The Great Chlamydia Control Bake Off: the same ingredients (evidence) but different recipes for success

Kate Soldan[1], **Gloria E Anyalechi**[2], **Kristen M Kreisel**[2], **Jane S Hocking**[3], **Kyle Bernstein**[2]

[1]Blood Safety, Hepatitis, Sexually Transmitted Infections (STI) and HIV Division, National Infection Service, Public Health England, London, UK

[2]Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[3]Melbourne School of Population and Global Health, University of Melbourne, Carlton, Victoria, Australia

Successful baking requires careful measurement, the precise mixing of ingredients and an attentive eye while the mixture is in the oven. However, the environment may have an impact on the final product. Humidity, quality of ingredients, type of oven used and altitude can all mean the difference between a perfect cake and a goopy mess. Although chlamydia control may seem quite different from baking, there are some important parallels, notably the context in which control programmes are developed, implemented and evaluated. The same inputs and approaches applied in different contexts may produce drastically different results.

van Bergen *et al*[1] describe the methods of and conclusions from addressing the question 'Where to go to in Chlamydia control?' for the Netherlands in this issue of *Sexually Transmitted Infections*.

The author and colleagues[1] convened a panel that met in November 2019 and discussed expert perspectives on chlamydia control. This panel considered the interpretation of available evidence on the impact and/or effectiveness of a variety of testing scenarios: asymptomatic screening including opportunistic testing of asymptomatic patients in routine healthcare settings, syndromic testing, and at-home specimen collection and/or testing. Their paper reports on a problem analysis and the consensus viewpoint that evolved from this expert meeting, which suggested that future strategies should reduce rather than expand the role of widespread testing for asymptomatic chlamydial infections, and therefore the

authors conclude that they 'do not recommend age-based screening and widespread testing for chlamydia in asymptomatic persons in the Netherlands'.[1]

In this thought-provoking paper, van Bergen *et al*[1] focus on the assessment of three points: evidence for prevalence reductions, the rate of severe long-term complications caused by chlamydia and the potential harms of overdiagnoses and overtreatment. They find that all three points argue for the need to reassess and question current practices.

Uncertainty around the pathogenesis of chlamydia and the value of chlamydia control programmes is a long-standing issue and has long been the subject of some heated debate.[2–7] The lack of evidence for reduced prevalence by chlamydia screening in practice, in contrast to theoretical expectations, leaves little room for further debate on this point now, and has led to a convergence of the aims of chlamydia testing to focus on reducing the consequences of infection rather than reducing prevalence. Along with this comes a need to prioritise better case management, including partner management and retesting. However, the debate is still going strong about the role of asymptomatic screening: do the preventable harms of chlamydia outcomes outweigh the potential harms of screening (or vice versa)? Those who support asymptomatic screening cite the evidence that chlamydia is a cause of severe reproductive complications (including pelvic inflammatory disease, tubal factor infertility and ectopic pregnancy), that identifying those infected can prevent these reproductive sequelae as well as reduce transmission to partners and that screening reaches those at highest risk who would otherwise suffer greater inequity in sexual health and reproductive outcomes, with or without the additional potential for a population-level benefit through reducing transmission.[8–14] Those who question the value in chlamydia screening cite the very same evidence about reproductive complications (we will come back to this), the plethora of challenges in interpreting chlamydia data and in achieving screening coverage, and place more importance on the risks of overdiagnosis (especially in lower prevalence populations) and the risks of treatment.[14][15][16]

The debate is not around which evidence to cite or even the facts available from that evidence, but rather about the weight allocated to the different benefits and harms (on both sides of the scale) and about the tolerance for uncertainty (again, on both sides). Most notably, the very same evidence about preventable sequelae can be argued either as weak and supportive of a position that benefits are likely to be infrequent or as robust and supportive of a position that benefits are likely to be substantial. Whether the evidence is weak or robust, and whether preventable sequelae are frequent or infrequent, important or not important, remains debatable and ultimately a matter of opinion. The risk of harms—most importantly antimicrobial resistance emerging for chlamydia or for other pathogens in treated populations—also requires judgement. Widespread azithromycin use for the treatment of chlamydia is thought to have contributed to antimicrobial resistance in gonorrhoea, syphilis and *Mycoplasma* (and potentially shigella).[17][18] While azithromycin exhibits reduced treatment efficacy in rectal chlamydia, the mechanism for this is unknown and is not suspected to be related to antimicrobial resistance.[19] Actual resistance in strains of chlamydia has not been demonstrated; however, resistance remains a potentially very serious outcome and is no less debatable as to its weight on the scales.

There is no universal regulation for chlamydia screening; its programmatic and public health impacts will vary based on where and how it is implemented. Therefore, there is value in exploring how others have evaluated the ambiguities in the evidence, and—perhaps more importantly—consider why the conclusions vary and whether this variation should trouble us.

In England, a group of national and international experts was convened and asked to peer-review a summary of the evidence relating to chlamydia screening prepared by Public Health England (PHE); this summary of the evidence was also used by the group in the Netherlands. The group met over 2 days in October 2017 and subsequently made recommendations that were operationalised by PHE and then put out for consultation to stakeholders and the public, as well as discussed in focus groups of young people. This review process recently concluded with recommendations to change the aim of the programme to focus on the direct harms from untreated chlamydia and, as these harms predominantly occur in women, to remove the offer of opportunistic chlamydia screening to asymptomatic young men outside of sexual health services.[20]

There is much in common with both the process and the outcome of the review in the Netherlands and in England: both conclude that reductions in prevalence are not a basis for continuing widespread screening, and both recommend a focus on more effective case management.[1 20] However, of note, despite reviewing the same evidence, and both groups purporting to base recommendations on this evidence, the English recommendations remain in favour of age-based screening and widespread testing for chlamydia in asymptomatic women. The potential harms caused by screening contributed to the recommendation to remove asymptomatic young men outside of sexual health services from the programme. However, this weighed in secondarily to the far lower value from the likely health benefits. For young women, these harms were not deemed to outweigh the likely benefits from continuing to aim for high screening rates. This clearly illustrates that, as van Bergen *et al*[1] note, there is 'a large element of expert opinion and judgement involved' in decisions about chlamydia control—in the Netherlands, in England and undoubtedly elsewhere too.

In the USA, there is an independent panel of primary care and prevention experts called the US Preventive Services Task Force (USPSTF) which systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services. The USPSTF focuses exclusively on patient-level benefits in their recommendations and does not consider population-level benefits. The USPSTF has updated their chlamydia screening guidelines a number of times, most recently in 2014, with a current revision underway, and has found themselves in a similar position as the Netherlands and England having to make recommendations based on limited evidence and studies of suboptimal quality.[2 21] Furthermore, The Centers for Disease Control and Prevention (CDC) makes recommendations independent of the USPSTF. The CDC currently recommends age-based and risk-based screening with a focus on detecting infection, preventing complications and testing/treating partners of infected women, while the primary focus for men is only in high-prevalence areas or in populations with a high burden of infection.[22] These recommendations are more similar to the new English recommendations.

In Australia, the primary care guidelines continue to recommend chlamydia screening for persons aged <30 years and high-risk populations (eg, men who have sex with men, Aboriginal and/or Torres Strait Islanders), although the recommendations for persons aged <30 years no longer suggest annual testing, but rather opportunistic testing for those requesting an STI check-up.[23] The Australian National STI Strategy has been informed by the results generated from the ACCEPt trial and aims to 'identify opportunities to scale up evidence based interventions aimed at reducing STI, with a focus on repeat chlamydial infections and infections causing pelvic inflammatory disease, and other complications in young people'.[24] In practice, this has led to more of a push towards focusing on improved chlamydia case management when diagnosed and less on screening uptake.

It is not surprising that national chlamydia control recommendations vary. This is often the case with public health interventions, where the certainty of the evidence is frequently debatable, and evidence is often gleaned from less than perfect data sets from non-controlled observations. The likely success of chlamydia control policies is also contingent on numerous factors that vary by country. These include the structure and provision of healthcare, aspects of cost to the national system and the patient, the role of the local health authority in interpreting data to inform guidelines and recommendations, and the real and perceived burden of disease both absolutely and relative to other health issues. Also, successful evaluation of chlamydia control policies, to support and inform them, relies on the availability of morbidity data for its reproductive sequelae, data which are equally suboptimal, debatable and lacking in many countries.

Heterogeneity in policies for chlamydia control is therefore inevitable, often justifiable (based on country-specific context) and not necessarily unhelpful. Should we pay greater attention to, and acknowledge, the influence of context, culture and already formed opinions of those joining evidence review groups? Possibly. But not with the intention of finding a perfect one-size-fits-all recipe for making a chlamydia control policy that gives identical results in different places.

We could do well to embrace the variation and seek to learn from differences in practice: vigilance against the development of antimicrobial resistance may be a more important accompaniment to pro-screening policies; and methods for accurate risk assessments and for improving the accessibility of sexual health services may work best alongside more restricted use of chlamydia testing. Given the acceptance that testing is not effective in substantially reducing prevalence, all policies need to consider additional methods for primary prevention of chlamydia along with other STIs (and unwanted pregnancies)—methods which are also likely to have varying levels of adoption and of success in different populations and locations.

Over 10 million people watched the latest finale of the Great British Bake Off. This television show exists because we expect and enjoy variation in the results from different bakers using the same ingredients, reflecting their different ways of handling the same ingredients, and the taste preferences of the baker and the judges. The creation of chlamydia control recommendations may be more similar to baking cakes than we—as scientists schooled to seek an evidence base for our recommendations—like to think.

Funding

REFERENCES

1. van Bergen JEAM, Hoenderboom BM, David S, et al. Where to go to in Chlamydia control? from infection control towards infectious disease control. Sex Transm Infect 2021. doi:10.1136/sextrans-2021-054992. [Epub ahead of print: 27 May 2021].

2. LeFevre ML, U.S. Preventive Services Task Force. Screening for Chlamydia and gonorrhea: U.S. preventive services Task force recommendation statement. Ann Intern Med 2014;161:902–10. [PubMed: 25243785]

3. Brunham RC, Rekart ML. The arrested immunity hypothesis and the epidemiology of Chlamydia control. Sex Transm Dis 2008;35:53–4. [PubMed: 18157065]

4. Miller WC. Epidemiology of chlamydial infection: are we losing ground? Sex Transm Infect 2008;84:82–6. [PubMed: 18372493]

5. Rekart ML, Brunham RC. Epidemiology of chlamydial infection: are we losing ground? Sex Transm Infect 2008;84:87–91. [PubMed: 18216155]

6. Gottlieb SL, Brunham RC, Byrne GI, et al. Introduction: The natural history and immunobiology of *Chlamydia trachomatis* genital infection and implications for chlamydia control. J Infect Dis 2010;201 Suppl 2:85–7.

7. Migchelsen SJ, Davis GS, Ong K, et al. National Chlamydia screening programme external peer review: evidence pack. London: Public Health England, 2017.

8. Oakeshott P, Kerry S, Aghaizu A, et al. Randomised controlled trial of screening for *Chlamydia trachomatis* to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. BMJ 2010;340:c1642. [PubMed: 20378636]

9. Scholes D, Stergachis A, Heidrich FE, et al. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med 1996;334:1362–6. [PubMed: 8614421]

10. Centers for Disease Control and Prevention (CDC). CDC grand rounds: Chlamydia prevention: challenges and strategies for reducing disease burden and sequelae. MMWR Morb Mortal Wkly Rep 2011;60:370–3. [PubMed: 21451447]

11. Macaluso M, Wright-Schnapp TJ, Chandra A, et al. A public health focus on infertility prevention, detection, and management. Fertil Steril 2010;93:16.e1–16.e10. [PubMed: 18992879]

12. Owusu-Edusei K, Bohm MK, Chesson HW, et al. Chlamydia screening and pelvic inflammatory disease: insights from exploratory time-series analyses. Am J Prev Med 2010;38:652–7. [PubMed: 20494242]

13. Gorwitz RJ, Wiesenfeld HC, Chen P-L, et al. Population-attributable fraction of tubal factor infertility associated with Chlamydia. Am J Obstet Gynecol 2017;217:336.e1–336.e16. [PubMed: 28532600]

14. Haggerty CL, Gottlieb SL, Taylor BD, et al. Risk of sequelae after *Chlamydia trachomatis* genital infection in women. J Infect Dis 2010;201 Suppl 2:134–55.

15. Miller WC, Siripong N. Estimates of sexually transmitted infection prevalence and incidence in the United States: time to embrace uncertainty. Sex Transm Dis 2013;40:194–6. [PubMed: 23403599]

16. National Committee for Quality Assurance. Chlamydia screening in women (CHL). Available: https://www.ncqa.org/hedis/measures/chlamydia-screening-in-women/ [Accessed 7 Jul 2021].

17. Kong FYS, Horner P, Unemo M, et al. Pharmacokinetic considerations regarding the treatment of bacterial sexually transmitted infections with azithromycin: a review. J Antimicrob Chemother 2019;74:1157–66. [PubMed: 30649333]

18. Ingle DJ, Easton M, Valcanis M, et al. Co-circulation of multidrug-resistant Shigella among men who have sex with men in Australia. Clin Infect Dis 2019;69:1535–44. [PubMed: 30615105]

19. Lau A, Kong FYS, Fairley CK, et al. Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*. N Engl J Med 2021;384:2418–27. [PubMed: 34161706]

20. Public Health England. Changes to the National Chlamydia screening programme: information on the changes. London: Public Health England, 2021: 1–12.

21. US Preventive Services Task Force. Screening for Chlamydia and gonorrhea, 2021. Available: https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/chlamydial-and-gonococcal-infections-screening [Accessed 28 Jun 2021].

22. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1–137.

23. Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. et al.th ed. East Melbourne, Victoria, 2016.

24. 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. [PubMed: 30343857]