PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A modelling-based evaluation of the costs, benefits and cost-effectiveness of multi-pathogen point-of-care tests for sexually transmitted infections in symptomatic genitourinary medicine clinic attendees
AUTHORS	Huntington, Susie; Burns, Richéal; Harding- Esch, Emma; Harvey, Michael; Hill-Tout, Rachel; Fuller, Sebastian; Adams, Elisabeth; Sadiq, S. Tariq

VERSION 1 – REVIEW

REVIEWER	Kaveh Manavi University Hospitals Birmingham
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	This manuscript is on an ambitious project to investigate the cost effectiveness of point of care testing strategies for sexually transmitted infections. The authors conclude that a POC test for chlamydia, gonorrhoea and mycoplasma for all patients with urethritis would be cost effective. I find this conclusion difficult to believe. I think the problem is with the authors' pre-assumptions in building their models: 1. The authors' definition of symptomatic patients is quite vague. In practice, symptomatic patients account for a small proportion of patients attending any clinic. The argument for each Sexual Health service to adopt/ acquire new POC tests in order to treat cases of mycoplasma, chlamydia, and gonorrhoea unidentified on microscopy would prove prohibitively expensive particularly for smaller centres. 2. Assuming that all POC assays would be cost effective for close to one million patients with symptoms fails to consider the cost of diagnosing so many patients. a) the entire of Sexual Health services in England would probably have to screen close to eight million patients to identify so many patients with symptoms, b) the delivery of such a vast number of service would be through over 300 services in England; some of which would see far less patients with symptoms. I cant see how the cost of POC assays in centres with smaller number of symptomatic patients be cost effective, c) the assumption of empirical treatment of symptomatic patients is incorrect. We do not treat everyone with urethritis for infections. Indeed that is what BASHH guidelines recommend. d) How would early diagnosis of mycoplasma be cost effective when the treatment guidelines for patients with urethritis, PID, and epididymorochitis all recommend antibiotic regimens that also treat this micro-organism? 3. I am not a statistician and found the paper quite difficult to follow. I think the authors assume a higher than average knowledge of statistical modelling of the readers. There are plenty references to supplement information that interrupts the flow of the manuscript. Many clinicians like me may find this a barrier to read the article.

REVIEWER	Vasilios Pergialiotis National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	This is a very interesting technical paper that evaluates the "the costs, benefits and cost-effectiveness of multi-pathogen point-of-care tests for sexually transmitted infections in symptomatic genitourinary medicine clinic attendees". To do so, the authors have constructed a hypothetical cohort that represents the annual number of people that attend GUM services. The study is of clinical importance and very interesting in this field. The authors have meticulously designed the statistical analysis and from the clinicians point of view it seems accurate, however, statistical reviewer is needed to confirm their findings and methodological accuracy. In several points of the manuscript the "Error! Reference source not found.." is detected and this should be corrected. The discussion section is accurate and to the point and needs no further amendment as it accurately presents strengths, pitfalls and directions for current clinical practice and future research.

REVIEWER	Prof.Dr. Abdulbari Bener Prof. Abdulbari Bener, Advisor to WHO, Professor of Public Health, Dept. of Biostatistics & Medical Informatics, Cerrahpaşa Faculty of Medicine, Istanbul University and Istanbul Medipol University, International School of Medicine, 34098 Cerrahpasa-Istanbul, TURKEY Mobile:+90-535 663 9090 Tel: +90-212-414 3041, Fax:+ 90-212-632 0033, e-mail: abdulbari.bener@istanbul.edu.tr, email:abener99@yahoo.com
REVIEW RETURNED	24-Dec-2017

GENERAL COMMENTS	Manuscript ID bmjopen-2017-020394 Title: "Evaluating the costs, benefits and cost-effectiveness of multi-pathogen point-of-care tests for sexually transmitted infections in symptomatic genitourinary medicine clinic attendees" Authors. Susie E Huntington, Richéal M Burns, Emma Harding-Esch, Michael J Harvey, Rachel Hill-Tout, Sebastian S Fuller, Elisabeth J Adam, S Tariq Sadiq Manuscript Type: Original Research Journal: BMJ Open Subject: Review of manuscript The authors evaluating and addresses the costs, benefits and cost-effectiveness of multi-pathogen point-of-care tests for sexually transmitted infections in symptomatic genitourinary medicine clinic attendees. Although, the increasing burden and emerging technologies are being developed that allow rapid and accurate point-of-care tests (POCTs)for multiple sexually transmitted infections, solutions which could address these challenges and help improve patient and public health outcomes. However, health services are under increasing financial pressure, and implementing new technologies may be prohibitively costly for both providers and commissioners of healthcare. 1. Title: The title is adequate.

	2. Abstract: The abstract is adequately addressed. 3. Introduction: The introduction is adequate. 4. Materials and methods: The methodology have been described perfectly. The study design based on the Modeling. The Setting is: Genitourinary medicine (GUM) services in England. The Population is very large: A hypothetical cohort of 965,988 people, representing the annual number attending GUM services symptomatic of lower genitourinary tract infection. Interventions based on: The decision tree model considered costs and reimbursement to GUM services associated with diagnosing and managing STIs. Three strategies using hypothetical point-of-care tests (POCTs) were compared to standard care (SC) using laboratory-based testing. The strategies were: A) dual POC test (POCT) for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG); B) triplex POCT for CT-NG and Mycoplasma genitalium (MG); C) quadruplex POCT for CT-NG-MG and Trichomonas vaginalis (TV). Data came from published literature and unpublished estimates. 5. Results: In the base-case analysis, POC strategy C, a quadruplex POCT, was the most cost-effectiverelative to the other strategies, with an ICER of £36,585 per QALY gained compared to SC when using micro-costing, and cost-savings of £26,451,382 when using tariff costing. POC strategy C also generated the most benefits, with 240,467 fewer clinic attendances, 808 fewer onward STI transmissions, and 235,135 averted inappropriate treatments compared to SC. 6. Discussion: The discussion is well written with the respect literature. 7. Contribution to the literature: The main strength of this study is that it presents the first estimates of the potential public health impact of multi-pathogen POCT strategies made possible by emerging diagnostic technologies. Also, the model used inputs from multiple sources including published studies, published data (for costs), national surveillance data plus expert opinion and in incorporated uncertainty in multiple input parameters by using a second order Monte Carlo PSA and numerous scenarios were assessed in sensitivity analysis. 8. Limitations: The authors reported some of the detailed limitations of this study. The main limitations were the paucity of published data on treatment pathways and gaps in treatment guidelines, which made building a representative SC pathway problematic. There were few published data for some input parameters, for example, the percentage of patients who are presumptively treated without a microbiological result, or percentage returning to clinics after initial treatment. 9. Conclusion: The results of this study suggest that study findings add to the growing evidence-base as many benefits can be achieved by using multi-pathogen POCTs to improve STI diagnosis and management. Further evidence is needed on the underlying prevalence of STIs and SC delivery in the UK to reduce uncertainty in economic analyses Overall, this study is well written and well designed with very large sample size. This study addresses an important public health issue. Although, the study does not contribute novel knowledge to the current literature, but, it would help local policy makers, therefore, the manuscript can be considered for the publication in the Journal “BMJ Open”.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
This manuscript is on an ambitious project to investigate the cost effectiveness of point of care testing strategies for sexually transmitted infections. The authors conclude that a POC test for chlamydia, gonorrhoea and mycoplasma for all patients with urethritis would be cost effective. I find this conclusion difficult to believe. I think the problem is with the authors' pre-assumptions in building their models:

1. The authors' definition of symptomatic patients is quite vague. In practice, symptomatic patients account for a small proportion of patients attending any clinic. The argument for each Sexual Health service to adopt/ acquire new POC tests in order to treat cases of mycoplasma, chlamydia, and gonorrhoea unidentified on microscopy would prove prohibitively expensive particularly for smaller centres.

Authors' response:
We define 'symptomatic' as "symptomatic of lower genitourinary tract infection". The number of symptomatic patients per year (which was included in the model) was estimated using national surveillance data and (GUMCAD 2015 data) and results of our clinician survey. This is mentioned in the methods. In the strengths and weakness section of the discussion (p10) we have now highlighted this as a parameter for which little data were available and may vary between sites.
The extent of the variation in these estimates are unknown which gives little merit to investigating ranges of proportions of symptomatic patients probabilistically. We do highlight throughout the paper where data has been limited and these are areas which we feel further research should focus on.
Regarding adoption of POC tests, we acknowledge in the Introduction that "health services are under increasing financial pressure and implementing new technologies may be prohibitively costly for both providers and commissioners of healthcare."

Reviewer 1:
2. Assuming that all POC assays would be cost effective for close to one million patients with symptoms fails to consider the cost of diagnosing so many patients. a) the entire of Sexual Health services in England would probably have to screen close to eight million patients to identify so many patients with symptoms.

Authors' response:
The model simulates a hypothetical cohort of people with symptoms of a lower genitourinary tract infection based on the actual number attending English GUM services (using GUMCAD data), the estimated proportion with symptoms (based on the clinician survey). Not all these patients have an STI; the prevalence of the different infections is based on published data.

The evidence we generated using a simulated cohort module with varying levels of data quality suggests that certain strategies are more cost-effective than others relative to current practice. However, we clearly acknowledge the degree of uncertainty in our estimates with the wide-ranging sensitivity analyses undertaken.

Reviewer 1:
b) the delivery of such a vast number of service would be through over 300 services in England; some of which would see far less patients with symptoms. I can't see how the cost of POC assays in centres with smaller number of symptomatic patients be cost effective.

Authors' response:
It is difficult to comment on to what extent the size of a clinic would impact costs – we used average national data for staff costs. We have included an additional paragraph in the discussion (p11) to highlight that costs will vary between sites.

Reviewer 1:
c) the assumption of empirical treatment of symptomatic patients is incorrect. We do not treat everyone with urethritis for infections. Indeed, that is what BASHH guidelines recommend.

Authors' response:
Sites differ in their use of empirical treatment. To address this, in the scenario analysis we included some scenarios (numbers 21-24) where different levels of presumptive treatment were represented, including no presumptive treatment.

Reviewer 1:
d) How would early diagnosis of mycoplasma be cost effective when the treatment guidelines for patients with urethritis, PID, and Epididymorochitis all recommend antibiotic regimens that also treat this micro-organism?

Authors' response:
In the Introduction, we reference a study which found that azithromycin and doxycycline are effective at curing only two-thirds and one-third of MG infections respectively.
The current recommendations are: for non-gonococcal urethritis, doxycycline 100mg twice a day for seven days or azithromycin 1g as a single dose; for PID, intramuscular ceftriaxone 500mg single dose plus oral doxycycline 100mg BD for 14 days plus oral metronidazole 400mg BD for 14 days or oral ofloxacin 400mg BD for 14 days plus oral metronidazole 400mg BD for 14 days; for epididymo-orchitis, ceftriaxone 500mg intramuscularly single dose, plus oral doxycycline 100mg bd for 10-14 days or doxycycline 100mg BD for 10-14 days, or Ofloxacin 200mg by mouth twice daily for 14 days. The empirical treatment for the latter two may include ceftriaxone for anti-gonococcal treatment dependent on context. None of these agents are very effective against Mycoplasma genitalium. In the case of tetracylines, this has been the case for decades and for macrolides such as azithromycin, increasing 23S rRNA mutant mediated resistance has meant that fewer circulating strains are likely to be susceptible. Mycoplasma genitalium has no cell wall and therefore is not susceptible to B-lactams such as ceftriaxone.

Reviewer 1:
3. I am not a statistician and found the paper quite difficult to follow. I think the authors assume a higher than average knowledge of statistical modelling of the readers. There are plenty references to supplement information that interrupts the flow of the manuscript. Many clinicians like me may find this a barrier to read the article.

Authors' response:
Although the paper assessed a clinical area, it is a health economic evaluation and is targeted at decision makers, policy analysts, applied researchers and health economists.

The aim of the paper was to undertake a robust statistical exercise using simulation modelling techniques and as such the nomenclature used needed to adhere to national and international guidance in the area of economic modelling.

We do understand the concerns of the reviewer in relation to the flow of the paper; however, the frequency of references included are necessary for validating the methods and findings. We feel the level of citation is consistent with other simulation studies. We have tried to include the main

information in the main body of the article whilst including additional content, which might be of interest to some readers, in the supplementary material.

Reviewer: 2
In several points of the manuscript the "Error! Reference source not found.." is detected and this should be corrected.

Authors' response:
This error occurred when the document was converted to a PDF and has now been fixed.

There were no further comments from Reviewer 2 or Reviewer 3 that required a response.

VERSION 2 – REVIEW

REVIEWER	Vasilios Pergialiotis National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	The present article is an excellent example of cost-effectiveness modelling and merits publication as it may be used as an example for future research in various medical sub specialties.

REVIEWER	Kaveh Manavi University hospitals birmingham, uk
REVIEW RETURNED	23-Feb-2018

GENERAL COMMENTS	I am sorry to appear negative here, but i seriously struggle with this modelling. The authors make a pivotal and incorrect assumption in their modelling, that all who attend GUM clinics are symptomatic and should therefore benefit from poc assays. The fact is that over 60% of patients attending gum services are asymptomatic and attend for peace of mind. This signifcantly reduces tbe arguement for cost effectiveness of the use of poc for mg. the authors acknowledge that in their cost effective analysis they have not included staff time or training. These are the most significant costs to any health services. also, the modelling is based on too many assumptions, for a number of which we have published data. The authors clarify that this study is aimed for commissioners to assist them to make decisions. This makes me quite concerned, a statistical modelling with limited appilcation, and significant personal (albeit from a small number of clinicians) assumptions, makes a conclusion that to the rest of us appears a costly excercise. How can that be justified? Finally, the only advantage of a poc assay over our current soc is that patients with mg will receive treatment on their first visit. The authors agree that the first line treatment for mg is similar to that for chlamydia. That is if one is diagnosed with ngu on microscopy on the day (based on authors' estimate with a sensitivity of 75%) then one would be treated for mg on the day. How can we then justify cost effectiveness of mg poc test for those patients? Based on the above, i regret that i would not be able to support the publication of the article.

VERSION 2 – AUTHOR RESPONSE

Reviewer Comments and Author's Revisions and Responses

Author responses are within text.

Reviewer: 2

The present article is an excellent example of cost-effectiveness modelling and merits publication as it may be used as an example for future research in various medical sub specialties.

No response needed

Reviewer: 1

1) I am sorry to appear negative here, but I seriously struggle with this modelling. The authors make a pivotal and incorrect assumption in their modelling, that all who attend GUM clinics are symptomatic and should therefore benefit from poc assays. The fact is that over 60% of patients attending gum services are asymptomatic and attend for peace of mind. This significantly reduces the argument for cost-effectiveness of the use of poc for mg.

Authors' Response:

The model does not assume that all patients are symptomatic but only symptomatic patients were included in the model. The number of symptomatic patients attending GUM clinics in England is calculated using national surveillance data, as this does not differentiate symptomatic and asymptomatic, and the median percentage symptomatic from the clinician survey data (50% MSM, 50% women and 40% MSW).

To clarify this point and to show the calculations, we have made changes to the text in the Epidemiology and clinical parameters sub-section of the methods (p6).

The text now reads:

"The total annual number of people attending English GUM services for STI testing was obtained from national surveillance data (GUMCAD 2015 data).7 The number of attendees who were symptomatic was then calculated using the median percentages reported in the clinician survey (50% of 1,181,574 for women; 40% of 647,661 for men-who-have-sex-with-women [MSW]; and 50% of 232,274 for men-who-have-sex-with-men [MSM]). The model simulated a total of 965,988 symptomatic attendees and by subgroup, 590,787 women, 259,064 MSW and 116,137 MSM."

2) The authors acknowledge that in their cost-effective analysis they have not included staff time or training. These are the most significant costs to any health services.

Authors' Response:

The cost of staff time was included in the cost calculations. This is stated in the Cost and utility parameters subsection (p9). The cost of implementing a change in practice including training staff to use the POC test was not considered.

To clarify these points, we have amended the text after Table 2 in the Methods (p12). The text now reads:

“Costs of implementing a change in practice, including training costs, were not considered. However, the unit costs used for staff time, which were considered, do incorporate the cost of training courses.”

3) The modelling is based on too many assumptions, for a number of which we have published data.

Authors' Response:

Published data were used where available. Assumptions are necessary in the absence of consensus on the pathway and published parameter estimates but all were extensively tested in the robust collection of scenarios which we feel greatly add to the evidence base. We performed probabilistic sensitivity analysis (PSA) using distributions parametrised to account for uncertainty (p12) and found that model results were still consistent.

We have outlined the limitations of the model, highlighting the level of uncertainty given the paucity of data and have been cautious in our language around cost-effectiveness.

4) The authors clarify that this study is aimed for commissioners to assist them to make decisions. This makes me quite concerned, a statistical modelling with limited application, and significant personal (albeit from a small number of clinicians) assumptions, makes a conclusion that to the rest of us appears a costly exercise. How can that be justified?

Authors' Response:

With regard to application, there is a dual CT/NG test currently available (mentioned on p4). Although no triplex or quadruplex POC STI tests are currently available, there is at least one multiplex STI assay currently being developed for the market www.digitalhealth.net/2017/08/atlas-genetics-awarded-2m-innovate-uk-contract/ We have not mentioned and referenced this in the discussion (p19).

5) Finally, the only advantage of a poc assay over our current soc is that patients with mg will receive treatment on their first visit. The authors agree that the first line treatment for mg is similar to that for chlamydia. That is if one is diagnosed with ngu on microscopy on the day (based on authors' estimate with a sensitivity of 75%) then one would be treated for mg on the day. How can we then justify cost effectiveness of mg poc test for those patients?

Authors' Response:

There are numerous advantages to a POC assay as outlined in the discussion section:

The model showed that fewer patients had return visits (not just those with MG) and fewer people were given inappropriate antibiotics (p18).

Previous research also shows that POC testing saves patient's out-of-pocket expenses, and productivity losses as well as reducing lost to follow up, anxiety, duration of symptoms and reproductive health sequelae (p19).

6) Based on the above, I regret that I would not be able to support the publication of the article.

Authors' Response:

I hope that we have responded to each of the points you raised and made the necessary changes to address them.