Abstract:

Chlamydia trachomatis and *Neisseria gonorrhoeae* testing guidance recommends extragenital screening with locally validated nucleic acid amplification tests, with anatomical sites tested separately. Evidence supports multi-patient combined aliquot pooled sampling (PS) for population screening; evidence for within-patient PS is sparse. Within-patient PS could be more cost-effective for triple-site testing, but requires distinct clinical pathways and consideration over loss of information to guide risk assessments and treatment. We explored PS attitudes and practices amongst clinicians in England. A cross-sectional web-based survey was distributed to clinical leads of sexual health services throughout England in February 2016. Fifty two (52/216, 23%) services responded. One service reported current within-patient PS and two were awaiting implementation. Of the 49 services not pooling, five were considering implementation. Concerns raised included the inability to distinguish infection site[s] (36/52, 69%), absence of national guidance (34/52, 65%), and reduced assay performance (18/52, 34%). Only 8/52 (15%) considered the current level of evidence sufficient to support PS, with 40/52 (77%) requesting further validation studies, and 39/52 (77%) national guidance. PS was rarely used by respondents to this survey, although the response rate was low. The clinical challenges presented by PS need to be addressed through further development of the evidence base.

Keywords:
CHLAMYDIA TRACHOMATIS
NEISSERIA GONORRHOEA
DIAGNOSIS
EQUIPMENT
SCREENING

Introduction

Increasing pressure on National Health Service (NHS) and public health budgets necessitates evaluation of clinical practice to reduce costs without negatively impacting on patient care. Pooled sampling (PS) is a potential cost-saving measure that involves testing multiple specimens using a single assay with further individual specimen testing only occurring if the pooled sample tests positive.[1] The potential value of PS for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) testing using nucleic acid amplification tests (NAATs) has been highlighted[2], with two possible approaches: Pooling specimens from multiple patients (multi-patient pooled sampling [MPPS]), or pooling specimens from multiple anatomical sites from the same patient (within-patient pooled sampling [WPPS]).

Although extragenital testing with NAATs is common in routine UK clinical practice, British and international guidance suggest caution due to potential issues with test performance and lack of manufacturer and regulatory authorisation; they further recommend that anatomical sites should be sampled and tested separately.[2,3,4,5,6] Only a few studies have evaluated PS in the NAAT era, using varied CT/NG testing platforms and sample types, and most focus on MPPS. However only one platform to date has a published validation study for the analysis of pooled urine samples.[7] NAAT performance using MPPS methodologies varies with pool size and site of infection[8] but similar data do not exist for WPPS methods.[9,10] Furthermore, prevalence thresholds at which PS can become cost-neutral or cost-saving require consideration of cohort heterogeneity, which can be difficult to assess.[1,8]

There is currently no British or European guidance on the use of PS for CT/NG testing. With an expanding PS evidence base, and currently unknown levels of PS implementation, we aimed to establish the prevalence of current and intended PS practice in sexual health services (SHS) in England and investigated the barriers and facilitators to its adoption in routine clinical practice.

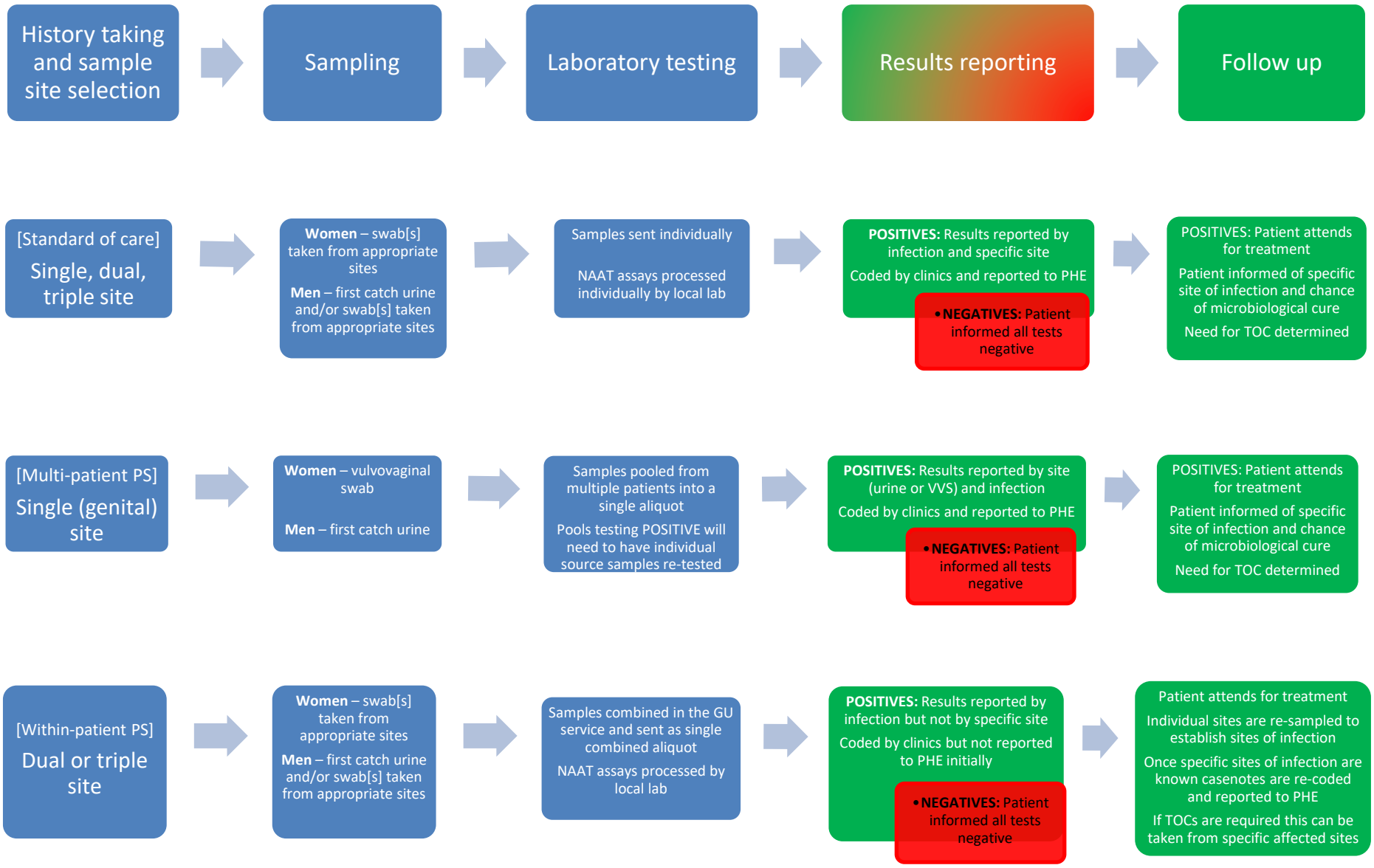

Figure 1: Comparison of theoretical PS pathways with current standard of care

Methods

We designed and distributed a web-based survey to explore attitudes and practices relating to PS among sexual health clinicians in England [Appendix]. Survey questions were devised to include key aspects of the evidence base identified from an initial literature review. Participants were asked about advantages and disadvantages of expanding PS within clinical practice, including consideration of the quality of current evidence and clinical guidance. Participants were presented with answer grids containing lists of possible responses identified in the literature, with some options for clarifications in free text. The survey was piloted by the authors and genitourinary medicine clinical specialist trainees, and revised following feedback.

A link to the survey was sent to the clinical leads of SHS in England. Participants were identified in contact lists for surveillance reporting to Public Health England (PHE) and through British Association of Sexual Health & HIV (BASHH) regional trainee representatives. Survey dissemination was supported by these established clinical networks and regional BASHH trainee representatives. The survey was run between 11/02/16 and 21/05/16, with a reminder email sent on 02/03/16 and a reminder message published in BASHH newsletter on 31/03/16. Survey responses were analysed using Microsoft Excel. Partially completed survey responses were excluded from the analysis.

Results

In total, 52/216 (23.3%) services returned complete responses to the survey. Seventeen incomplete and four duplicate responses were excluded from the analysis. Responses were received from all PHE regions apart from the East Midlands.

Table 1: Location in England of sexual health service clinical leads who responded to this online survey of current implementation and prospective viewpoints of pooled sampling

Clinic Location	N	%
East Midlands	0/12	0
East of England	3/22	13. 6
London	13/34	38.2
North East	4/14	28. 6
North West	11/35	31.4
South East	8/33	24.2
South West	8/25	32.0
West Midlands	1/20	5.0
Yorkshire & the Humber	4/21	19.0
Total	**52**	

Current or considered use of PS

One service reported current WPPS and two were awaiting imminent implementation of PS. Of the 49 services not pooling, five were considering implementation. Services with PS experience, or plans to implement PS, were introducing PS to facilitate cost-saving (3/3) and to be innovative (3/3), with 2/3 introducing PS as part of clinical research assessing PS. The single

service which had introduced WPPS found benefits of cost-saving and increased clinic capacity, but experienced challenges with patient acceptability and a lack of national PS guidance.

Prospective view of PS

Of the 49 services without current or imminent PS activity, 15 (31%) were expecting PS to become future standard practice in SHS. The key benefit of PS identified by services was the potential for cost-saving (41/49, 84%), with a smaller proportion looking to increase clinic capacity (9/49, 18%). Opportunities for innovation (12/49, 25%) and clinical research (11/49, 22%) were also identified.

Barriers to the wider implementation of PS

All respondents, regardless of PS experience, were asked about the negative aspects and perceived barriers to wider PS implementation. Commonly reported barriers to the wider implementation of PS were: loss of infection site information (36/52, 69%), absence of national guidance (34/52, 65%), lack of supportive evidence (21/52, 40%) and reduced assay sensitivity/specificity (18/52, 35%).

Current PS evidence base

Only 8/52 (15%) respondents considered the existing evidence sufficient to support PS, with 40/52 (77%) requesting further validation studies, 39/52 (77%) national guidance, and 25/52 (48%) more cost effectiveness data.

Table 2: Online survey of current implementation and prospective viewpoints of pooled sampling methods for CT/NG NAATs completed by clinical leads of sexual health services in England between 11th February and 21st March 2016

Response	N	%
What would you consider to be potential positive aspects of introducing pooled sampling within your service?	**49**	**94.2**
Potential for cost savings	41	83.7
Anticipation of future changes in practice	15	30.6
Innovation	12	24.5
Involvement in research	11	22.4
Increase clinic capacity	9	18.4
I see no benefits	2	4.1
Patient satisfaction	1	2.0
What do you believe to be the barriers to the wider implementation of pooled sampling?	**52**	**100**
Impact on clinical care		
Concern over not knowing anatomical sites of infection	36	69.2
Negative effects on patient care	7	13.5
Laboratory and test aspects		
Decrease in assay sensitivity/specificity	18	34.6
Increase in inhibitory results	17	32.7
Challenges with local laboratory validation	15	28.8
Guidance and evidence		
Absence of national guidance or testing policy	34	65.4
Not enough supportive evidence	21	40.4
Service issues		
Other priorities within services	8	15.4
Influence of high local STI prevalence on cost effectiveness	4	7.7
Cost implications	3	5.8
Time required to make the change	3	5.8
Local commissioning policy	2	3.8
Other		
I do not foresee any barriers	1	1.9
Which aspects of pooled sampling would you like more research or guidance to focus on?	**52**	**100**
Validation of the sensitivity and specificity of pooled sampling	40	76.9
Clinical guidelines on pooled sampling	39	75.0
Opinion from BASHH on the utilisation of pooled sampling	38	73.1
Cost effectiveness data	25	48.1
Clinical research on the implementation of pooled sampling	18	34.6

Discussion

To our knowledge, this is the first survey to assess current practice and opinion on the utilisation of MPPS or WPPS for CT/NG NAATs within sexual health services. We have established that the use of PS is uncommon but almost a third of services responding to the survey expected PS to become standard practice, highlighting the need for a robust evidence base and national guidance. The key driver for PS introduction was the potential for cost-saving. The majority of respondents expressed concerns about the wider implementation of PS from clinical and laboratory standpoints, underpinned by a lack of supportive evidence.

Despite concerted efforts to engage SHS, the response rate was low, which influences the representativeness of the findings. Clinicians may have been more likely to respond if they had an interest in PS, or were considering introducing it. Conversely others may have opted not to respond if they felt they had insufficient knowledge to answer accurately. Our study may therefore overestimate the proportion anticipating PS to become standard practice. However survey responses were from geographically diverse locations across England. The survey content was informed by the existing evidence base and highlights concerns to inform future research.

Competitive re-tendering of SHS in England is encouraging novel approaches to find efficiencies within existing clinical pathways. Studies from Australia and Lithuania examining MPPS have reported potential cost savings of between 39%[11] and 70%[12], although modelling

suggests that savings may be more limited with increasing prevalence of chlamydia and inhibitors of PCR.[13] Whilst financial considerations are important, this should not be at the detriment of the patient experience and outcomes, nor public health. No qualitative data are available regarding patients' opinions on WPPS, and the single site who had implemented PS in our survey found that challenges with patient acceptability were encountered. Consideration must be given to re-sampling individual anatomical sites in patients testing positive from WPPS to ensure the identification of extragenital infections. Whilst not influencing treatment choice directly according to current clinical guidance, re-sampling provides accurate monitoring of transmission dynamics. Knowledge of specific infection sites informs not only individual risk reduction advice, but collectively informs public health surveillance data around risk behaviours associated with STI acquisition.[14] Treatment choice for any positive CT result which included a rectal sample should also ensure adequate therapy with doxycycline.[3] With widespread antimicrobial resistance amongst NG populations it is important to ensure that PS does not hinder NG culture or test of cure pathways.

Within our survey, clinicians expressed concerns about a potential decrease in NAAT performance using PS. Caution with regards to the sensitivity/specificity of NAATs for WPPS seems appropriate with existing studies showing mixed results: one study found a superior sensitivity of WPPS for identifying CT infection than vulvovaginal sampling alone[9], whilst another demonstrated inferior sensitivity amongst triple-site samples in men-who-have-sex-with-men (MSM)[10, 15]. The potential effect of inhibitors on PS validity is also of some concern.

There are no studies reviewing the effect of inhibitors on WPPS methods, and studies on MPPS have conflicting findings.[11,16] These concerns could eventually be mitigated by developing PS methods and ensuring rigorous local laboratory validation. PS requires new laboratory processes for combining NAAT samples prior to assay testing, which need to consider handling, mixing and potential contamination of combining samples, as well as storing individual samples for re-testing if required. However if equivalence to standards of care can be shown for WPPS, then the inclusion of extragenital specimens for patients who would previously only have been tested genitally could increase identification and treatment of CT/NG infections.

With the vast majority of clinicians feeling the current evidence base insufficient to confidently support PS it is clear that significant unanswered questions remain. SHS considering implementation of MPPS are likely to find an existing example of practice to base service change upon. WPPS is not a widely validated technique on many current commercial NAAT platforms. The practical implementation of any new sampling methodology is likely to generate challenges and we would welcome more data on services' experience with PS implementation. Further data assessing WPPS assay performance and cost-effectiveness are required.

The current financial pressures within sexual health services in England are encouraging services to innovate to maintain standards of care with increasingly smaller budgets. We found that pooling of samples was uncommon among survey respondents. However, several services

were considering implementing pooling and the majority of respondents saw potential cost savings of pooling as a positive feature. Considered debate regarding the level of influence that cost should have on clinical care needs to continue, and with PS this needs to recognize that with infinite resources separate site NAAT testing would remain gold standard practice. Further evidence and guidance from professional bodies would be helpful for clinicians and service commissioners

Declarations

This work has been completed as part of a Public Health England Fellowship. It has not received any funding throughout its design or implementation. SelectSurvey use was authorised and utilized via Public Health England servers. The authors have no conflicts of interest to declare.

Supplementary Materials:

The web-based survey design is included in this manuscript as an appendix. Survey data is archived on Public Health England servers.

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Appendix 1: Web-based survey

Many thanks for taking the time to complete this survey. It should take between 5 and 10 minutes to complete. A response is required for all questions marked with a red asterisk.

The survey explores current and planned activity in relation to pooling of Chlamydia trachomatis (CT) / Neisseria gonorrhoeae (NG) nucleic acid amplification test (NAAT) samples.

This pooling may include, for example:
- pooled aliquots of multiple urine samples in the laboratory prior to assay testing
- multi-site swab samples for the same patient being collated and tested as a single aliquot

This survey is being done as part of the BASHH/ PHE Fellowship by Dr Jonathan Shaw, supervised by Drs Gwenda Hughes and John Saunders at Public Health England.

All responses will be anonymised and confidential. If you have any questions please contact jonathan.shaw@phe.gov.uk

1. In which region is your clinic situated?
    a. East Midlands
    b. East of England
    c. London
    d. North East
    e. North West
    f. South East
    g. South West
    h. West Midlands
    i. Yorkshire & the Humber

2. At which site is your clinic located?

3. Do you, or have you previously, pooled samples within your service?
    a. Yes
    b. No, but we are planning to
    c. No

For services answering "Yes" to Q3:

- In which patient group(s) do you, or have you, pooled samples within your service? (please select all that apply)

	Asymptomatic	Symptomatic	Contacts of infections
Men who have sex with women only	□	□	□
Men who have sex with men	□	□	□
Women who have sex with men	□	□	□
Women who have sex with women only	□	□	□

- Taking an example patient who requires triple-site testing in clinic, which of the following samples would you pool together in your service?
  (Please only complete rows for patient groups that you currently pool or have pooled with)

	Urine	Genital swab	Pharyngeal swab	Rectal swab
Men who have sex with men	□	□	□	□
Women who have sex with men	□	□	□	□
Women who have sex with women only	□	□	□	□

- Would you be willing to share your clinic's pooled sampling protocol and/or be contacted to discuss it?
  - Yes
  - No
  - We do not have a clinic protocol on pooled sampling

- When did pooling of samples commence in your service?

- Why did you introduce pooled sampling within your service?(please select all that apply)
    - Cost saving
    - Innovation
    - Anticipation of future changes in practice
    - Research
    - Patient satisfaction
    - Increase clinic capacity
    - Other, please specify (free text)

- Did you perform a local validation study on your pooled samples?
    - Yes
    - No
    - Unsure

- Have you discontinued pooled sampling?
    - Yes
        - When did you discontinue pooling of samples in your service?
        - Why did you discontinue pooling in your service?
            - Decrease in assay sensitivity/specificity
            - Inhibitors affecting assay performance
            - Challenges with local laboratory validation
            - Cost implications
            - Influence of high local STI prevalence on cost effectiveness
            - Concern over not knowing anatomical sites of infection
            - Negative effects on patient care
            - Patient acceptability
            - Time required to make the change
            - Local commissioning policy
            - Not enough supportive evidence
            - Absence of national guidance or testing policy
            - Completion of a research study
    - No

- In patients who test CT/NG positive on a pooled sample do you re-test individual sites before treatment to ascertain patients' specific site[s] of infection?
  (please select all that apply)
  - No
  - Yes if CT monoinfection
  - Yes if NG monoinfection
  - Yes if CT/NG dual infection

- Would you wait for the specific site of infection to be identified before issuing treatment?
  - Yes
  - No

- Have you performed an evaluation of pooled sampling since introducing it into practice within your service?
  - Yes
    - If yes, what have you evaluated?
      - Impact on assay sensitivity/specificity
      - Inhibitors affecting assay performance
      - Laboratory costs
      - Influence of local STI prevalence on cost effectiveness
      - Treatment choice
      - Treatment costs
      - Patient acceptability
      - Staff costs
  - No
  - Unsure

- Did you experience any of the following challenges when implementing pooled sampling?(please select all that apply)
  - Decrease in assay sensitivity/specificity
  - Inhibitors affecting assay performance
  - Challenges with local laboratory validation
  - Cost implications
  - Influence of high local STI prevalence on cost effectiveness
  - Concern over not knowing anatomical sites of infection

    - Negative effects on patient care
    - Patient acceptability
    - Time required to make the change
    - Local commissioning policy
    - Not enough supportive evidence
    - Absence of national guidance or testing policy
    - None of the above
    - Other, please specify (free text)

- Did you find any benefits from introducing pooled sampling within your service?(please select all that apply)
    - Cost saving
    - Innovation
    - Anticipation of future changes in practice
    - Research
    - Patient satisfaction
    - Increase clinic capacity
    - None of the above
    - Other, please specify (free text)

- Have you been involved, or are you currently involved, in clinical research with pooled sampling?
    - Yes, we are currently involved
    - Yes, we have previously been involved
    - No, but we are currently planning research
    - No
    - Unsure

For services answering "No, but we are planning to" to Q3:

- When do you anticipate that pooling of samples will commence in your service?

- Have you generated a testing protocol for pooling samples?
    - Yes
        - Would you be willing to share this with us?

        - Yes
        - No
    - This is in progress
    - No

- Which patient group(s) will be eligible for pooled sampling within your service?(please select all that apply)

	Asymptomatic	Symptomatic	Contacts of infections
Men who have sex with women only	□	□	□
Men who have sex with men	□	□	□
Women who have sex with men	□	□	□
Women who have sex with women only	□	□	□

- How are you considering pooling your samples?(please select all that apply)
    - Pooled urine aliquots (multiple samples from more than one patient)
    - Pooling swabs from genital and extragenital sites (from a single patient)
    - Pooling extragenital swabs with a first catch urine (from a single patient)
    - Pooling only extragenital swabs (from a single patient)
    - Other, please specify (free text)

- Why are you considering introducing pooled sampling within your service?(please select all that apply)
    - Cost saving
    - Innovation
    - Anticipation of future changes in practice
    - Research
    - Patient satisfaction
    - Increase clinic capacity
    - Other, please specify (free text)

- Do you have any concerns about introducing pooled sampling in your service?(please select all that apply)
    - Decrease in assay sensitivity/specificity
    - Inhibitors affecting assay performance
    - Challenges with local laboratory validation
    - Cost implications
    - Influence of high local STI prevalence on cost effectiveness
    - Concern over not knowing anatomical sites of infection
    - Negative effects on patient care
    - Patient acceptability
    - Time required to make the change
    - Local commissioning policy
    - Not enough supportive evidence
    - Absence of national guidance or testing policy
    - No
    - Other, please specify (free text)

For services answering "No" to Q3:

- Are you considering a future introduction of pooled sampling within your service?
    - Yes
    - No
    - Don't know

- Do you have any reservations regarding the introduction of pooled sampling within your service? (please select all that apply)

    - Decrease in assay sensitivity/specificity
    - Inhibitors affecting assay performance
    - Challenges with local laboratory validation
    - Cost implications
    - Influence of high local STI prevalence on cost effectiveness
    - Concern over not knowing anatomical sites of infection
    - Negative effects on patient care
    - Patient acceptability

- Time required to make the change
- Local commissioning policy
- Not enough supportive evidence
- Absence of national guidance or testing policy
- We have other priorities within the service
- No
- Other, please specify (free text)

- What would you consider to be potential positive aspects of introducing pooled sampling within your service?(please select all that apply)
    - Cost saving
    - Innovation
    - Anticipation of future changes in practice
    - Research
    - Patient satisfaction
    - Increase clinic capacity
    - I see no benefits
    - Other, please specify (free text)

All respondents:

4. What do you believe to be the barriers to the wider implementation of pooled sampling?(please select all that apply)

    - Decrease in assay sensitivity/specificity
    - Inhibitors affecting assay performance
    - Challenges with local laboratory validation
    - Cost implications
    - Influence of high local STI prevalence on cost effectiveness
    - Concern over not knowing anatomical sites of infection
    - Negative effects on patient care
    - Not enough supportive evidence
    - Time required to make the change
    - Local commissioning policy
    - Absence of national guidance or testing policy
    - Other priorities within services

- I do not forsee any barriers
- Other, please specify (free text)

5. In your opinion does the evidence you have reviewed support the use of pooled sampling in GU services?
    - Yes
    - No
    - Unsure
    - I am not familiar with the evidence

6. Which aspects of pooled sampling would you like more research or guidance to focus on?(please select all that apply)
    - Cost effectiveness data
    - Validation of the sensitivity and specificity of pooled sampling
    - Clinical research on the implementation of pooled sampling
    - Clinical guidelines on pooled sampling
    - Opinion from BASHH on the utilisation of pooled sampling
    - I don't think further research/guidance is required
    - Other, please specify (free text)

Thank you very much for giving your time to complete this survey.

All responses will be anonymised and confidential. If you have any questions please contact jonathan.shaw@phe.gov.uk

Would you be willing to be contacted as part of discussions regarding the development of best practice pooled sampling guidance?

- Yes (please provide a contact email)
- No