

APPENDIX 1: List of PICO Questions

PICO QUESTION 1. What is the prevalence of asymptomatic *M. genitalium* in the following populations?

- o Heterosexual men;
- o Heterosexual women;
- o MSM: HIV-negative;
- o MSM: HIV-positive;
- o Pregnant women;
- o Transgender people;
- o Non-conforming people.

• **Outcome:** Prevalence related to anatomical distribution, prevalence of risk factors, *C. trachomatis* co-infection and *N. gonorrhoeae* co-infection.

PICO QUESTION 2. What is the prevalence of symptomatic *M. genitalium* in the following clinical presentations?

- o NGU/non-specific urethritis (first presentation);
- o NGU/non-specific urethritis (persistent and recurrent episodes);
- o Muco-purulent cervicitis/intermenstrual bleeding/post-coital bleeding;
- o PID/salpingitis;
- o Proctitis;
- o Vaginal discharge;
- o Pharyngitis;
- o Prostatitis;
- o Conjunctivitis;
- o Reactive arthritis.

• **Outcome:** Prevalence, odds ratio, *C. trachomatis* co-infection and *N. gonorrhoeae* co-infection

PICO QUESTION 3. What are the clinical features of *M. genitalium* infection?

• **Outcome:** Evidence for testing *M. genitalium* infection in the populations and clinical scenarios examined above.

PICO QUESTION 4. What are the adverse outcomes associated with *M. genitalium* in pregnancy?

• **Outcome:** Adverse outcomes.

PICO QUESTION 5. What are the optimal specimen types for testing for *M. genitalium* in men and women?

PICO QUESTION 6. What is the incubation/window period for *M. genitalium* detection?

PICO QUESTION 7. What are the country specific data for the prevalence of macrolide- and quinolone-associated resistance mutations?

• **Population:**

- o Heterosexual men;
- o Heterosexual women;
- o Gay and bisexual MSM;

• **Outcome:** macrolide- and quinolone-associated resistance mutations by group

PICO QUESTION 8. What is the correlation of the presence of resistance mutations with treatment failure/clinical cure/microbiological cure?

• **Outcome:** treatment failure/clinical cure/microbiological cure and associated symptoms by type of mutations (macrolide- or quinolone-resistant).

PICO QUESTION 9. What are the rates of microbiological cure/clearance rate/clinical cure/treatment failure for each of the following antimicrobial regimens?

- o Azithromycin (all regimens);
- o Moxifloxacin;
- o Doxycycline;
- o Minocycline;
- o Pristinamycin;
- o Lefamulin;
- o Gepotidacin;
- o Two-drug regimen (sequential);
- o Two-drug regimen (concurrent).

PICO QUESTION 10. Is a test of cure required, and if so, what is the optimal time to conduct a test-of-cure following treatment?

PICO QUESTION 11. Does notification of partners of patients with *M. genitalium* infection independently influence outcomes/relapse/re-infection in treated index patients?

• **Outcome:** successful outcome (decrease of relapse/re-infection of index patient).

APPENDIX 2: GRADE System for Assessing Evidence

Introduction:

There has been a general move to using the GRADE system by many guideline producing bodies in recent years and the BMJ published a series of papers about the method in 2008^{1,2,3,4,5,6}.

The GRADE system applied in its purest form requires scientific analyses of evidence to produce “tables” from a series of “PICO” questions: Questions that identify the patient problem or population (P), intervention (I) (or aetiology/diagnosis/frequency/prognosis), comparison (C) and outcome(s) (O). Practically this is very labour intensive and requires someone very experienced in this area, and many large guideline writing bodies employ a scientist to do this for them. However, some bodies adapt the GRADE system according to their own needs, assess the evidence in the way they have done in the past, and then make strengths of recommendations according to the GRADE system, which when applied in this way is quite simple to do and understand. BASHH have adopted GRADE to use in this manner.

The principles of GRADE:

1. Assessment of the evidence

GRADE offers four levels of evidence quality: high, moderate, low, and very low, with randomised trials classed as high-quality evidence and observational studies as low-quality evidence. Quality may be downgraded because of limitations in study design or implementation, imprecision of estimates (wide confidence intervals), variability in results, indirectness of evidence, or publication bias. Quality may be upgraded because of a very large magnitude of effect, a dose-response gradient, and if all plausible biases would reduce an apparent treatment effect.

Summary of factors affecting quality of evidence:

Study limitations	Imprecision	Large magnitude of effect
Inconsistency of results	Publication bias	Dose-response gradient
Indirectness of evidence	Factors that might increase quality of evidence	Plausible confounding, which would reduce a demonstrated effect

Based on the analysis of the evidence with these factors borne in mind the evidence should be graded as follows:

A	A body of evidence of high-quality meta-analyses, systematic reviews of and RCTs directly applicable to the target population
B	As above but relating to high quality case control or cohort studies with low risk of bias or confounding and high probability that a relationship is causal
C	As B but trials may have some flaws
D	Non-analytic evidence (e.g., case reports or series or expert opinion)

However, when reviewing evidence graded A-D as above the grading can be altered follows:

- The strength of recommendation should be higher if the following apply:
 - A large effect of an intervention is demonstrated.
 - Dose response/evidence of gradient.
 - All plausible confounding would reduce a demonstrated effect or would suggest a spurious effect when results show no effect.
- Lower if there is evidence of:
 - Serious/very serious study limitations
 - Inconsistency
 - Indirectness
 - Imprecision
 - Publication bias
 - Study limitations
 - Inconsistency of results
 - Indirectness of evidence
 - Imprecision

- Publication bias

2. Formulating recommendations

There are only two strengths of recommendation, which may be either for or against an intervention: 1 = strong or 2 = weak. Pragmatically, this means the following:

- Strong recommendation for intervention:

For patients — Most people in this situation would want the recommended course of action and only a small proportion would not.

For clinicians — Most people should receive the intervention.

For quality monitors — Adherence to this recommendation could be used as a quality criterion or performance indicator. If clinicians choose not to follow such a recommendation, they should document their rationale.

- Weak recommendation for intervention:

For patients — Most people in this situation would want the suggested course of action, but many would not.

For clinicians — Examine the evidence or a summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences.

For quality monitors — Clinicians' discussion or consideration of the pros and cons of the intervention, and their documentation of the discussion, could be used as a quality criterion.

- No specific recommendation:

- The advantages and disadvantages are equivalent.

- The target population has not been identified.

- Insufficient evidence on which to formulate a recommendation.

3. Consideration of using PICO

This may be helpful if guideline writing committee wish to utilise this method, this is explained in the NICE guideline manual; chapter 4:6.

Patients/population	Which patients or population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?
Intervention	Which intervention, treatment or approach should be used?
Comparison	What is/are the main alternative/s to compare with the intervention?
Outcome	What is really important for the patient? Which outcomes should be considered, such as intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning? Should other measures such as quality of life, general health status and costs be considered?

4. Consideration of costs

These may or may not legitimately be included in the GRADE system, but it would be sensible in the current climate to always consider these, and if they are not considered this should be stated and why – for example, there is no significant difference in cost between the recommended treatments.

Generally speaking, GRADE suggests a balance sheet should inform judgments about whether the net benefits are worth the incremental costs. Evidence profiles should always present resource use, not just monetary values.

5. Using the GRADE grid to resolve differences:

This supports the Delphi technique we already adopt, i.e., to develop a consensus within the group.

6. GRADE training for BASHH guideline authors

Authors need to be familiar and confident in using the GRADE system, and training for this is available as follows:

- The papers from the BMJ series in 2008, as listed in the introduction to this appendix. The articles can be accessed through the grade working group web site at: <http://www.gradeworkinggroup.org/publications/index.htm>
- McMaster GRADE online modules: these have been recommended by the GRADE working group and take about 20 minutes each to complete. The web address is: <http://cebgrade.mcmaster.ca/>
- Journal of Clinical Epidemiology 2011: published a 20-part series that is available through the GRADE working group website (link above).

Summary:

BASHH have now moved to the GRADE system for evaluating evidence and making recommendations by asking guideline authors and reviewers to apply the principles outlined in sections 1-3 above. Authors should consider structuring their analysis of evidence into PICO questions addressing Population / Intervention / Comparison / Outcome as stated in section 4. Costs should be included in the evaluation and formulation of recommendations as stated in section 5. When resolution of conflicting opinions is required, the GRADE grid should be used. This appendix is a brief summary of the GRADE system how it is to be adopted by BASHH guideline authors.

APPENDIX 3: Equality Impact Assessment Table

BASHH Guideline Equality Impact Assessment (based on NICE documentation shared with BASHH August 2019)			
Guidance title: BASHH Guidelines for the Management		Completed by: Suneeta Soni	
How relevant is the topic to equality?	Inequalities in health impact of the condition or public health issue	Potential of guidance to add value	Priority for other gov or other gov depart
	• Prevalence and impact of condition or public health problem; • Prevalence of risk factors.	• Inequalities in access, uptake or impact; • Timeliness; • Equality issues identified by proposers of the topic; • Equality issues identified by patient or lay organisations.	• Department of Health or centralised bodies such as NHS England • Local authorities • Home Office • Other agencies

BASHH Guideline Equality Impact Assessment (based on NICE documentation shared with BASHH August 2019)			
Guidance title: BASHH Guidelines for the Management		Completed by: Suneeta Soni	
Sex/gender	<i>M. genitalium</i> affects all individuals regardless of gender.	The guideline highlights that despite consequences in female reproductive tract morbidity, a screening programme as currently exists in the UK for <i>C. trachomatis</i> / <i>N. gonorrhoeae</i> is not warranted given the lack of clear association with infertility and also the issues around overtreatment leading to further AMR.	NA
Race	From population-based samples, <i>M. genitalium</i> has been found to be more prevalent among people of black ethnicity	NA	UKHSA un sentinel sur annually or to ensure th resistance r tracked. Th ongoing sur of resistanc highlighted government action Plan
Disability	<i>M. genitalium</i> affects all people although there are no specific data that determine the prevalence in those living with disability	There are potential issues regarding access to care for those with physical disability given that the guideline has stressed that where possible, testing and management e.g. <i>M. genitalium</i> should be managed in specialist settings ie. level 3 services.	Increased fu sexual heal to be able to outreach ca needed, is e
Age	<i>M. genitalium</i> affects individuals of all ages and the distribution across ages groups is relatively even	NA	NA
Sexual orientation	Rectal prevalence of <i>M. genitalium</i> is high. Pharyngeal infection is not implicated in the onward transmission	The guideline highlights prevalence of infection in PrEP users who are GBMSM and variation by anatomical site in these individuals.	UKHSA sh continue its surveillance annually or to ensure th

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	of infection. The presence of macrolide-associated resistance mutations has been found to be more prevalent among people of black ethnicity.		resistance r tracked. Th ongoing sur of resistanc highlighted government action Plan
Gender reassignment	There is a paucity of data for <i>M. genitalium</i> in people following gender reassignment. The reproductive harms of untreated <i>M. genitalium</i> can affect transgender men, non-binary (assigned female at birth) and other people who have not had a hysterectomy or bilateral oophorectomy.	NA	NA
Religion/belief	Surveillance data does not tell us about any association between <i>M. genitalium</i> and religion/ belief.	NA	NA
Pregnancy & maternity	Data are still unclear around maternity and neonatal outcomes in <i>M. genitalium</i> . The use of most antimicrobial treatments for this infection is contraindicated	The guideline addresses issues of diagnosis in pregnancy and the difficulty of treatment success given the limited antibiotics available to treat <i>M. genitalium</i> in pregnancy	NA
Other definable characteristics & socioeconomic factors that may be affected by protected characteristics, including: • Prisoners and young offenders; • Refugees and asylum seekers; • Migrant workers;	There is geographical variation in access to testing and treatment for STIs, including <i>M. genitalium</i> . Surveillance data does not offer sufficient	The guidelines are primarily for those working in level 3 specialist sexual health services and safeguarding concerns should be addressed by departmental policies. Genitourinary physicians	Safeguardin concerns addressed.

BASHH Guideline Equality Impact Assessment (based on NICE documentation shared with BASHH August 2019)			
Guidance title: BASHH Guidelines for the Management		Completed by: Suneeta Soni	
• Looked after children; • Homeless people; • Deprivation; • Disadvantage associated with geographical distinctions.	granularity to comment on how other inclusion populations may be more affected by <i>M. genitalium</i> .	receive level 3 safeguarding training.	

AMR: antimicrobial resistance; BASHH: British Association for Sexual Health and HIV; GBMSM: gay, bisexual and other men who have sex with men; NA: not applicable; PrEP: pre-exposure prophylaxis; STIs: sexually transmitted infections; UKHSA: UK Health Security Agency.

APPENDIX 4: AGREE II User Manual

The AGREE II consists of 23 key items organized within 6 domains followed by 2 global rating items (“Overall Assessment”). Each domain captures a unique dimension of guideline quality⁷.

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

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¹ Guyatt GH, Oxman AD, Vist G, et al; GRADE Working Group. BMJ 2008; 336:924-926.

² Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7651):995-8.

³ Schünemann HJ, Oxman AD, Brozek J, et al; GRADE Working Group. BMJ 2008; 336(7653):1106-10.

⁴ Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7654):1170-3.

⁵ Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7652):1049-51.

⁶ Jaeschke R, Guyatt GH, Dellinger P, et al; GRADE working group. BMJ 2008; 337:a744.

⁷ Appraisal of Guidelines for Research & Evaluation (AGREE) II User Manual, update from December 2017. Access: <https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf>