Public Health England

Chlamydia trachomatis Testing, Treatment and Prevention

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Blood Safety, Hepatitis, HIV & STI Division
National Infection Service
Public Health England

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Testing is easy

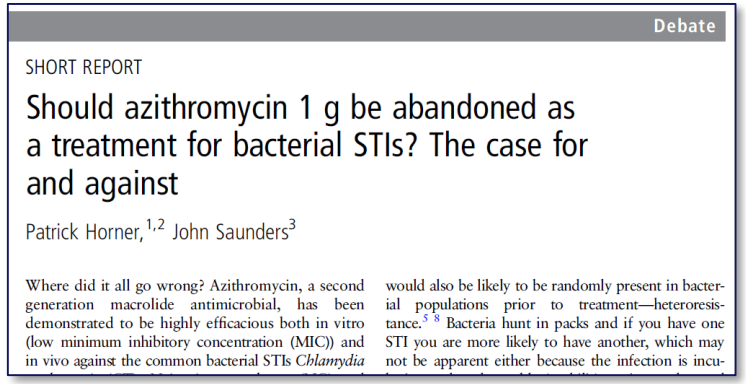
Self-sampling possible; tests are highly acceptable and highly sensitive

Simple treatment

Doxycycline first line, well tolerated, inexpensive and efficacious

Very common

In 2018 there were approximately 218,000 diagnoses of chlamydia made in England


Debate

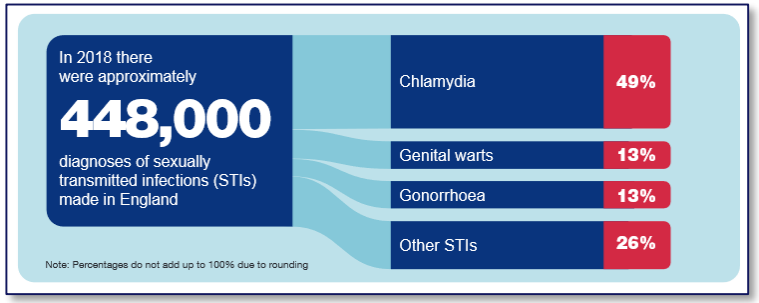
SHORT REPORT

Should azithromycin 1 g be abandoned as a treatment for bacterial STIs? The case for and against

Patrick Horner,[1,2] John Saunders[3]

Where did it all go wrong? Azithromycin, a second generation macrolide antimicrobial, has been demonstrated to be highly efficacious both in vitro (low minimum inhibitory concentration (MIC)) and in vivo against the common bacterial STIs *Chlamydia*

would also be likely to be randomly present in bacterial populations prior to treatment—heteroresistance.[5 8] Bacteria hunt in packs and if you have one STI you are more likely to have another, which may not be apparent either because the infection is incu-



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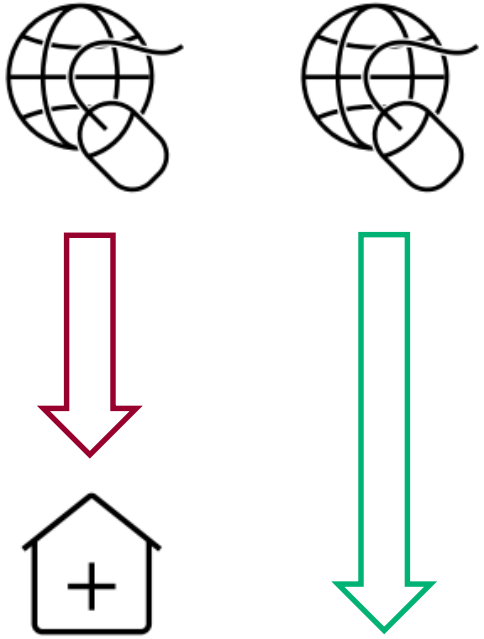
Testing is easy

Chlamydia as a stealth pathogen

Simple treatment

Optimising care pathways



Very common

Prophylaxis for prevention

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Testing

New variant chlamydia

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24th April

EPIS-STI Alert

Public Health England

24th April

EPIS-STI Alert

Early 2019

Heterosexual woman
Chlamydia <u>detected</u>

- **Abbott RealTime**

Public Health England

24th April

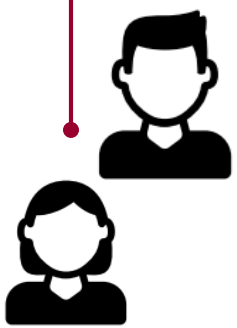
EPIS-STI Alert

February

Symptomatic male contact

Chlamydia negative

- **Aptima Combo 2**



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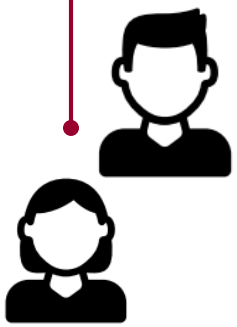
24th April

EPIS-STI Alert



February

Symptomatic male contact

Chlamydia <u>negative</u>

- **Aptima Combo 2**

Chlamydia <u>detected</u>

- **Allplex**
- **Aptima CT**

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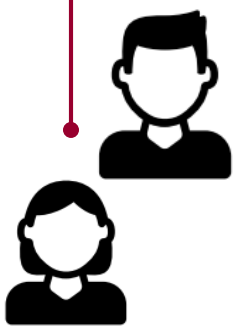
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL



RAPID COMMUNICATION

Chlamydia trachomatis samples testing falsely negative in the Aptima Combo 2 test in Finland, 2019

Kaisu Rantakokko-Jalava[1,3], Kati Hokynar[4], Niina Hieta[2,3], Anniina Keskitalo[1,3], Pia Jokela[5], Anna Muotiala[6], T. Sakari Jokiranta[7], Rutta Kuusela[8], Hannu Sarkkinen[9], Janne Aittoniemi[10], Tytti Vuorinen[1,3], Antti J Hakanen[1,3], Mirja Puolakkainen[5]

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7. Synlab Finland Ltd, Helsinki, Finland
8. Satadiag, Pori, Finland
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10. Fimlab Laboratories, Tampere, Finland

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Article submitted on 14 May 2019 / accepted on 30 May 2019 / published on 30 May 2019

30th May

Eurosurveillance manuscript

Public Health England

TABLE 2

Samples re-analysed with Aptima CT test in HUSLAB, Finland, 6 March–30 April 2019 (n = 757)

Qualitative result in the original AC2 test according to the instrument display	RLU in the original AC2 test	Number of samples tested by ACT test	Positive in the ACT n	%	The AC2 test RLU values in the ACT positives
Negative or equivocal for CT and negative for GC	≤10	330	2	0.6	5–7
	11–15	266	7	2.6	14–15
	16–19	71	13	18	16–19
	20–84	73	68[a]	93	20–46
	85–250	3	3[b]	100	89–97
Negative for CT and positive for GC	48–1,492	14	1	7.1	1,492

AC2: Aptima Combo 2; ACT: Aptima CT; CT: *Chlamydia trachomatis*; GC: *Neisseria gonorrhoeae*; RLU: relative light units.

[a] Of 50 samples ≥ 25 RLU, one sample was flagged as equivocal in the original AC2 test.

[b] Of three samples with RLU between 85 and 99, three samples were flagged as equivocal in the original AC2 test.

10 AC2-/ACT+ sequenced
Single nt change in 23S rRNA

C1515T

Proportion of positive cases that may have been missed

6-10%

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	Real-time	Artus	GeneXpert	Cobas 4800/6800 /8800	BD Viper /probetec	BD Max	Aptima Combo 2 (AC2)	Aptima CT mono
	Abbott	**Qiagen**	**Cepheid**	**Roche**	**Becton Dickinson**	**Becton Dickinson**	**Hologic**	**Hologic**
Target/s	2 targets on cryptic plasmid	Cryptic plasmid & 2nd target on genome	1 genomic target	Cryptic plasmid & 2nd target on genome	Cryptic plasmid	TBD	rRNA - 23S	rRNA - 16S
Technology	RT-PCR	RT-PCR	PCR	PCR	SDA	RT-PCR	TMA	TMA

Acknowledgement: Dr Michelle Cole

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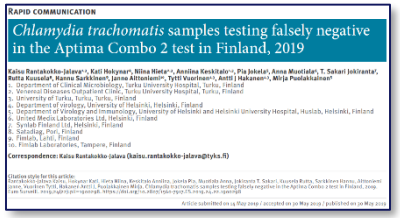
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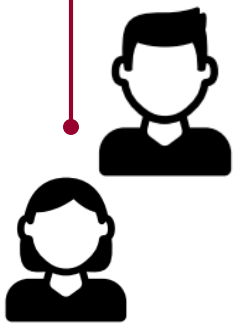
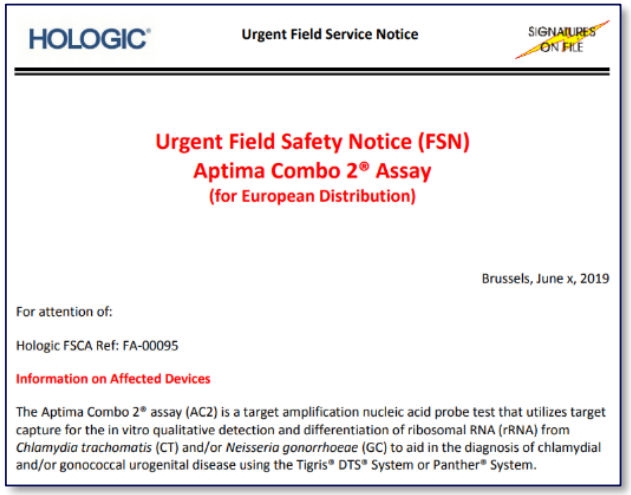



HOLOGIC

Urgent Field Service Notice

SIGNATURES ON FILE

Urgent Field Safety Notice (FSN)
Aptima Combo 2® Assay
(for European Distribution)

Brussels, June x, 2019

For attention of:

Hologic FSCA Ref: FA-00095

Information on Affected Devices

The Aptima Combo 2® assay (AC2) is a target amplification nucleic acid probe test that utilizes target capture for the in vitro qualitative detection and differentiation of ribosomal RNA (rRNA) from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC) to aid in the diagnosis of chlamydial and/or gonococcal urogenital disease using the Tigris® DTS® System or Panther® System.

4th June

PHE briefing note to Labs in England

7th June

Hologic Field Safety Notice

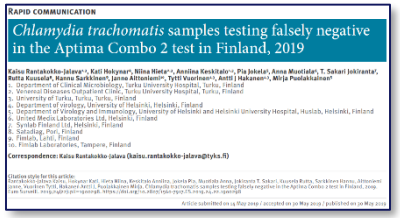
Public Health England

14th June

Alert to BASHH Clinicians

17th June

ECDC Rapid Risk Assessment published

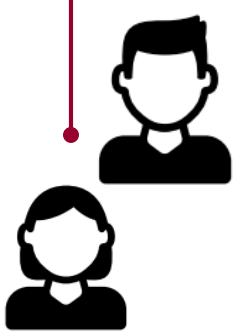


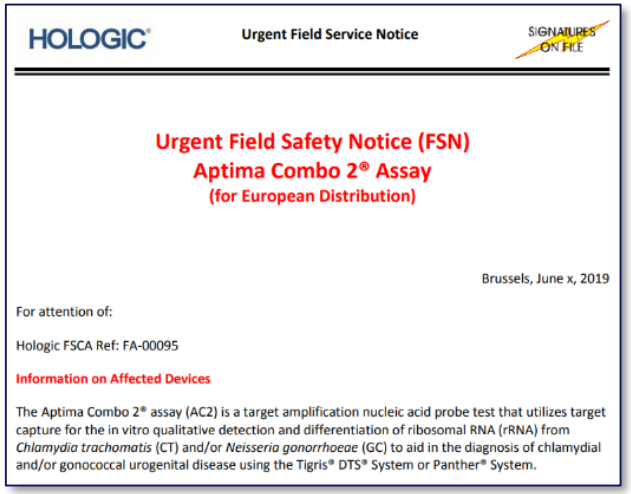
RAPID COMMUNICATION

Chlamydia trachomatis samples testing falsely negative in the Aptima Combo 2 test in Finland, 2019

21st June

Labs start reporting discrepant results to PHE





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4th June

PHE briefing note to Labs in England

7th June

Hologic Field Safety Notice

Public Health England

Chlamydia tests
in England, 2018

~3.8 million

Public Health England

Chlamydia tests in England, 2018 | **~3.8 million**

~40% tested on AC2 platform | **~1.6 million**

- 1 lab in Scotland
- None in Wales or Northern Ireland

Public Health England

Chlamydia tests in England, 2018 — **~3.8 million**

~40% tested on AC2 platform — **~1.6 million**

~90% negative test result — **~1.4 million**

Public Health England

Chlamydia tests in England, 2018 → **~3.8 million**

~40% tested on AC2 platform → **~1.6 million**

~90% negative test result → **~1.4 million**

~1.5% within affected RLU range → **~2,000 a month**

Public Health England

AC2

- CT Negative and RLU <15
- CT Positive

~99%

Public Health England

AC2

- CT Negative and RLU <15
- CT Positive

~99%

- CT Negative and RLU ≥15
- CT Negative and GC equivocal/positive
- CT equivocal
- Equivocal

~1.5%

Public Health England

AC2

- CT Negative and RLU <15
- CT Positive

~99%

- **CT Negative and RLU ≥15**
- **CT Negative and GC equivocal/positive**
- **CT equivocal**
- **Equivocal**

~1.5%

Alternative target

Negative

True Negative

No further action

Positive

Discrepant Result

Refer to PHE

Public Health England

AC2

- CT Negative and RLU <15
- CT Positive

~99%

- **CT Negative and RLU ≥15**
- **CT Negative and GC equivocal/positive**
- **CT equivocal**
- **Equivocal**

~1.5%

Alternative target

Negative
True Negative
No further action

Positive
Discrepant Result
Refer to PHE

Sequencing

Wild Type
AC2 False Negative
No further action

C1515T
nv-CT

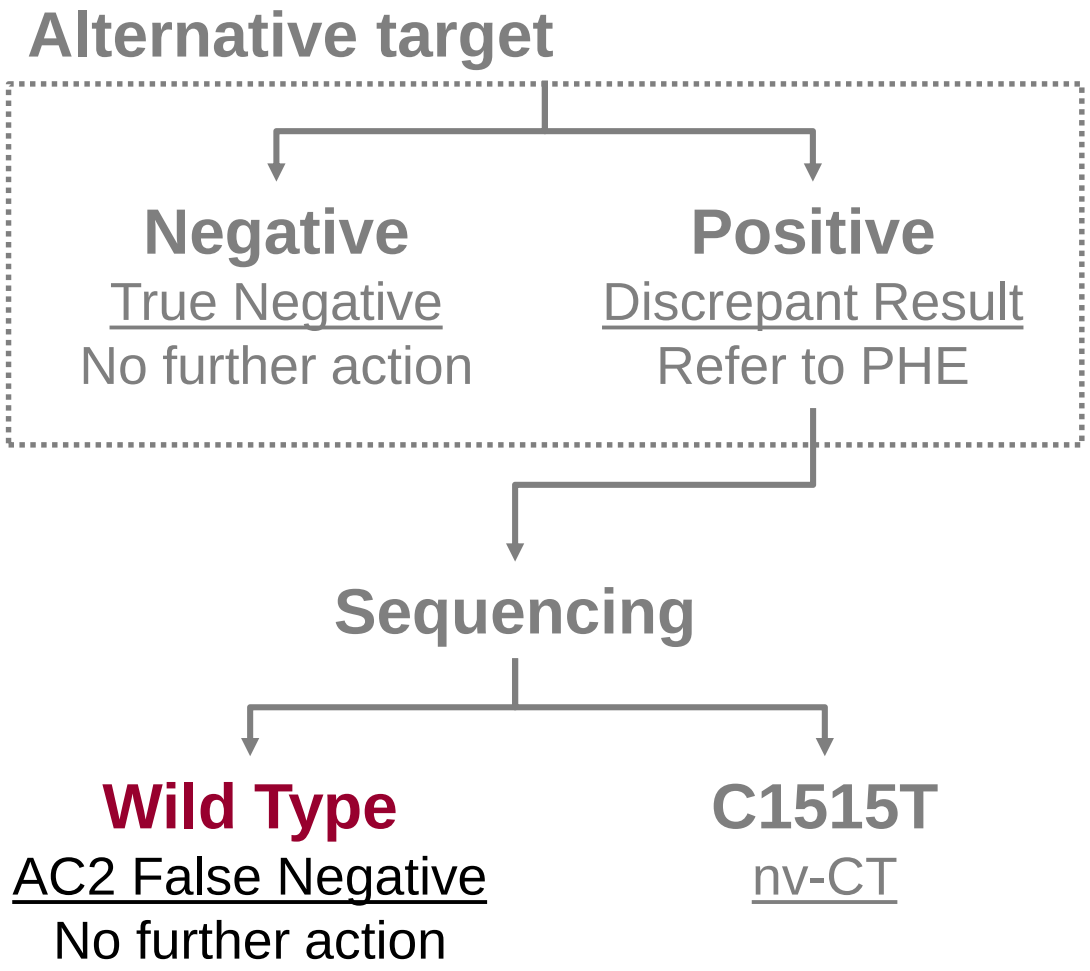
Public Health England

Sensitivity

The fraction of those with chlamydia correctly identified as positive by the test

Specificity

The fraction of those without chlamydia correctly identified as negative by the test



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Sensitivity

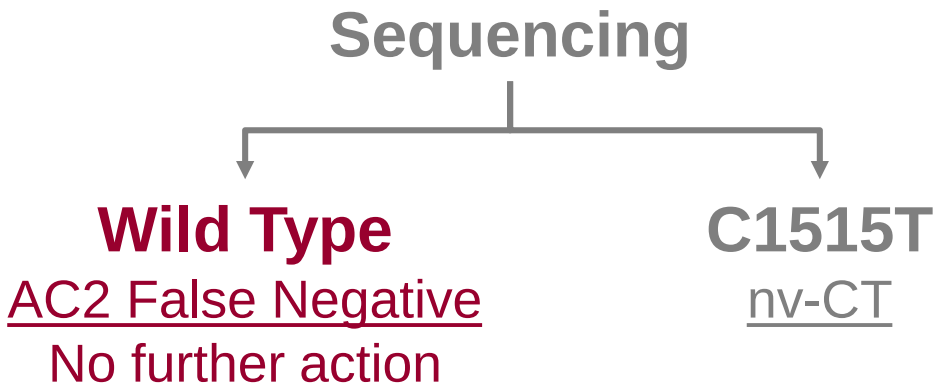
96.7%

Specificity

99.2%

Assuming 10% prevalence
For every 1000 tests:

3-4 false negatives



ECDC Laboratory Guidelines on Bacterial STIs, 2012

Public Health England

Current situation

- Two confirmed C1515T nvCT outside of Finland (Sweden)
- All labs in England using AC2 following field safety notice and reporting results weekly to PHE
- Preliminary data do not show any sign of nvCT
- Membership of National Management Team includes BASHH
- Aim to update BASHH membership at End of July

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Treatment

Optimising online clinical care pathways

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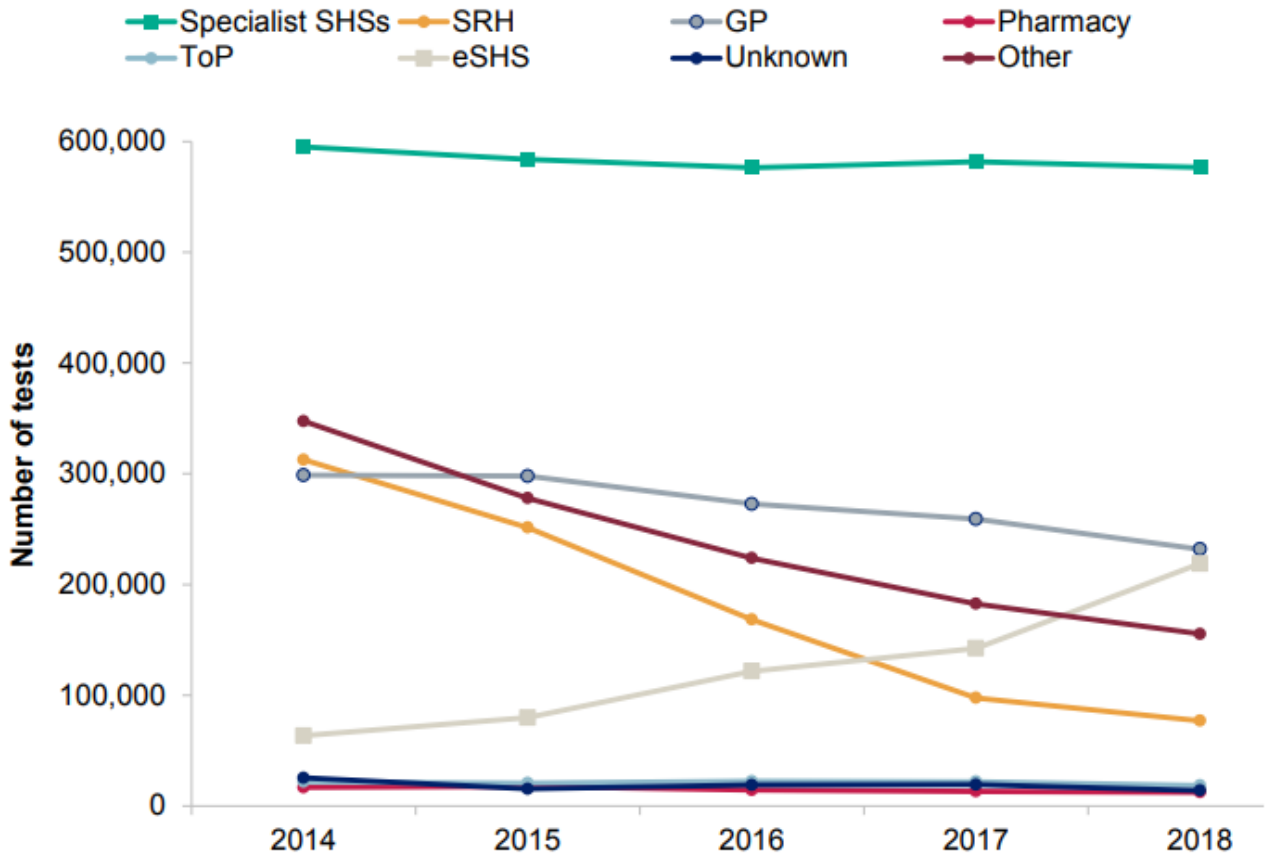
Chlamydia tests among 15 to 24 year olds by test setting 2014-2018, England

eSHS

>200,000 tests
54% increase (2017 to 2018)
17% of all tests
14% of all diagnoses



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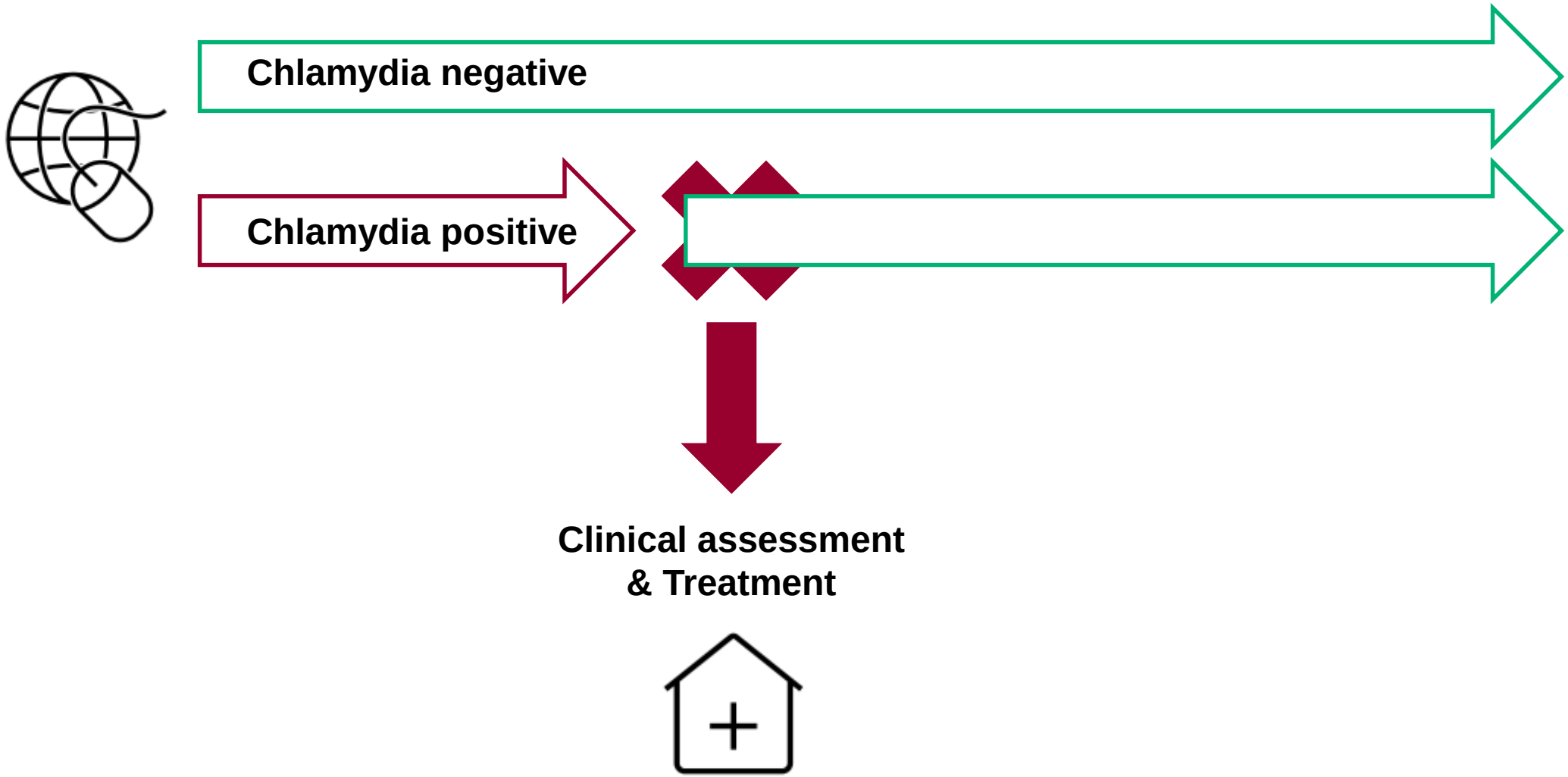
Chlamydia negative

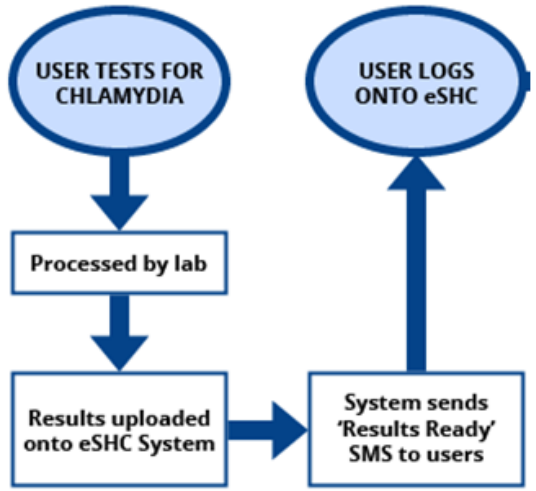
Chlamydia positive

Clinical assessment & Treatment

Public Health England



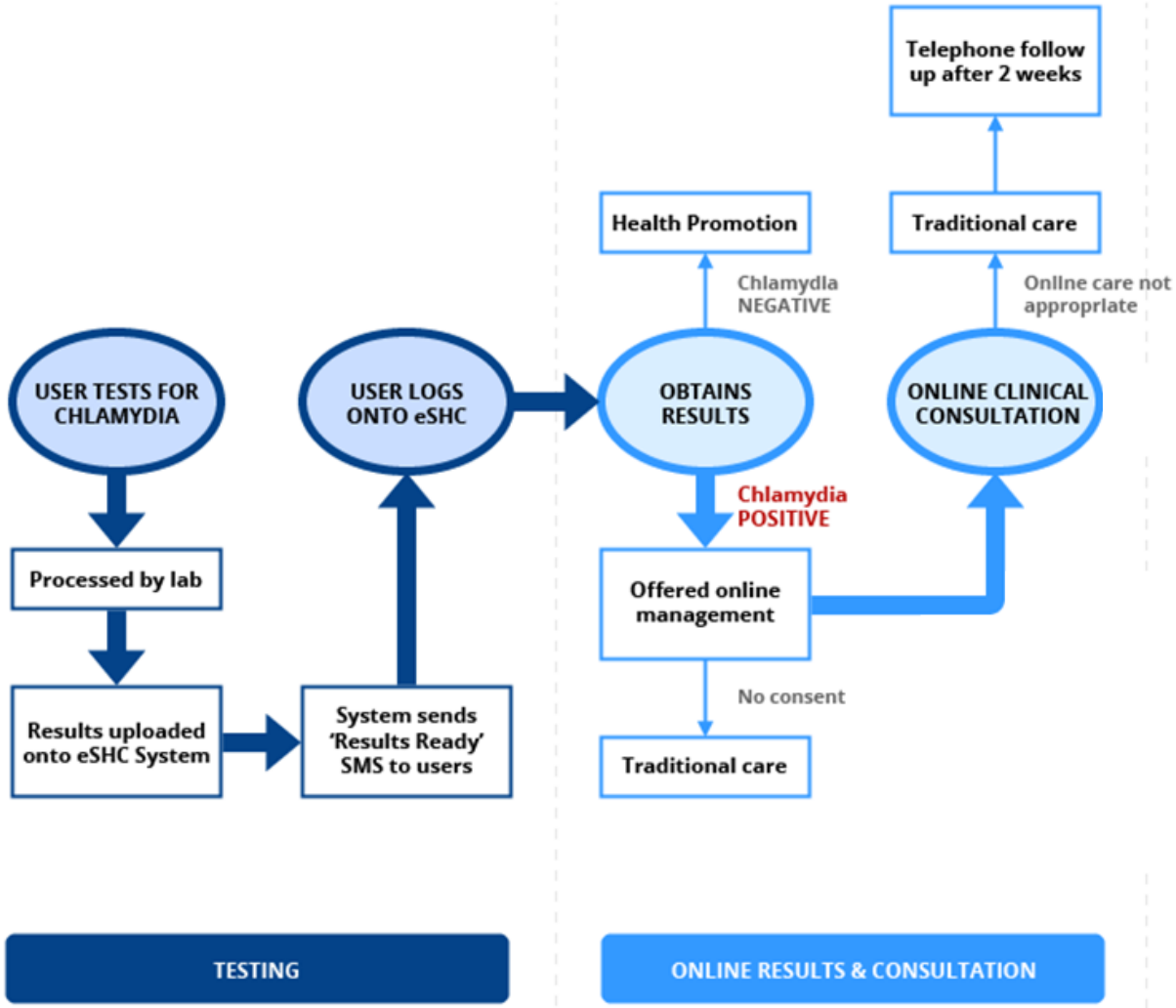
eSexual Health Clinic System



TESTING

Slide acknowledgement:
Dr Jo Gibbs, UCL

eSexual Health Clinic System



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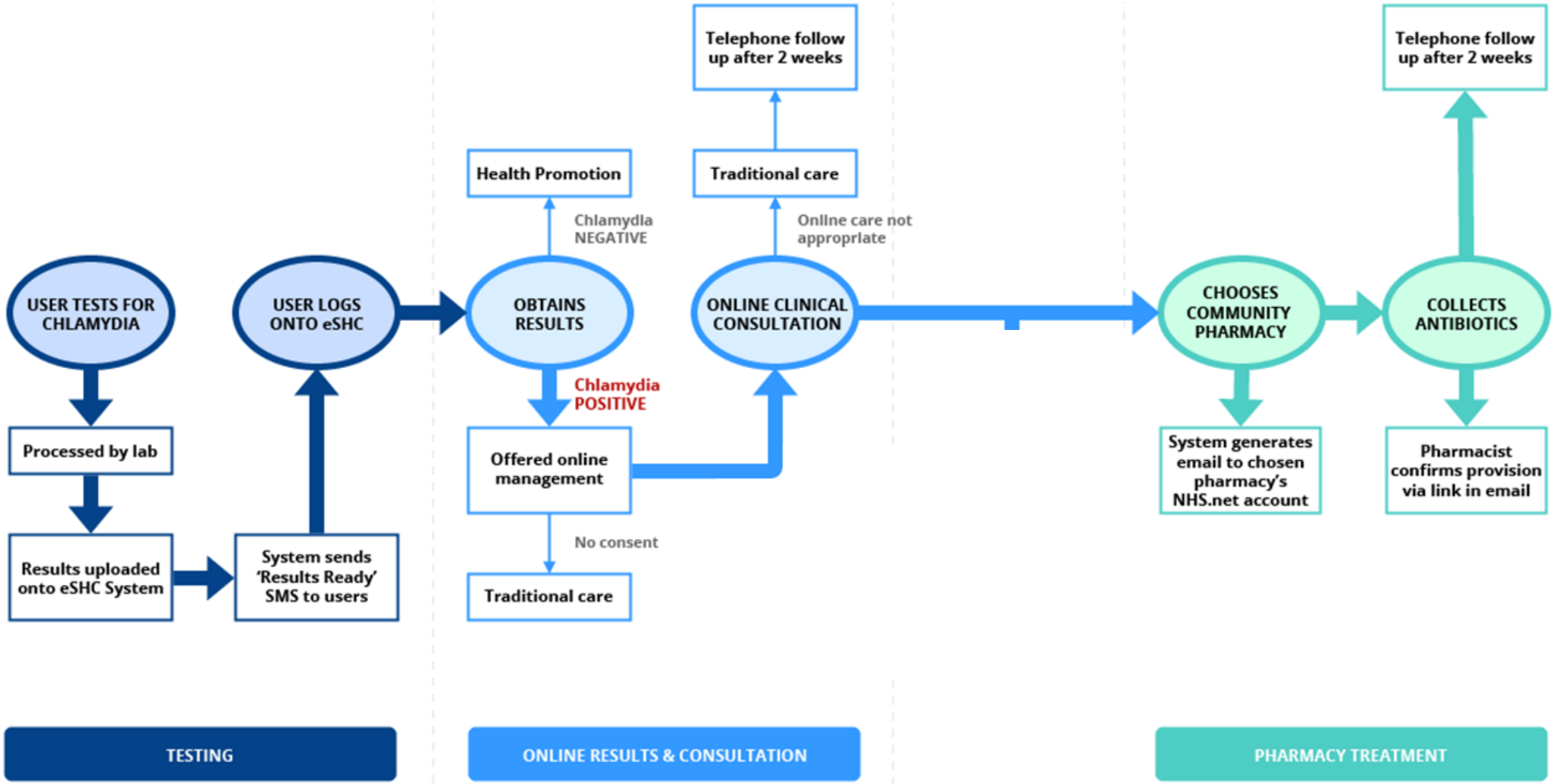

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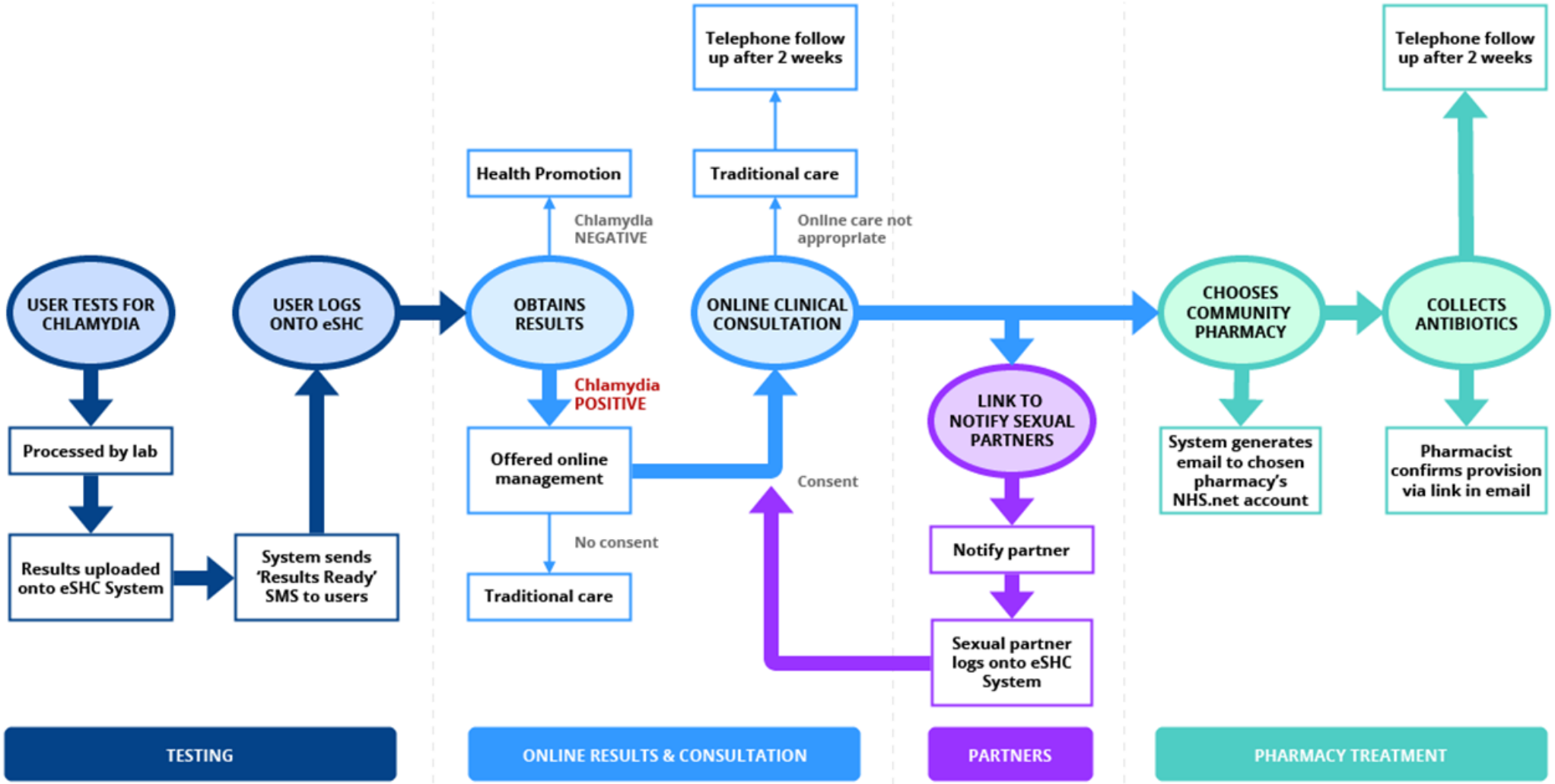

Slide acknowledgement:
Dr Jo Gibbs, UCL

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Exploratory studies

- 221 people with chlamydia (GUM & NCSP), nearly 2000 negatives
- 97% GUM patients received treatment
  - 74 exclusively online, in median 1 day
- 89% NCSP patients received treatment
  - 60 exclusively online in median 1 day
- High user satisfaction
- Partner treatment feasible online
- ~ 25% of patients used the clinical helpline

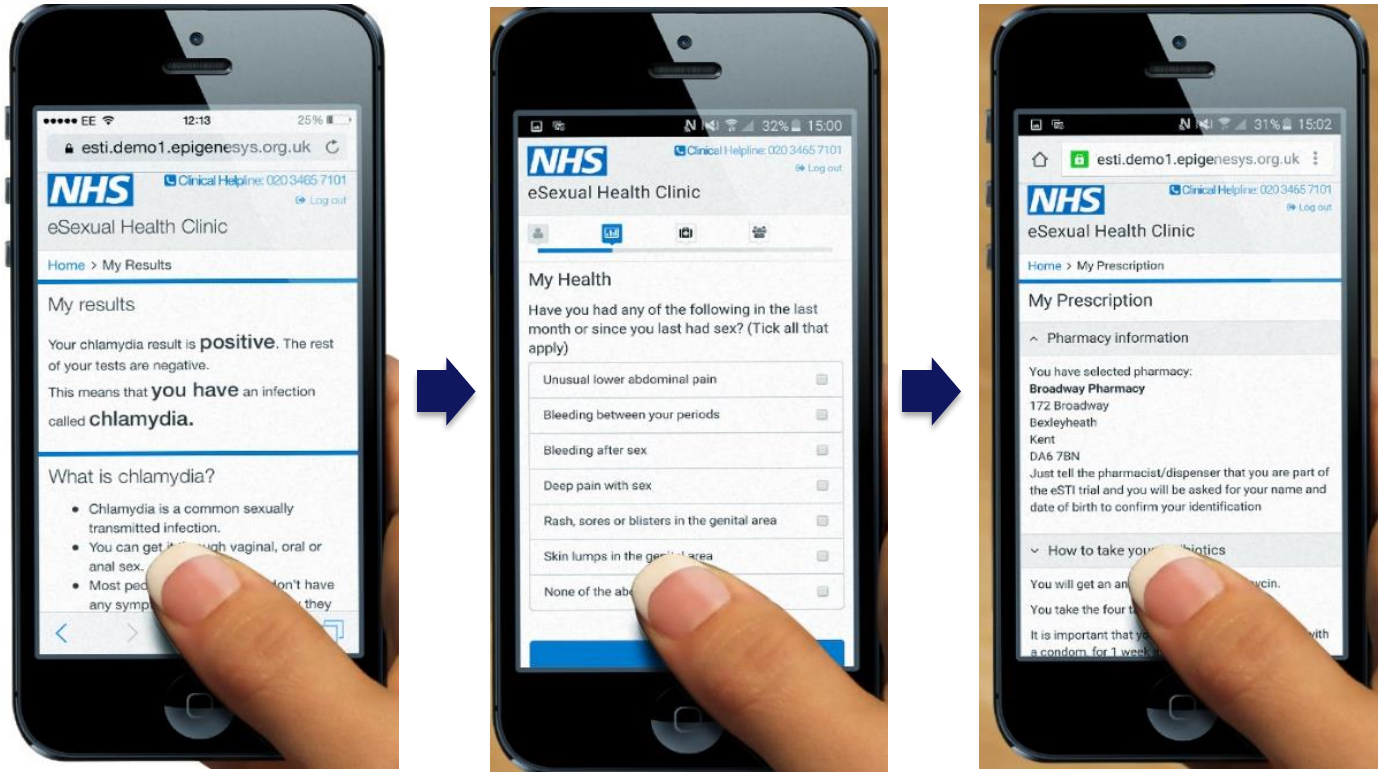
eSTI2

Slide acknowledgement:
Dr Jo Gibbs, UCL

The eSexual Health Clinic system for management, prevention, and control of sexually transmitted infections: exploratory studies in people testing for *Chlamydia trachomatis*

Lancet Public Health 2017
2: 182–90

Claudia S Estcourt, Jo Gibbs, Lorna J Sutcliffe, Voula Gkatzidou, Laura Tickle, Kate Hone, Catherine Aicken, Catherine M Lowndes, Emma M Harding-Esch, Sue Eaton, Pippa Oakeshott, Ala Szczepura, Richard E Ashcroft, Andrew Copas, Anthony Nettleship, S Tariq Sadiq, Pam Sonnenberg



eResults Service

Online clinical consultation

ePrescription

- Proof of concept **NHS & world first,** showed preliminary evidence of effectiveness of **online automated** chlamydia pathway within an eSexual Health clinic
- Median time to treatment: **1 day & fastest 32 minutes!**
- Next steps: **RCT of cost-effectiveness, maximising digital inclusion**

Slide acknowledgement:
Dr Jo Gibbs, UCL

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Cost effectiveness

Are online care pathways cost effective?

Clinical effectiveness

Are there differences in clinical outcomes?

Health inequalities

Who is less likely to engage with online services?

Risk behaviour

Are there missed opportunities for prevention?

PN and PrEP modules

Is it feasible to include additional modules?

Other infections

Is it feasible to manage other infections online?

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Prevention

Doxycycline prophylaxis for STIs

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Antibiotic prophylaxis is not new

Malaria

Neutropenia

Pneumocystis pneumonia

Clostridium difficile colitis

Rheumatic Fever & Endocarditis

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Traveller's diarrhoea[1]

100mg daily; 85% efficacy

Scrub typhus[2]

200mg weekly; 89% efficacy

Lyme disease[3]

200mg stat; 87% efficacy

Leptospirosis[4]

200mg weekly; 95% efficacy

Doxycycline prophylaxis also not new

1. Sack RB, *et al. Gastroenterology* 1979;76(6):1368-73. **2. Twartz JC** *et al. J Infect Dis* 1982;146(6):811-8. **3. Nadelman RB**, *et al. N Engl J Med* 2001;345(2):79-84. **4. Takafuji ET**, *et al. N Engl J Med* 1984;310(8):497-500.

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Current evidence for doxycycline prophylaxis for STIs

Model of sexual behaviour[1]	~50% reduction in syphilis after 12 months if 50% uptake in gay men and 70% efficacy
Survey and focus groups[1]	52.7% very or slightly likely to use chemoprophylaxis to reduce risk of syphilis
RCT of Doxy PrEP[2]	30 MSM 100mg daily 73% reduction in any bacterial STI
RCT of Doxy PEP[3]	232 HIV PrEP users 200mg within 72 hours 70% reduction in chlamydia

1. Wilson, *et al. Sex Transm Dis* 2011;38(7):573-9. **2. Bolan**, *et al. Sex Transm Dis* 2015;42(2):98-103. **3. Molina**, *et al. Lancet Infect Dis* 2018;18(3):308-317

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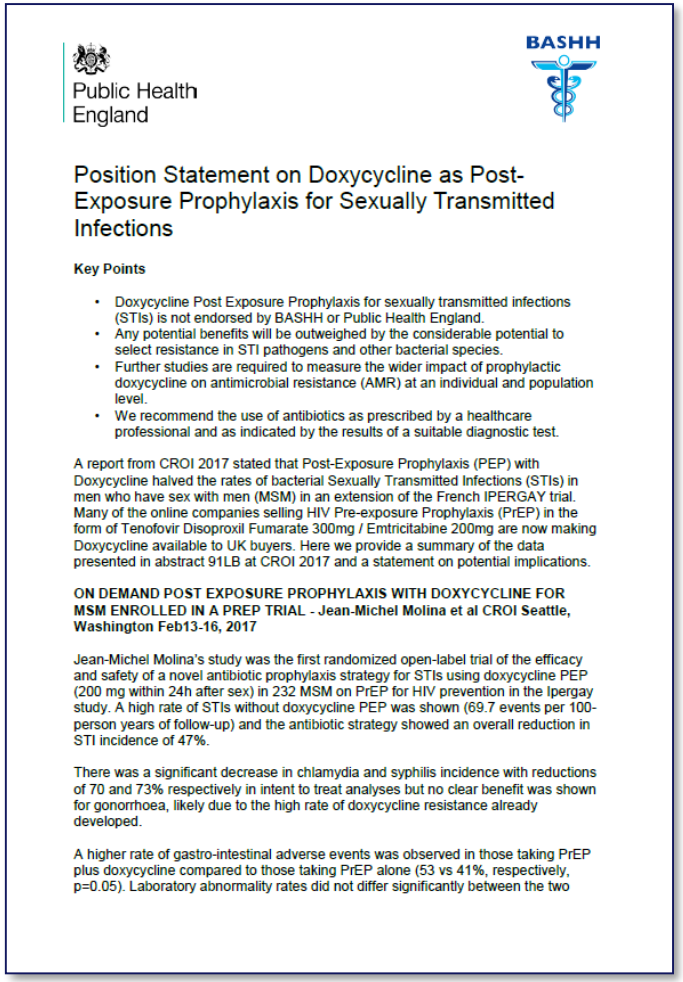

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BASHH

Position Statement on Doxycycline as Post-Exposure Prophylaxis for Sexually Transmitted Infections

Key Points

- Doxycycline Post Exposure Prophylaxis for sexually transmitted infections (STIs) is not endorsed by BASHH or Public Health England.
- Any potential benefits will be outweighed by the considerable potential to select resistance in STI pathogens and other bacterial species.
- Further studies are required to measure the wider impact of prophylactic doxycycline on antimicrobial resistance (AMR) at an individual and population level.
- We recommend the use of antibiotics as prescribed by a healthcare professional and as indicated by the results of a suitable diagnostic test.

A report from CROI 2017 stated that Post-Exposure Prophylaxis (PEP) with Doxycycline halved the rates of bacterial Sexually Transmitted Infections (STIs) in men who have sex with men (MSM) in an extension of the French IPERGAY trial. Many of the online companies selling HIV Pre-exposure Prophylaxis (PrEP) in the form of Tenofovir Disoproxil Fumarate 300mg / Emtricitabine 200mg are now making Doxycycline available to UK buyers. Here we provide a summary of the data presented in abstract 91LB at CROI 2017 and a statement on potential implications.

ON DEMAND POST EXPOSURE PROPHYLAXIS WITH DOXYCYCLINE FOR MSM ENROLLED IN A PREP TRIAL - Jean-Michel Molina et al CROI Seattle, Washington Feb13-16, 2017

Jean-Michel Molina's study was the first randomized open-label trial of the efficacy and safety of a novel antibiotic prophylaxis strategy for STIs using doxycycline PEP (200 mg within 24h after sex) in 232 MSM on PrEP for HIV prevention in the Ipergay study. A high rate of STIs without doxycycline PEP was shown (69.7 events per 100-person years of follow-up) and the antibiotic strategy showed an overall reduction in STI incidence of 47%.

There was a significant decrease in chlamydia and syphilis incidence with reductions of 70 and 73% respectively in intent to treat analyses but no clear benefit was shown for gonorrhoea, likely due to the high rate of doxycycline resistance already developed.

A higher rate of gastro-intestinal adverse events was observed in those taking PrEP plus doxycycline compared to those taking PrEP alone (53 vs 41%, respectively, p=0.05). Laboratory abnormality rates did not differ significantly between the two

1. Doxy PEP for STIs is **not endorsed** by BASHH or PHE
2. Any potential benefits will be outweighed by the **considerable potential to select resistance in STIs and other bacterial species**
3. Further **studies are required** to measure the wider impact on AMR at an individual and population level
4. Recommend use of Abx as prescribed by HCP and as indicated by results of suitable diagnostic test

RCT of Doxy PEP[3]

232 HIV PrEP users
200mg within 72 hours
70% reduction in chlamydia

1. Wilson, *et al. Sex Transm Dis* 2011;38(7):573-9. **2. Bolan**, *et al. Sex Transm Dis* 2015;42(2):98-103. **3. Molina**, *et al. Lancet Infect Dis* 2018;18(3):308-317

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Planned and ongoing studies

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DuDHS

Dual Daily HIV & Syphilis PrEP

N=50 MSM on HIV PrEP
Condomless sex in last 6 months
Syphilis diagnosis in last 3 years

Single blind RCT
Immediate/ deferred initiation
Daily doxycycline 100mg vs. delayed

- Adherence & tolerability
- STI incidence
- Change in sexual behaviour
- Tetracycline resistance
- Resistance in oral flora
- Rectal microbiome

DaDHS

Daily Doxycycline in HIV+ for Syphilis PrEP

N=52
MSM living with HIV

Single blind RCT
Daily doxycycline 100mg or placebo

- Adherence & tolerability
- STI incidence
- Change in sexual behaviour
- Tetracycline resistance
- Resistance in oral flora
- Rectal microbiome

Public Health England

ANRS Prevenir sub-study

Efficacy of meningococcal type B vaccine in preventing *Neisseria gonorrhoeae* and the use of Doxycycline Post Exposure Prophylaxis 200mg to prevent syphilis and chlamydia

N=700
MSM on HIV PrEP
Prior STI diagnosis in the past 18 months

Open-label RCT
2:1 Doxycycline PEP 200mg or no PEP and 1:1 vaccine or no vaccine

- NG, CT and syphilis diagnosis
- Culture and molecular based resistance testing
- Rectal and oral microbiome sub-study on antimicrobial resistance

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Luetkemeyer & Celum

Evaluation of doxycycline Post Exposure Prophylaxis to reduce STIs in PrEP users and MSM living with HIV

N=780 MSM & TGW
390 living with HIV, 390 HIV PrEP users
≥1 bact. STI and ≥1 CSI with ≥1 male partner in 12m

Open-label RCT 2:1 randomisation
Doxycycline PEP 200mg versus standard of care

- Incidence of NG, CT or syphilis
- Culture and molecular based resistance testing
- Commensal flora and gut microbiome resistance testing

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‘Syphilaxis’

N=350 MSM & TGW
Condomless SI with men, diagnosed with syphilis in prior 12 months, or any STI in last 12m and syphilis in last 24m and at least two episodes on STI screening in last 12m

Single-arm trial
Daily doxycycline 100mg

- NG, CT and syphilis diagnosis
- Use and acceptability
- Rectal and oropharynx microbiome sub-study on antimicrobial resistance (n=100)

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Challenges and knowledge gaps

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Challenges and knowledge gaps

1. Efficacy

- Two studies show approx. 70% but samples small and underpowered
- Precise estimate important to inform cost-effectiveness analyses, community education and patient counselling

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Challenges and knowledge gaps

1. Efficacy
2. **Target population**
   - Modelling suggests targeting MSM with >20 partner/6m almost as effective as broader DoxyPrEP use[1]
   - Controlling STIs in core HR populations important for reducing STIs in broader populations

1. Wilson, *et al. Sex Transm Dis* 2011;38(7):573-9.

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. **Community acceptability**
   - Surveys suggest acceptable to MSM for personal health and community health[1]
   - Some evidence that MSM already using Abx prophylaxis[2]

8%

Of 106 had taken antibiotics to prevent STIs

1. Wilson, *et al. Sex Transm Dis* 2011;38(7):573-9. **2. Carveth-Johnson**, *et al. Lancet HIV* 2018

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. Community acceptability
4. **Risk compensation**

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. Community acceptability
4. Risk compensation
5. **Dose, regimen and formulation**
   - Monohydrate or enteric coated hyclate (fewer GI SE), vs. uncoated hyclate

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. Community acceptability
4. Risk compensation
5. Dose, regimen and formulation
6. **Duration of use and long term safety**
   - c.f. malaria, acne

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. Community acceptability
4. Risk compensation
5. Dose, regimen and formulation
6. Duration of use and long term safety
7. **Antimicrobial resistance**

Sexually transmitted infections

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Mycoplasma genitalium*
- *Treponema pallidum*

Other infections

- Respiratory infections (COPD/ CAP)
- Hospital acquired infections (MRSA)

➢ Relieve pressure on carbapenems

➢ Lower risk of *C. difficile*

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Challenges and knowledge gaps

1. Efficacy
2. Target population
3. Community acceptability
4. Risk compensation
5. Dose, regimen and formulation
6. Duration of use and long term safety
7. Antimicrobial resistance
8. **Risk/ benefit and cost effectiveness**
   - If risks a/w chlamydia are primarily borne by women then Doxy prophylaxis in MSM may have limited impact on serious health outcomes

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Testing is easy

Not as simple as A, B, Pee..?

Health professionals central to identifying potential new variants

Simple treatment

Getting treatment to those who need it

Evidence gaps relating to optimal online pathways of care

Very common

Doxycycline prophylaxis already being used

Several ongoing & planned studies to address important unanswered questions

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