Price, M. J., Horner, P. J., & Ades, A. E. (2016). Risk of reproductive complications following chlamydia testing: Time to take causation seriously. *Lancet Infectious Diseases*, *16*(11), 1223-1224. https://doi.org/10.1016/S1473-3099(16)30379-6

Title: Time to take causation seriously

Authors:

Price MJ[1*], Horner PJ[2,3], Ades AE[2]

[1]Institute for Applied Health Research, University of Birmingham, Birmingham UK

[2]School of Social and Community Medicine, University of Bristol, Bristol, UK

[3]Bristol Sexual Health Centre, University Hospital Bristol NHS Foundation Trust, Bristol, UK

***Author for Correspondence**:

Malcolm J Price

Institute of Applied Health Research,

Public Health Building,

University of Birmingham

Edgbaston,

Birmingham,

B15 2TT

m.price.2@bham.ac.uk

Conflicts of Interest:

PJH reports personal fees from Aquarius Population Health, grants, personal fees and non-financial support from Cepheid, personal fees from Crown Prosecution Service, personal fees from British Association for Sexual Health and HIV, grants from Mast Group Ltd, grants and personal fees from Hologic, outside the submitted work; in addition, PJH has a patent A sialidase spot test to diagnose bacterial vaginosis, issued to University of Bristol. The remaining authors declare no conflicts of interest.

Davies *et al* use data from a cohort of chlamydia tested and never-chlamydia tested women constructed from the Danish registry study to estimate the risk of reproductive complications[1]. The analyses show associations between chlamydia testing (positive, negative, untested) and reproductive outcomes over the subsequent 15 years. However, the paper and an accompanying editorial seriously over-interpret the data.

Loose language crosses the line between causation and association. For example, statements like "a positive chlamydia test increased the risk… by at least 30%", "a single diagnosed infection increases the risk…" or "… a repeat diagnosis increases the risk …." strongly imply causality. The design is similar to the earlier Uppsala study[2]. A CDC expert group[3] identified a series of methodological difficulties with studies of this type, among them the already insurmountable problem that women testing positive were treated. It is simply not possible to derive meaningful, causal estimates from studies of this type, and the editorialist's assertion that the paper "quantified the risk of reproductive complications attributable to chlamydia infection" is incorrect.

As the study gives no evidence that the single or repeat events of CT diagnosis (positive or negative) cause an increase in the risk of complications, it cannot substantiate claims that interrupting this will be effective. So although the conclusion that "control programs must prevent first and repeat infections to improve women's reproductive health" could be correct, this study adds no relevant information to support it, nor to the editorialist's recommendation of "a more intensive approach than test and treat".

We recently published estimates of the risks of reproductive damage attributable to chlamydia[4] in the UK. Central estimates are that every 1,000 CT infections in women on average cause 170 episodes of PID, 70 of salpingitis, 2 ectopic pregnancies (EP) and 5 of Tubal Factor Infertility (TFI). These estimates, which include undiagnosed chlamydia, PID and salpingitis, were based on estimates of chlamydia incidence, prevalence and duration in the UK, an estimate of the risk of PID following CT infection based on randomized evidence, and many other sources of systematically identified evidence. These estimates were constructed in a way that makes them internally coherent and consistent with data on the incidence of PID, EP and TFI in the UK.

Finite mixture modeling of serology data may be another route towards estimating the proportion of reproductive damage attributable to chlamydia[5], but this needs further validation.

References

1. Davies B, Turner KME, Frølund M, *et al*. Risk of reproductive complications following chlamydia testing: a population-based retrospective cohort study in Denmark. *Lancet Inf Diseases* 2016; **16** 1057-1064.
2. Low N, Egger M, Sterne JAC *et al*. Incidence of severe reproductive tract complications associated with diagnosed genital chlamydia infection: the Uppsala Women's Cohort Study. *Sex transm infect* 2006; **82**: 212-218.
3. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of Sequelae after *Chlamydia trachomatis* genital Infection in Women. *J Infect Dis* 2010; **201** (Suppl 2): S134-55.
4. Price MJ, Ades AE, Soldan K. The natural history of Chlamydia trachomatis infection in women: a multi-parameter. evidence synthesis. *Health Technol Asses 2016*; **20**.
5. Ades AE, Price MJ, Kounali D. Proportion of TFI due to Chlamydia: finite mixture modelling of serum antibody titers. *Am J Epidemiol*. In press.