacy Officer for CDC / ATSDR has assessed this package for applicability of 5 U.S.C. § 552a (**Attachment** 6). The Privacy Act is applicable because PII is being collected under this CDC-funded activity. Records are covered under CDC Privacy Act System of Records Notice (SORN) No. 0920-0136 "Epidemiologic Studies and Surveillance of Disease Problems" and SORN No. 09-20-0113, "Epidemic Investigation Case Records Systems Notice."
82. The Health Insurance Portability and Accountability Act (HIPAA) permits covered entities such as clinicians to disclose patient's protected health information (PHI) to public health authorities for public health purposes without the patient's authorization. The Registry will consist of a

limited data set of variables, there will be no other PHI other than full dates of treatment (month, day, year). The data will only be used for the purposes for which it is intended, i.e., surveillance of *M. genitalium* treatment failure to inform clinical recommendations and guidelines. In the Case Report Form (**Attachment 4**), CDC is collecting full dates of treatment (month, day, year) as a public health authority, defined in the HIPAA and its implementing regulations. Standards for Privacy of Individually Identifiable Health Information (45 CFR § 164.501), ("Privacy Rule").

83. Other patient data on race and ethnicity are collected on Case Report Form (**Attachment 4**) as many STDs disproportionally impact African Americans and Latino/as. However, it is unknown at the present time whether cases of *Mycoplasma genitalium* treatment failure are more likely to occur in patients from racial/ethnic minority groups. Because antibiotic resistance in *Mycoplasma genitalium* is an emerging issue, it is crucial to collect this data to determine whether disparities exist by race/ethnicity. Other key patient variables collected include patient's gender, gender of sex partners and HIV status. All of these are factors associated with risk of bacterial sexually transmitted infections, but it is unknown whether any of these factors will influence *Mycoplasma genitalium* treatment failure.
84. Original indications for testing (anatomic location of symptoms) and prior antibiotic resistance testing (if performed) to determine whether such testing should be performed at the CDC laboratory. Dates of antibiotic treatment will also be collected to determine the length of the antibiotic regimen being utilized and the spacing between multiple treatment courses.
85. A unique identifier will be generated for the case report form to enable linking with laboratory testing data, if specimens are sent to CDC for testing. This will also allow linkage of data internally in case a patient experiences multiple episodes of treatment failure. The unique identifier will consist of the patients first and last initial, 2-digit year of birth, and last 4 digits of the Medical Record Number. (e.g., John Smith, born 1973, MRN 1234567 = JS734567). There will be no links to personally identifiable information.
86. The Case Report Form **(Attachment 4)** will collect categories of information in identifiable format from respondent clinicians such as: clinician's name, work mailing address, work phone numbers, work email address. These identifiable data elements are needed to determine where cases of antibiotic failure are occurring geographically, and for future correspondence/communication with the clinician.
87. There are several safeguards in place to handle data submitted to the CDC. Data will be stored and managed based on current CDC/OCISO (Office of the Chief Information Security Officer) requirements and standards. This includes protecting stored data within the CDC Internet Firewall. The data are stored and managed based on current CDC/OCISO requirements and standards which also includes the process for handling security incidents and the event monitoring and incident response. All administrative controls required by OCISO are validated through a "Certification and Authorization" (C&A) process as conducted by OCISO prior to moving any software application into "Production" on the CDC network.
88. Files are backed up daily and stored both onsite in accordance with CDC standards and OCISO guidelines. All users' access is "role based" and reflects a "need to know" policy established by CDC. Accountability is maintained with a user access log file which tracks users' access to the system. Records will be retained and destroyed in accordance with the applicable CDC Records Control Schedule as mandated by OCISO.
89. (http://www.cdc.gov/about/leadership/leaders/seligman.htm" (http://aops-mas-iis.od.cdc.gov/Policy/Doc/policy449.htm)
90. The CDC will not include any information in reports that may identify cases or patients, including specified dates of diagnosis and treatment. Only deidentified data will be presented in case reports or in aggregate. Aggregate data will not be stratified into subcategories that might allow for identification of individuals.
91.

92. 11. Institutional Review Board (IRB) and Justification for Sensitive Questions

93. IRB Approval

94. This project involves collection of retrospective patient medical record data. The case report form used to conduct this information collection request has been reviewed and approved by NCHHSTP's Human Subjects Advisor, who determined that this project does not constitute Human Subjects Research under 45 CFR 46.102(d). (**Attachment 6**)

95. Justification for Sensitive Questions

96. Forms are used to collect medical and laboratory data which is sensitive information

- Age, sex, race/ethnicity, gender identity, gender of sex partners are all factors associated with increased risk of other bacterial sexually transmitted infections and may be related to *M. genitalium* treatment failure.
- Dates of diagnosis, treatment and treatment rendered are needed to determine the spacing between treatments and which treatments were given
- HIV status. HIV status can influence the natural history of other sexually transmitted infections (e.g., syphilis), and it is currently unknown whether HIV-coinfection might influence the natural history of *M. genitalium* treatment failure

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98. 12. Estimates of Annualized Burden Hours and Costs

99. The estimate for burden hours is based on informal review of the information collection instruments by both physicians and nurse practitioners. Table 12A summarizes the average time to complete the instruments, including gathering needed information and completing the instrument. See **Attachment 4** for a copy of the instrument.

100. The estimated number of respondents is 100. The number of respondents is based on an estimated 8-10 cases per month that could be reported to CDC. Currently there are several case reports of treatment failure reported from the US in the scientific literature. It is possible that the actual number of reported cases could be less than is estimated. We estimate 100 clinicians will provide one response each per year at an estimated 1 hour per response for a total of 100 total annualized burden hours. (Table 12A).

101.

102. Table 12A: Estimated Annual Burden Hours

103.

104. Type of Respondent	105. Form Name	106. No. of Respondents 107.	108. No. Responses per Respondent	109. Average Burden per Response (in hours)	110. Total Burden Hours
111. 112. Physician or Nurse Practitioner	113. M. genitalium Treatment Failure Registry Case Report Form (Att	114. 100	115. 1	116. 1	117. 100

	4)				

118.

119.

120. Estimates for the average hourly wage for respondents are based on the Bureau of Labor Statistics May 2018 mean estimate for physicians and surgeons as $98.02, and for nurse practitioners as $52.90 (http://www.bls.gov/oes/current/oes290000.htm). The following table shows estimated time burden and cost information.

121. Table 12B: Estimated Annual Cost Burden to Respondents

122. Type of Respondent	**123. Form Name**	**124. Total Burden Hours**	**125. Hourly Wage Rate**	**126. Total Respondent Costs**
127. Physicians	128. Case Report Form	129. 70	130. $98.02	131. $6 861.40
132. Nurse Practitioners	133. Case Report Form	134. 30	135. $52.90	136. $1 587.00
137. **Total**	138.	**139. 100 hours**	140.	**141. $8 448.40**

142.

143. 13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

144. There will be no direct costs to the respondents other than their time to participate in each information collection.

145.

146. 14. Annualized Cost to the Federal Government

147. There are no equipment or overhead costs. The only cost to the federal government would be the salary of CDC staff supporting the data collection activities, laboratory testing and associated tasks.

148. Annually the estimated cost of the assessment is $ **$20,287.80**. The personnel cost of the CDC oversight of the project and contractors will be $2914.00 for the Health Scientist who will be the primary project manager. The cost of the Medical Officer who will oversee project activities will be $5791, and the cost of the laboratorian who will coordinate specimen transport and testing will be $11,582.

149. **Table 14: Estimated Annualized Cost to the Federal Government**

150. Staff (FTE)	**151. Average Hours per Collection**	**152. Average Hourly Rate**	**153. Average Cost**
154. Health Scientist (GS-13): OMB package preparation; review and oversight of	155. 4 0	156. 48.58	157. $2914.8

assessment design, instrument development, pilot testing, data collection, quality control, data analysis and report preparation			0
158. Medical Officer (GS-14): oversight of Health Scientist, liaising with CDC laboratory and medical providers reporting cases, preparing and delivering presentations	159. 160. 1 00	161. 162. 57.91	163. 164. 165. 5791.00
166. Laboratorian (GS-14): Liaising with laboratories that will send specimens, conducting resistance testing at CDC laboratory	167. 168.200	169. 170.57. 91	171. 172. 173.11,5 82.0 0
174. Estimated Total Cost of Information Collection	**175.**	**176.**	**177. $20,287. 80**

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179. 15. Explanation for Program Changes or Adjustments

180. This is a new data/information collection.

181.

182. 16. Plans for Tabulation and Publication and Project Time Schedule

183. Quantitative analyses will be performed. Prior to conducting any formal analyses on quantitative data, exploratory univariate and bivariate tests will be performed first to determine trends and patterns in the data. This will be accomplished using frequencies and cross-tabulations, and by examining univariate distributions and correlations. The frequency analysis will give various chi-squared tests for association for categorical ordinal or nominal data, while the ANOVA will provide F-tests for continuous data.

184.

185. Table 16: Project Time Schedule

186. Collect, enter, code, quality control, and analyze data	187. Upon OMB approval to 36 months
188. Prepare report	189. 12 months after OMB approval to 36 months
190. Disseminate results/reports	191. 12 months after OMB approval to 36 months

192.

193. 17. Reason(s) Display of OMB Expiration Date is Inappropriate

194. The display of the OMB expiration date is not inappropriate.

195.

196. 18. Exceptions to Certification for Paperwork Reduction Act Submissions

197. There are no exceptions to the certification.

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199.