UNIVERSITY OF BIRMINGHAM University of Birmingham Research at Birmingham

What do diagnoses of pelvic inflammatory disease in specialist sexual health services in England tell us about chlamydia control?

Davis, Grahame S; Horner, Patrick J; Price, Malcolm; Mitchell, Holly D; Soldan, Kate

License: Other (please specify with Rights Statement)

Document Version Peer reviewed version

Citation for published version (Harvard):

Davis, GS, Horner, PJ, Price, M, Mitchell, HD & Soldan, K 2021, 'What do diagnoses of pelvic inflammatory disease in specialist sexual health services in England tell us about chlamydia control?', The Journal of Infectious Diseases, vol. 224, no. Supplement 2, pp. S113–S120. <http://10.1093/infdis/jiab175>

Link to publication on Research at Birmingham portal

Publisher Rights Statement:

This is a pre-copyedited, author-produced version of an article accepted for publication in The Journal of Infectious Diseases following peer review. The version of record Grahame S Davis, Patrick J Horner, Malcolm J Price, Holly D Mitchell, Kate Soldan, What Do Diagnoses of Pelvic Inflammatory Disease in Specialist Sexual Health Services in England Tell Us About Chlamydia Control?, The Journal of Infectious Diseases, Volume 224, Issue Supplement_2, 15 August 2021, Pages S113–S120, available online at: https://doi.org/10.1093/infdis/jiab175is

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

2 What do diagnoses of pelvic inflammatory disease in specialist sexual health services in England tell3 us about chlamydia control?

4

-	
5	Authors:
5	Autions.

- 6 Grahame S Davis¹, Patrick J Horner^{2,3}, Malcolm J Price^{4,5}, Holly D Mitchell¹, Kate Soldan^{1,3}
- ⁷ ¹Blood Safety, Hepatitis, Sexually Transmitted Infections (STI) and HIV Service, Public Health England,

8 London, UK

- 9 ²Population Health Sciences, University of Bristol, Bristol, UK
- ³NIHR Health Protection Research Unit in Behavioural Science and Evaluation at University of Bristol
- ⁴ Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT,

12 UK

- ⁵ NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation
- 14 Trust and University of Birmingham, UK

15

16 Corresponding author: Dr Grahame S. Davis, Blood Safety, Hepatitis, Sexually Transmitted Infections

17 (STI) and HIV Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK

18

19 Funding:

20 PH was funded by the NIHR Health Protection Research Unit in Behavioural Science and Evaluation

- 21 at University of Bristol. MJP is supported by the NIHR Birmingham Biomedical Research Centre. The
- views expressed are those of the author and not necessarily those of the NIHR, the Department of
- 23 Health and Social Care, or Public Health England.

- 25 Abstract: 225 words
- 26 Main Text: 2976 words

27 ABSTRACT

Background. Pelvic inflammatory disease (PID) is an outcome measure for the evaluation of chlamydia
 screening programmes. We explore PID diagnoses in specialist sexual health services (SSHS) in England
 to inform the evaluation of the national chlamydia screening programme (NCSP), which was
 implemented nationally in 2008.

Methods. We conducted descriptive analyses using data on diagnoses of PID- with and without chlamydia (CT) and/or gonorrhoea (GC)- by age and year of birth, in SSHS between 2009 and 2019 from the GUMCAD database. Rates were calculated per 100,000 females residing in England.

35 *Results.* CT screening activity peaked in 2010. The rates of all PID diagnoses decreased between 2009-

36 2019 by 39%. CT-associated PID (CT-PID) declined by 58%, and non-specific PID declined by 37%. GC-

PID increased by 34%. CT-PID decreased across all age groups with the highest observed decline, 71%,

38 in 15 to 19-year olds. A dose response relationship was observed between CT-PID rates and screening,

39 with rates lowest in those with the greatest exposure to screening.

40 *Discussion.* There was a marked decline in diagnoses of CT-PID, and non-specific PID, at SSHS after the 41 introduction of wide-spread chlamydia screening, whilst GC-PID diagnoses increased. This ecological 42 trend was broadly consistent with what we would have expected to see if widespread screening 43 reduced the incidence of chlamydia-associated PID (and of non-specific PID), as has been observed in 44 randomised controlled trails of screening.

45

46 **Keywords:** chlamydia, chlamydia screening, pelvic inflammatory disease, surveillance.

- 47
- 48
- 49
- 50

51

53 BACKGROUND:

54

The National Chlamydia Screening Programme (NCSP) was established in England in 2003 and nationally implemented by 2008 with the aim of controlling chlamydia in young, sexually-active people, where incidence was known to be higher. Together with the introduction of nucleic acid amplification testing (NAAT) technologies from 2003, this resulted in large increases in chlamydia screening and diagnoses: 2.3 million tests were reported in 2010 among 15 to 24 year-olds, equivalent to 44% of females and 24% of males in this age group, if only one test per person.

61 Pelvic inflammatory disease (PID) encompasses a range of upper genital tract inflammatory disorders 62 in females that result from the spread of microorganisms from the lower to the upper genital tract.[1, 63 2] Genital infection with *Chlamydia trachomatis* (CT) is one of the principle causes of PID and has been 64 estimated to account for around 35% of cases in females aged 16-24 years decreasing to around 11% 65 in females aged 25-44 years in England.[1-3] Other sexually transmitted infections (STI) which can 66 cause PID include Neisseria gonorrhoeae (GC) and Mycoplasma genitalium.[1, 2, 4, 5] The importance 67 of PID as an outcome measure for the evaluation of STI control lies not only in its direct impact on 68 health, but also as a precursor of more serious conditions including ectopic pregnancy and 69 infertility.[1, 2, 6] However as the proportion of PID caused by chlamydia decreases with age, changes 70 in all cause PID, which is what is usually reported nationally, tells us little about the effectiveness of 71 chlamydia control programmes.[3, 7]

In England, females with PID can present to primary care, hospital or specialist genitourinary medicine (GUM) and integrated GUM/Sexual and Reproductive Health (SRH)) sexual health services (SSHSs).[3, 6] While it is unclear what proportion of females with PID are diagnosed at SSHs, these services are available free of charge to all females at risk of STIs.[3, 6] Attendance at SSHS increased year on year particularly among asymptomatic males and females requesting screening. It is unknown if this could affect access by symptomatic females. We explore available data about PID diagnoses and associated infections in SSHSs in England to inform evaluation of chlamydia screening.

79	
80	
81	METHODS:
82	
83	Data source
84	We used data from the GUMCAD STI Surveillance System (GUMCAD), the national STI surveillance
85	system in England. It is a pseudo-anonymised patient-level dataset that includes information on all
86	attendances, tests and diagnoses at SSHS in England. Each attendance is reported with demographic
87	information including age, gender, sexual orientation, ethnicity and patient area of residence. Patient
88	records can be linked within, but not across clinics, using a clinic patient number that is unique to each
89	individual.[8, 9]
90	We included data on all diagnoses of PID- with and without CT and/or GC-, of bacterial vaginosis and
91	of anogenital candidosis made at SSHSs between 2009 and 2019. Counts and rates of diagnoses were
92	calculated for 15 to 34-year olds in five-year age groups, for females only.
93	
94	Validation and data management
95	To explore the potential effect of changes in access to (or use of) SSHS over this time, we used data
96	on the total number of female attendances and changes in diagnoses of vaginosis/vaginitis (bacterial
97	vaginosis and candidosis). This measure was chosen as a symptomatic clinical presentation with no
98	active control programme, with the assumption that the frequency of these conditions in the
99	population is relatively stable, and therefore likely – we proposed - reflective of variations in service
100	use for symptomatic conditions. Attendances were used as a measure of access for symptomatic and
101	asymptomatic care.
102	To investigate the potential impact of changes in service use, indicated by attendance for symptomatic
103	conditions with stable epidemiology, the ratio of CT PID and non-specific PID to any vaginosis/itis

104 diagnoses was calculated.

Individuals who had a diagnosis of non-specific PID and CT on the same day were considered to have CT-associated PID (herein referred to as CT-PID), and those who had a diagnosis of non-specific PID and GC were considered to have GC-PID. PID codes were de-duplicated with a patient only able to have one diagnosis of PID in a 42 day period reflecting the standard duration of an episode of care in SSHS [8, 10]; if there were multiple codes within a 42 day period then a CT/GC PID diagnosis was kept over any non-specific PID diagnosis, and a GC-PID coding was kept over a CT-PID coding.

111

112 Chlamydia screening activity data

Pre-2012, community (non-SHSS) chlamydia tests and diagnoses in England were reported using two systems; the NCSP core data return and an aggregate laboratory reporting system. In 2012, these two data sources were replaced by a single laboratory reporting system, the Chlamydia Testing Activity Dataset (CTAD). CTAD now provides detailed reports at national and local levels on chlamydia screening activity in 15-to-24-year olds. Data were extracted for 2009-2019 to show trends in this wider screening activity alongside testing data from SSHS.

119

120 Population data

121 Rates were calculated per 100,000 females residing in England using Office for National Statistics

122 (ONS) mid-year population estimates as denominators.[11]

123

124 Birth cohorts

To evaluate the dose response relationship between PID and chlamydia screening, birth-cohort groupings were defined by exposure to widespread screening through the NCSP. The groups were defined as:

Full exposure: females aged 10 years old or less in 2008 (born after 1997) who should have
 had the greatest access to screening since sexual debut.

130	• High exposure: females aged 16 years old or less in 2008 (born between 1992 and 1997) who
131	should have had good access to screening since sexual debut.
132	• Partial exposure: females aged between 17 and 20 years in 2008 (born between 1988 and
133	1991) who should have had some access to screening whilst under 20.
134	• Low exposure: females aged between 21 and 24 years in 2008 (born between 1984 and 1987),
135	who should have had access to screening over 20 years of age.
136	• Very Low exposure: females aged more than 24 years in 2008 (born between 1976 and 1983),
137	who would only have had access to screening during the initial roll-out phase of the NCSP
138	(from 2003).
139	• No exposure: females aged more than 33 years in 2008 (born between 1965 and 1975) who
140	would have reached 24 years before any screening was offered through the NCSP.
141	
142	
143	RESULTS:
144	
145	Changes in chlamydia testing activity in England
146	Testing activity in 15-to-24-year olds varied over the time period (2009-2019) with a peak in testing
147	seen in 2010 of around 2.3 million tests. Subsequent years saw a decline with 1.3 million tests
148	recorded in 2019; a 39% decline since 2010. Data by gender were available since 2012 and the
149	percentage decline since 2012 was greater in males than females, 35% and 24%, respectively.
150	Testing was more stable in SSHS; in 15-to-24-year olds, there were around 580,000 tests carried out
151	in SSHS in 2019 and this was a 2.4% decrease since a peak (n=595,222) in 2014. Testing in females was
152	also stable in SSHS with 372,305 tests in 2019, a negligible increase since 2014 (n=371,821).
153	
154	Changes in population utilising SHSS

155 The rate of all age female attendances (including new and follow-up consultations) at SHSS increased 156 by 50% between 2009 and 2019 to 6,275 per 100,000 population: consultation rates increased in 15 157 to 24-year old and 25 to 34-year old females by 53% and 46%, respectively. 158 Rates of any vaginosis/itis overall peaked in 2012 at 662 diagnoses per 100,000 female population, 159 before decreasing to 490 per 100,000 in 2019, a drop of 21% between 2009 and 2019. 160 161 Trends in PID diagnoses 162 The rates of PID diagnoses decreased during the study period by 38% although the scale of the decline 163 varied by PID type (Figure 1). CT-PID declined by 58%, and non-specific PID declined by 37%. GC-PID 164 fluctuated but showed an overall increase of 34% between 2009 and 2019 (Figure 1b). During the initial 2009 to 2012 period (during which the NCSP recorded highest levels of screening), CT-PID 165 166 diagnoses decreased by 36%, and non-specific PID decreased by 4% whilst GC-PID diagnoses increased 167 by 5%. 168 169 170 Figure 1 171 172 173 CT-PID decreased across all age groups (Figure 2); the decline was highest in 15 to 19-year olds, 71%, 174 compared to declines of between 44% and 54% in the older age groups. A similar trend was observed 175 in non-specific PID, as diagnoses decreased in all age groups but more so in the younger age groups, 176 ranging from 60% (in 15-19year olds) to 21% (in 30-34year olds). GC-PID did not follow the same 177 pattern: it also had a decline, though less, of around 6% in the 15 to 19-year olds but increases in 20 178 to 24, 25 to 29 and 30 to 34-year olds by 22%, 77% and 128%, respectively. 179

181 Figure 2

182

183	Focusing on the age group eligible for screening, CT-PID declined between 2009 and 2019 with a
184	greater decrease in the 15 to 24-year old age group than the 25 to 34-year olds, 62% and 52%
185	respectively. Both age groups showed a reduction between 2009 and 2012, however the trends post
186	2012 differ. Diagnoses in the 15 to 24-year old age group reduced consistently post 2012, a decrease
187	of 43% by 2019; whilst there was a decrease of 14% in the 25 to 34-year old age group between 2012
188	and 2019.
189	
190	Adjusting for changes in attendance for symptomatic conditions using the ratio of non-specific PID
191	and of CT-PID to any vaginosis/itis diagnoses, the declining trend in CT PID persisted but was lessened
192	(51% for this ratio compared to 58% for the rate, 2009-2019). For both CT-PID and non-specific PID,
193	the decline post 2012 was lessened when this ratio was considered, however the declining trend from
194	2009 to 2012 remained and the lower rate was maintained after 2012 (Figure 3).
195	
196	
197	Figure 3

198

199 Trends in NCSP birth cohorts

200

CT-PID rates were lowest in the cohort with the greatest exposure to the NCSP programme, with each
cohort with less exposure showing higher observed rates. In 20 years-olds, the "Full Exposure" cohort
had a lower CT-PID rate of 36 per 100,000 population compared to the "High Exposure" and the
"Partial Exposure" cohorts, 43 and 61 respectively (Figure 4).
A similar dose-response pattern was observed with non-specific PID rates, but not with GC-PID (Figure

206 5 in Supplementary Data).

208

209 Figure 4

- 210
- 211 **DISCUSSION:**
- 212

213 Between 2009 and 2019 PID diagnoses in females attending SSHS decreased by 39% with CT-PID 214 diagnoses decreasing by 58% and non-specific PID by 37%. The proportion of all PID that was CT-PID 215 fell from 14.1% to 9.6% (data not shown). This decline in CT-PID was greatest in females aged 15 to 216 24-years old (62%) with the greatest decline observed between 2009 and 2011. The decrease in the 217 number of CT-PID cases persisted when the number and types of attendances were controlled for by 218 examining the population based PID rates and adjusting for the annual number of females diagnosed 219 with vaginal candidiasis and/or bacterial vaginosis. The declines in CT-PID and non-specific PID show 220 a dose-response relationship with access to NCSP-driven screening during years of sexually-active, 221 young adulthood.

222

223 Strengths

224 This was a large study which used comprehensive national surveillance data which records all 225 attendances at SSHS in England. All attendances were coded using standardised definitions based on 226 the clinical and/or microbiological diagnosis.[9] The guidelines used in these settings have, since 2005, 227 advised a low index of clinical suspicion when diagnosing PID, particularly in females under 25 years, 228 as the symptoms and signs lack sensitivity and specificity. [2, 12, 13]. Thus, these criteria have remained essentially unchanged over the study period. The fraction of PID associated with CT 229 230 decreases with increasing age, being greatest in females under 25 years old.[3] In this study we were 231 able to look at changes in CT-PID rates in 15-to-24-year olds and 25-to-34-year olds enabling us to 232 adjust for potential changes in age distribution of female attendees over time.

Access to SSHS has changed over the study time period with the number of attendances increasing.[14, 15] Changes in access i.e. reduction in clinical capacity associated with rising demand for asymptomatic screening could potentially reduce the number of PID attendances. We were able to explore this by examining the changes in PID diagnoses compared to vaginal discharge caused by candidosis and bacterial vaginosis, rates of which should remain constant within the population. Falls in CT-PID were still observed after adjusting for changes in these other diagnoses, although they were not as great.

240

241 Limitations

242 This was an ecological study and although the changes in PID rates were consistent with what one would expect to see if higher levels of screening, as facilitated by the NCSP, were effective it was not 243 244 possible to infer that the CT-PID rate fall was caused by the NCSP policy and its implementation since 245 2008. We were not able to analyse changes in PID in the same way prior to 2009 due to changes in 246 data collection. An increase in all PID and CT-PID was observed between 2004 and 2009, however this 247 was alongside increased attendance following the Governments 2004 white paper [16] which 248 identified improving sexual health services as a priority, and was associated with an increase in 249 funding. Similar increases in capacity following service improvements have been reported as the cause 250 of increase in PID rates in SSHS in Australia.[17]

251

Other studies have looked at changes in PID over time, however, the associated infections were often not available and many studies used rates for females with PID treated in hospital.[6, 7, 18-20] The majority of females diagnosed with PID are managed in an out-patient or community setting with some evidence that CT-PID may have a milder clinical presentation than other causes and thus be less likely to require admission to hospital.[6, 19] In addition, the proportion of PID caused by CT decreases with age.[3] It is thus difficult to use such data to examine the effect of CT control measures when using all PID as an outcome measure.[7]

Nevertheless, our results are not inconsistent with the findings from the following studies. The pooled risk ratio for all cause PID after one year of follow up in females invited to have a chlamydia screening test in four randomised controlled trials was 0.64 (95% CI 0.45, 0.90, I2=20%) after one year.[21] In the recent Australian Chlamydia Control Effectiveness Pilot (ACCEPt) trial the incidence of PID diagnosed in hospital decreased by 1.37 per 100,000 women (95% CI 0.5–26.9).[20] However, there was no change in the incidence of PID diagnosed in clinics.

The NCSP was nationally implemented in 2008 and it is unclear why a drop was only observed from 2009. The official estimated coverage in females (assuming one test per female) increased from 30.9% in 2008/9 to 42.1% in 2010/11 but is likely to be lower as some females will have tested more than once in any given year.[22, 23] The NCSP promotes annual testing which in the first year would only prevent 55-66% of CT-PID cases in those screened.[24] It is possible that any reductions in CT-PID in 2008 and 2009 may have been obscured by the increases in SSHS attendances between 2004-2009 as described above.

Finally, CT positivity in females with PID attending SSHS is lower than that estimated through a recent multiparameter evidence (MPES) synthesis.[3, 6] It is unclear why that is but the CT positivity is similar to that observed in Australian SSHSs.[25] This may reflect a low index of suspicion as recommended in the BASHH PID guidelines and would include females with "possible" PID whereas the MPES analysis considered only females with probable or definite PID and used data obtained before the introduction of screening.[6, 26]

278

Our data and analyses show an ecological trend that is broadly consistent with widespread screening through the NCSP reducing the incidence of CT-PID as observed in previous RCTs.[21] It is of interest that non-specific PID rates also decreased, but to a lesser extent and later than the CT-PID rates with the proportion of CT- PID decreasing from 14.1-9.6% between 2009 and 2019, whilst GC-PID increased. One explanation as discussed by Horner et al in a separate paper in this special supplement is that CT infection of the fallopian tubes can result in a persistent epithelial-to-mesenchymal transition (EMT)

285 state as a result of epigenetic changes. [27] Such a state is pro-inflammatory and could increase the 286 risk of non-specific PID developing in females whose upper genital tract is colonised by bacterial 287 vaginosis associated bacteria (BVAB).[27, 28] EMT reduces the integrity of the epithelium potentially 288 making it more susceptible to invasion and disease from BVAB .[27] BVAB are the most common cause 289 of non-specific PID.[1, 2, 27] It is likely if CT-PID rates decreased so did upper genital tract CT infection 290 which is not always symptomatic.[6, 27] This would then reduce the subsequent risk of developing PID 291 from any cause.[18, 19, 27] Horner et al argue that this hypothesis merits further investigation as it 292 would increase our understanding of the risks of sequelae associated with chlamydial genital tract 293 infection and thus better inform public health interventions and cost effectiveness models of 294 interventions such as screening and vaccination. [27, 29, 30]

295 Consideration should be given to investigating whether serology as discussed by Horner elsewhere in 296 this supplement can be used to evaluate whether there is an observable birth cohort effect on CT 297 tubal factor infertility similar to what we have demonstrated for CT-PID.[31] Most females with 298 infertility present years after the inciting infection has resolved and would no longer be detected by 299 nucleic acid amplification testing or other tests for active urogenital infection.[6, 31]

300

301 Conclusion

There was a marked decline in diagnoses of CT PID, and non-specific PID, at SSHS after the introduction of wide-spread chlamydia screening, whilst GC-PID diagnoses increased. This occurred despite an increase in attendances at SSHS and alongside a far smaller decline in diagnoses of vaginosis/vaginitis due to bacterial vaginosis and candidosis. Further work is needed, including to explore trends in general practice and hospital admissions, to determine whether the frequency of CT-PID (rates, or more likely as a proportion of all PID) in SHSS might offer a useful national and local metric for the success of chlamydia control.

309

С	1	1
Э	т	т

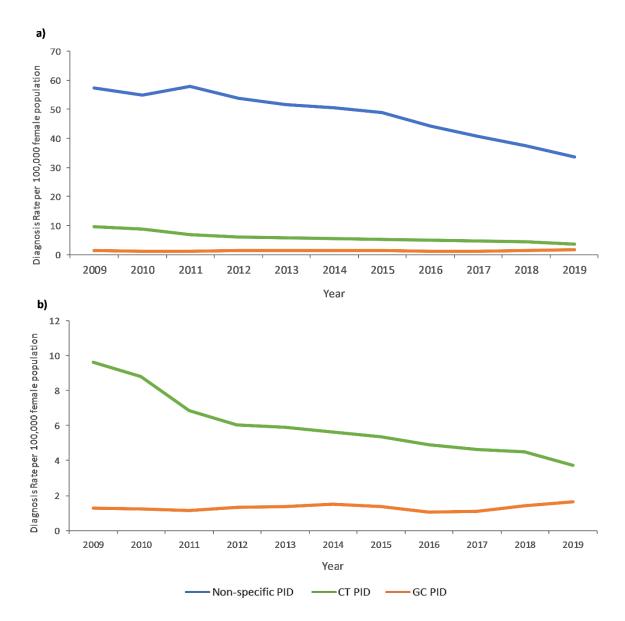
313	Ethical statement:
314	No specific consent was required from the patients whose data were used in these analyses. In its role
315	providing infectious disease surveillance Public Health England has permission to handle data
316	obtained by the GUMCAD STI Surveillance System and the CTAD Chlamydia Surveillance System under
317	Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002.
318	
319	Potential Conflicts of Interest:
320	The Authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for
321	Disclosure of Potential Conflicts of Interest.
322	
323	Meetings previously presented at:
324	PH presented early findings at the STI & HIV 2019 World Congress, Joint Meeting of the 23rd ISSTDR
325	and 20th IUSTI, Vancouver, Canada July 14 – 17, 2019, http://stihiv2019vancouver.com/
326	
327	Acknowledgements:
328	The authors thank Paula Blomquist, Bersabeh Sile and Hamish Mohammed for their support with
329	accessing and analysing the GUMCAD data.
330	
331	
332	
333	
334	
335	

- 337 **REFERENCES**:
- 338

339 1. Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. N Engl J Med, 2015; 372:203948.

- 341 2. British Association for Sexual Health and HIV. 2018 United Kingdom National Guideline for the
 342 Management of Pelvic Inflammatory Disease, **2018**.
- 343 3. Price MJ, Ades AE, Welton NJ, Simms I, Macleod J, Horner PJ. Proportion of Pelvic Inflammatory
- Disease Cases Caused by Chlamydia trachomatis: Consistent Picture From Different Methods. J Infect
 Dis, 2016; 214:617-24.
- 4. Haggerty CL. Evidence for a role of Mycoplasma genitalium in pelvic inflammatory disease. CurrOpin Infect Dis, **2008**; 21:65-9.
- 348 5. Lewis J, Horner PJ, White PJ. Incidence of Pelvic Inflammatory Disease Associated With
- 349 Mycoplasma genitalium Infection: Evidence Synthesis of Cohort Study Data. Clin Infect Dis, **2020**;
 350 71:2719-22.
- 351 6. Price MJ, Ades AE, Soldan K, et al. The natural history of Chlamydia trachomatis infection in
- women: a multi-parameter evidence synthesis. Health Technol Assess, **2016**; 20:1-250.
- 353 7. Bender N, Herrmann B, Andersen B, et al. Chlamydia infection, pelvic inflammatory disease,
- ectopic pregnancy and infertility: cross-national study. Sex Transm Infect, **2011**; 87:601-8.
- 8. Savage EJ, Mohammed H, Leong G, Duffell S, Hughes G. Improving surveillance of sexually
- 356 transmitted infections using mandatory electronic clinical reporting: the genitourinary medicine
- clinic activity dataset, England, 2009 to 2013. Euro Surveill, **2014**; 19:20981.
- 358 9. Public Health England. GUMCAD: clinical guidelines, **2019**.
- 10. Hughes G, Nichols T, Peters L, Bell G, Leong G, Kinghorn G. Repeat infection with gonorrhoea in
- 360 Sheffield, UK: predictable and preventable? Sex Transm Infect, **2013**; 89:38-44.
- 11. Office for National Statistics. Mid-2001 to mid-2019 detailed time series, **2019**.
- 362 12. British Association for Sexual Health and HIV. UK National Guideline for the Management of
- 363 Pelvic Inflammatory Disease, **2005**.
- 13. British Association for Sexual Health and HIV. UK National Guideline for the management of
- 365 Pelvic Inflammatory Disease 2011 2011.
- 14. White C. Sexual health services on the brink. BMJ, **2017**; 359:j5395.
- 367 15. Mitchell H AH, Sonubi T, Kuyumdzhieva G, Harb A, Shah A, Glancy M, Checchi M, Milbourn H,
- Folkard K, Mohammed H and contributors. Sexually transmitted infections and screening for chlamydia in England, 2019., **2020**.
- 16. Health Do. A health promoting NHS: transforming sexual health services. In: Choosing Health:
- 371 Making healthy choices easier: Department of Health, **2004**.
- 17. Goller JL, Fairley CK, De Livera AM, et al. Trends in diagnosis of pelvic inflammatory disease in an
- Australian sexual health clinic, 2002-16: before and after clinical audit feedback. Sex Health, 2019;
 16:247-53.
- 18. den Heijer CDJ, Hoebe C, Driessen JHM, et al. Chlamydia trachomatis and the Risk of Pelvic
- Inflammatory Disease, Ectopic Pregnancy, and Female Infertility: A Retrospective Cohort Study
 Among Primary Care Patients. Clin Infect Dis, **2019**; 69:1517-25.
- 378 19. Davies B, Turner KME, Frølund M, et al. Risk of reproductive complications following chlamydia
- testing: a population-based retrospective cohort study in Denmark. Lancet Infect Dis, **2016**; 16:1057 64.
- 381 20. Hocking JS, Temple-Smith M, Guy R, et al. Population effectiveness of opportunistic chlamydia
- testing in primary care in Australia: a cluster-randomised controlled trial. Lancet, **2018**; 392:1413-22.
- 21. European Centre for Disease Prevention and Control. Chlamydia control in Europe: literature
- 384 review. Stockholm, **2014**.

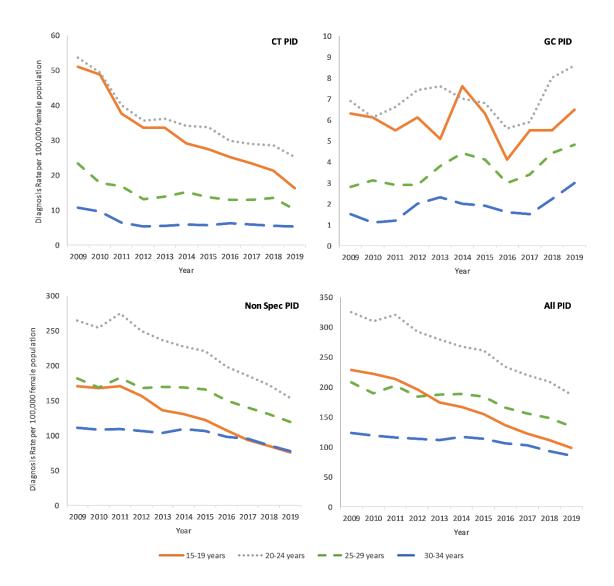
- 22. Health Protection Agency. HIV-STIs: Further increase in chlamyida screeing coverage in 2010/11.
 Health Protection Report **2011**; 5(24).
- 387 23. Turner KM, Horner PJ, Trela-Larsen L, Sharp M, May M. Chlamydia screening, retesting and
 388 repeat diagnoses in Cornwall, UK 2003-2009. Sex Transm Infect, **2013**; 89:70-5.
- 24. Price MJ, Ades AE, De Angelis D, et al. Risk of pelvic inflammatory disease following Chlamydia
 trachomatis infection: analysis of prospective studies with a multistate model. Am J Epidemiol, **2013**;
- 391 178:484-92.
- 392 25. Goller JL, De Livera AM, Fairley CK, et al. Population attributable fraction of pelvic inflammatory
- disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual
 health clinic data. Sex Transm Infect, **2016**; 92:525-31.
- 26. Taylor-Robinson D, Stacey CM, Jensen JS, Thomas BJ, Munday PE. Further observations, mainly
- serological, on a cohort of women with or without pelvic inflammatory disease. Int J STD AIDS, 2009;
 20:712-8.
- 398 27. Horner P FH, Horne A. Is there a hidden burden of disease as a result of epigenetic epithelial-to-
- mesenchymal transition following Chlamydia trachomatis genital tract infection? . J Infect Dis, 2021;
 In Press.
- 401 28. Mitchell CM, Haick A, Nkwopara E, et al. Colonization of the upper genital tract by vaginal
- 402 bacterial species in nonpregnant women. Am J Obstet Gynecol, **2015**; 212:611.e1-9.
- 403 29. Ong KJ, Soldan K, Jit M, Dunbar JK, Woodhall SC. Chlamydia sequelae cost estimates used in
- 404 current economic evaluations: does one-size-fit-all? Sex Transm Infect, **2017**; 93:18-24.
- 30. Woodhall SC, Gorwitz RJ, Migchelsen SJ, et al. Advancing the public health applications of
 Chlamydia trachomatis serology. Lancet Infect Dis, **2018**; 18:e399-e407.
- 407 31. Horner P AG, Geisler W. What can serology tell us about the burden of infertility in women
 408 caused by chlamydia? J Infect Dis, **2021**; In Press.
- 409
- 410
- 411
- 412
- 413
- 414
- 415
- 416
- 417
-
- 418
- 419
- 420
- 421
- 421
- 422





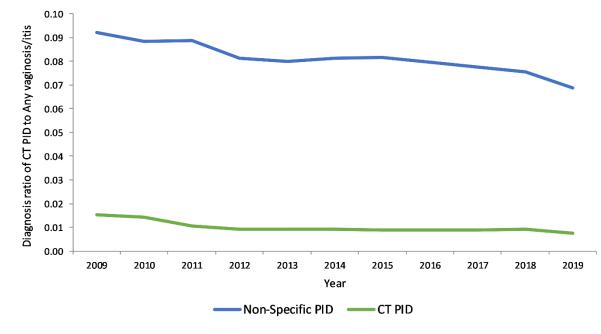
424 Figure 1 a) All-age PID diagnosis rates per 100,000 female population between 2009-2019 for non-specific PID, CT-PID and

- 425 GC-PID b) CT-PID and GC-PID rates per 100,000 female population between 2009-2019 presented on smaller scale.



436 Figure 2 PID diagnosis rates per 100,000 female population between 2009-2019 for CT-PID, GC-PID, non-specific PID and all

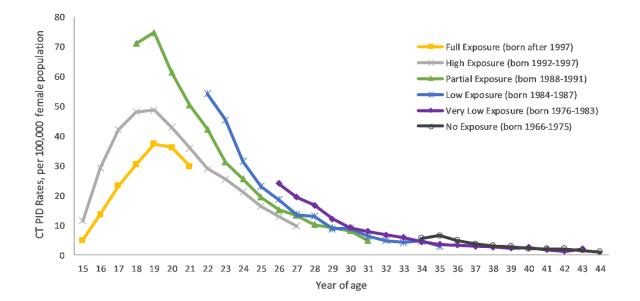
PID by age group, 15-19 years, 20-24 years, 25-29 years and 30-34 years.



449 Figure 3 Diagnosis ratio of all-age non-specific PID and CT-PID to any vaginosis/itis in females between 2009-2019

- ----

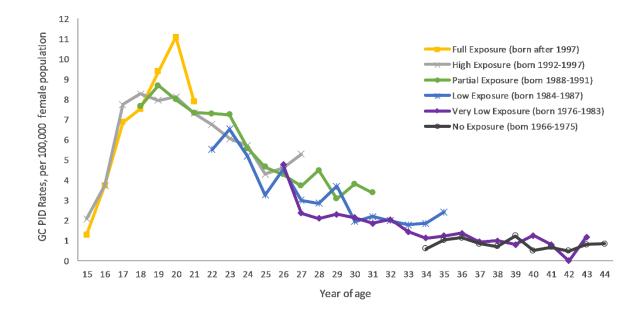
-





470 Figure 4 CT-PID rates per 100,000 female population aged 15 to 44 years old by year of age and birth-cohort with varying

471 exposure to widespread chlamydia screening through the NCSP, 2009-2019



490 Figure 5 GC PID rates per 100,000 female population aged 15 to 44 years old by year of age and birth-cohort
491 with varying exposure to widespread chlamydia screening through the NCSP, 2009-2019

Supplementary Table 1- data for Figure 1. All-age PID diagnosis rates per 100,000 female population

507	between 2009-2019 by type for non-specific PID, CT-PID and GC-PID

	Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	Non-specific PID	57.2	54.8	57.9	53.8	51.5	50.5	48.8	44.3	40.7	37.5	33.6
	CT-PID GC-PID	9.6 1.3	8.8 1.2	6.9 1.1	6.0 1.3	5.9 1.4	5.6 1.5	5.4 1.4	4.9 1.1	4.6 1.1	4.5 1.4	3.7 1.6
508		1.5	1.2	1.1	1.5	1.4	1.5	1.4	1.1	1.1	1.4	1.0
509												
510												
511												
512												
513												
514												
515												
516												
517												
518												
519												
520												
521												
522												
523 524												
525												
526												
527												
528												
529												
530												
531												
532												
533												

- **Supplementary Table 2- data for Figure 2.** PID diagnosis rates per 100,000 female population
- between 2009-2019 for CT-PID, GC-PID, non-specific PID and all PID by type and age group, 15-19
- 536 years, 20-24 years, 25-29 years and 30-34 years.

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
15-19												
Non-specific PID	170.6	167.0	170.5	156.4	135.9	130.1	121.5	107.2	93.1	84.9	75.3	
CT-PID	51.0	48.7	37.5	33.4	33.5	29.1	27.3	25.1	23.2	21.2	16.2	
GC-PID	6.3	6.1	5.5	6.1	5.1	7.6	6.3	4.1	5.5	5.5	6.5	
All PID	227.9	221.8	213.6	195.9	174.5	166.7	155.0	136.4	121.9	111.6	98.1	
20-24												
Non-specific PID	264.4	254.2	273.9	249.3	236.0	226.7	220.6	198.1	184.6	172.2	153.2	
CT-PID	53.5	49.3	39.9	35.5	36.0	34.0	33.7	29.7	28.8	28.5	25.1	
GC-PID	6.9	6.1	6.6	7.4	7.6	7.0	6.8	5.6	5.9	8.0	8.6	
All PID	324.7	309.5	320.5	292.1	279.6	267.7	261.1	233.3	219.3	208.7	186.9	
25-29												
Non-specific PID	181.4	168.4	182.4	167.5	169.7	168.4	165.6	150.0	139.5	129.9	119.3	
CT-PID	23.3	17.8	16.7	13.1	13.9	15.1	13.7	12.8	12.8	13.5	10.1	
GC-PID	2.8	3.1	2.9	2.9	3.8	4.4	4.1	3.0	3.4	4.4	4.8	
All PID	207.5	189.4	202.0	183.6	187.5	187.9	183.4	165.8	155.7	147.8	134.1	
30-34	30-34											
Non-specific PID	111.1	107.9	108.5	106.5	103.4	109.1	106.0	98.0	95.2	85.7	77.2	
CT-PID	10.6	9.6	6.3	5.2	5.4	5.8	5.6	6.2	5.9	5.5	5.2	
GC-PID	1.5	1.1	1.2	2.0	2.3	2.0	1.9	1.6	1.5	2.2	3.0	
All PID	123.2	118.6	115.9	113.8	111.1	116.9	113.5	105.9	102.7	93.4	85.4	

Supplementary Table 3- data for Figure 3. Diagnosis ratio of all-age non-specific PID & and CT-PID to 555 any vaginosis/itis in females between 2009-2019.

	Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	Non-specific PID	0.015	0.014	0.011	0.009	0.009	0.009	0.009	0.009	0.009	0.009	0.008
556	CT-PID	0.092	0.089	0.089	0.081	0.080	0.081	0.081	0.079	0.078	0.076	0.069
557												
558												
559												
560												
561												
562												
563												
564												
565												
566												
567												
568												
569												
570												
571												
572												
573												
574												
575												
576												
577												
578												
579												
580												
581												
582												

- Supplementary Table 4- data for Figure 4. CT-PID rates per 100,000 female population aged 15 to 44
- years old by year of age and birth-cohort with varying exposure to widespread chlamydia screening through the NCSP, 2009-2019.

Age	Full Exposure (born after 1997)	High Exposure (born 1992-97)	Partial Exposure (born 1998-91)	Low Exposure (born 1984-87)	Very Low Exposure (born 1976-83)	No Exposure (born 1966-75)
15	5.0	11.6	-	-	-	-
16	13.6	29.3	-	-	-	-
17	23.3	42.2	-	-	-	-
18	30.4	48.0	70.9	-	-	-
19	37.3	48.6	74.7	-	-	-
20	36.1	42.9	61.3	-	-	-
21	29.7	35.9	50.3	-	-	-
22	-	29.0	42.2	54.1	-	-
23	-	25.5	31.1	45.3	-	-
24	-	21.2	25.5	31.4	-	-
25	-	16.3	19.4	22.9	-	-
26	-	12.9	15.2	18.6	24.0	-
27	-	9.8	13.3	13.6	19.4	-
28	-	-	10.2	13.0	16.8	-
29	-	-	9.2	8.8	12.2	-
30	-	-	8.2	8.9	9.2	-
31	-	-	4.9	6.3	8.0	-
32	-	-	-	4.8	6.8	-
33	-	-	-	4.2	5.9	-
34	-	-	-	4.8	4.5	5.6
35	-	-	-	2.9	3.6	6.5
36	-	-	-	-	3.3	4.8
37	-	-	-	-	3.0	3.8
38	-	-	-	-	2.7	3.1
39	-	-	-	-	2.3	2.9
40	-	-	-	-	2.6	2.2
41	-	-	-	-	1.8	2.0
42	-	-	-	-	1.3	2.0
43	-	-	-	-	2.1	1.6
44	-	-	-	-	-	1.1

595 Supplementary Table 5- data for Supplementary Figure 5. GC-PID rates per 100,000 female

596 population aged 15 to 44 years old by year of age and birth-cohort with varying exposure to

597 widespread chlamydia screening through the NCSP, 2009-2019.

Age	Full Exposure (born after 1997)	High Exposure (born 1992-97)	Partial Exposure (born 1998-91)	Low Exposure (born 1984-87)	Very Low Exposure (born 1976-83)	No Exposure (born 1966-75)
15	1.3	2.1	-	-	-	-
16	3.7	3.7	-	-	-	-
17	6.9	7.7	-	-	-	-
18	7.5	8.3	7.6	-	-	-
19	9.4	7.9	8.7	-	-	-
20	11.1	8.1	8.0	-	-	-
21	7.9	7.3	7.3	-	-	-
22	-	6.7	7.3	5.5	-	-
23	-	6.1	7.2	6.5	-	-
24	-	5.7	5.6	5.2	-	-
25	-	4.3	4.6	3.2	-	-
26	-	4.6	4.3	4.5	4.8	-
27	-	5.3	3.7	3.0	2.4	-
28	-	-	4.5	2.8	2.1	-
29	-	-	3.1	3.7	2.3	-
30	-	-	3.8	1.9	2.1	-
31	-	-	3.4	2.2	1.8	-
32	-	-	-	2.0	2.0	-
33	-	-	-	1.8	1.4	-
34	-	-	-	1.9	1.1	0.6
35	-	-	-	2.4	1.2	1.0
36	-	-	-	-	1.4	1.1
37	-	-	-	-	0.9	0.8
38	-	-	-	-	1.0	0.7
39	-	-	-	-	0.8	1.2
40	-	-	-	-	1.2	0.5
41	-	-	-	-	0.8	0.7
42	-	-	-	-	0.0	0.5
43	-	-	-	-	1.2	0.8
44	-	-	-	-	-	0.8