PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study
AUTHORS	Kasaie, Parastu; Schumacher, Christina; Jennings, Jacky; BERRY, STEPHEN; Tuddenham, SA; Shah, Maunank; Rosenberg, Eli; Hoover, Karen; Gift, Thomas; Chesson, Harrell; German, Danielle; Dowdy, David

VERSION 1 – REVIEW

REVIEWER	Janneke Heijne National Institute for Public Health and the Environment (RIVM), the Netherlands
REVIEW RETURNED	19-Jul-2018

GENERAL COMMENTS	Thank you for giving me the opportunity to review this paper. The authors used an individual based model to analyse the impact of CT/NG diagnoses as entry point for starting PrEP among MSM. They conclude that it is an effective strategy in terms of reducing HIV incidence.
	The research question addressed in this manuscript is very topical. I have however, major concerns about the way certain aspects are incorporated in the model.
	I appreciate that the authors submitted the reviewer comments from another journal along with the paper. I agree with the points made by the reviewers, especially regarding their concern about combining CT and NG as one entity. However, I do not think that the authors correctly addressed this comment in the manuscript. Both infections have very different transmission dynamics. NG has a short infectious period, is often symptomatic and has a high transmission probability per sex act. Due to this specific natural history, NG can mainly be sustained in high risk networks. On the other hand, CT has a longer infectious period (over a year), few symptomatic infections and hence a low transmission probability per sex act. CT is therefore not necessarily concentrated in high risk networks, and is also seen among MSM with only a few partners in the last year. By combining parameters of both infections, neither transmission dynamics are accurately captured. I suggest the authors to make a decision on parameter values based on one infection only, being NG the preferred infection of choice.

As also highlighted by the previous reviewers as a key concern, is the way how the anatomical sites of infections are incorporated. And again, I feel that the authors did not adequately address this comment in the manuscript. The model simply distribute the infections randomly to the three atomic locations, but does not incorporate oral sex (or different condom use percentage for this type of sex as mentioned by a previous reviewer), or differences in clearance rates per sites or different transmission probabilities of CT/NG per site. This is again trying to incorporate something complex in the model in a simplified way, but not capturing the transmission dynamics accurately.

Since the authors used an individual based model, it is difficult to grasp how the model really works and how much of the results are a result of the assumptions in the model. The authors did a good job by providing an extensive supplementary document describing the model. However, many details are missing. First, the percentage of MSM in each of the 3 activity classes and the number of partners in each activity class (by age) is lacking. A comparison of data and model regarding sexual behavior data would improve the credibility of the model. The authors tried to do this in Figure S5 (where, by the way, model and data are not that similar), but I would like to see this Figure for each activity class separately and a Figure for casual partnerships (per activity class). Furthermore, it would be informative to see how the number of partners change per age(group). Second, it is important to know what the HIV prevalence in each activity class is in the model. Without knowing this, a reduction in HIV incidence can also be caused by a saturation effect in which (almost all) MSM in a certain activity class are HIV infected. Third, it is important to understand the mixing in the model. From the supplementary material it is unclear how this is incorporated, i.e. is mixing only based on age and race and not on activity class? If not, than mixing is random across activity classes, which can have major consequences on HIV transmission dynamics (if one group has high HIV prevalence). Furthermore, is serosorting incorporated in the model? If not, again, this can have major implications for HIV transmission. Fourth, it is important to know whether the model captures the HIV and CT/NG co-infection rates accurately. If the CT/NG infections are mainly concentrated in people without HIV in the model, a strategy of providing PrEP to those diagnosed with CT/NG is more effective than when all CT/NG infections are in HIV positive MSM. Therefore, I suggest the authors to compare model output and data on co-infection rates. If data is not available, please provide co-infection rates from the model only. Last, please provide a Figure with the PrEP uptake percentage over time in each risk class under each of the 3 studied interventions.

Other comments:
1) From the supplementary material it looks like most of the behavioural data that is used in the model comes from the BESURE study. Looking at Table S2, the participants in this study have very high prevalence of HIV infection, suggesting that this reflects a high risk group. So how generalizable are the results from this model to the entire MSM population?
2) It is striking that after about 10 years the percentage of total MSM on PrEP is less than 1% (2C), but an enormous amount of HIV infections are averted (2B). Please explain. Is this real or is this a result of the assumptions in the model and the network it's

	creating?
	3) Last lines of the last paragraph of the results section: this belongs to the discussion section.
	4) Discussion: please add as a limitation that all MSM are "born" in a risk class and stay there their entire life.
	5) Discussion: please expand the limitation section and describe how each limitation influences the results.
	6) Figures: I assume that this is the result of multiple runs, please provide credible intervals (or inter quartile ranges) around each line.
	7) Figure S6A: this is what the model is calibrated too, so it is logic that it looks identical to the data. Please remove.
	8) Figure S7: please use more informative labeling than "pStartStbPart+" and enlarge the figures to improve readability.

REVIEWER	Randolph D. Hubach, PhD, MPH Oklahoma State University--Center for Health Sciences USA
REVIEW RETURNED	20-Aug-2018

GENERAL COMMENTS	The authors have gone to great lengths to address the comments presented from the original reviewers. By doing so the manuscript is greatly improved and is ready for publication.

Reviewer: 1
Reviewer Name: Janneke Heijne
Institution and Country: National Institute for Public Health and the Environment (RIVM), the Netherlands
Please state any competing interests or state 'None declared': None declared

Thank you for giving me the opportunity to review this paper. The authors used an individual based model to analyse the impact of CT/NG diagnoses as entry point for starting PrEP among MSM. They conclude that it is an effective strategy in terms of reducing HIV incidence.

The research question addressed in this manuscript is very topical. I have however, major concerns about the way certain aspects are incorporated in the model.

1. I appreciate that the authors submitted the reviewer comments from another journal along with the paper. I agree with the points made by the reviewers, especially regarding their concern about combining CT and NG as one entity. However, I do not think that the authors correctly addressed this comment in the manuscript. Both infections have very different transmission dynamics. NG has a short infectious period, is often symptomatic and has a high transmission probability per sex act. Due to this specific natural history, NG can mainly be sustained in high risk networks. On the other hand, CT has a longer infectious period (over a year), few symptomatic infections and hence a low transmission probability per sex act. CT is therefore not necessarily concentrated in high risk networks, and is also seen among MSM with only a few partners in the last year. By combining parameters of both infections, neither transmission dynamics are accurately captured. I suggest the authors to make a decision on parameter values based on one infection only, being NG the preferred infection of choice.

We thank the reviewer for this comment and agree that there are important differences in CT and NG infections with regard to the period of infectiousness, onset of symptoms and per act risk of transmission. Despite these differences in natural history, however, we chose to combine these entities because the primary focus of this analysis is on the impact of using gonorrhea and chlamydia diagnosis as an entry point for PrEP, not on precisely characterizing the transmission dynamics of CT and NG in our population. For example, we do not focus on CT/NG control strategies but rather use a primary outcome of HIV infections averted. There is tremendous overlap in terms of clinical practice across the two infections, including: (a) gonorrhea and chlamydia are generally diagnosed (and often empirically

treated) in tandem, (b) CDC STD Treatment Guidelines recommend screening sexually active MSM for both gonorrhea and chlamydia at the same intervals, and (c) CDC PrEP guidelines include both gonorrhea and chlamydia infection as indicative of substantial HIV risk. As such, in considering the most likely policy or decision-making outcomes, we think it is unlikely that only one of these two infections (and not the other) would be considered as an entry point for PrEP. If one were to include only one infection in a model, therefore, such a model would probably greatly underestimate the potential impact (on the primary outcome of HIV infections averted) of the more likely policy scenario that would include both infections. This is especially true for gonorrhea, as the prevalence of gonorrhea is substantially lower than that of chlamydia.

An alternative would be to build a model of NG and CT as separate infections, but unfortunately, calibrating a model of 3 co-circulating epidemics of HIV, NG and CT is a tremendous task (as each additional infection included expands the complexity of the model exponentially). Not only do we lack good data for calibrating such a three-epidemic model, but to construct such a model would likely take months, far beyond the firm 30-day deadline given by the journal to respond. We have now included this as a limitation in our Discussion section.

As a final note, there is also substantial uncertainty regarding these natural history parameters. In a systematic review of dynamic models of Chlamydia infections, Davies et al. (2014)* found wide variation in published estimates of natural history parameters; for example, the proportion asymptomatic ranged from 25% to 100% across models. This level of uncertainty suggests that – even if NG and CT were modeled as separate infections – the uncertainty ranges of such parameter values would greatly overlap between the two infections. To address the specific points raised by the reviewer, NG may be more likely to be symptomatic than CT in the case of urethral infection, but in MSM, asymptomatic NG (and CT) are common. For example, Kent CK, et al. 2005** reports that >85% of rectal NG infections among MSM were asymptomatic. Furthermore, the concept that virtually all urogenital NG/CT infections are symptomatic is being challenged by the use of NAAT (with a higher sensitivity than culture). NAAT-based community prevalence studies have found high prevalence of asymptomatic urogenital NG (and CT) infection; for example, Farley TA, et al. 2003*** found that that 45% of all prevalent cases of NG were never symptomatic. Such emerging evidence suggests that – despite classical teaching to the contrary – gonorrhea may not have a significantly greater propensity toward asymptomatic infection than chlamydia, particularly among MSM populations where rectal and oral infection is common, and screening for both diseases is performed among asymptomatic individuals.

Due to the importance of this particular concern, we discussed the best approach among all coauthors, and after much consideration, we believe that the optimal approach – considering all of these factors – remains to combine NG and CT into a single entity. We hope that the Reviewer can appreciate the reasoning behind this decision. To further elucidate the limitations of this approach, we have modified the discussion section (Page 9, line 257-Clean version) to make it clear that despite the fact that we are treating these infections as a single entity and have used composite parameter values to describe the natural history of both diseases, there are indeed important difference between NG and CT infections. Further research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics.

* Davies B, Anderson SJ, Turner KM, Ward H. How robust are the natural history parameters used in chlamydia transmission dynamic models? A systematic review. Theoretical Biology and Medical Modelling. 2014 Dec;11(1):8.

* *Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, Klausner JD. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clinical Infectious Diseases. 2005 Jul 1;41(1):67-74.

***Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. Preventive medicine. 2003 Apr 1;36(4):502-9.

2. As also highlighted by the previous reviewers as a key concern, is the way how the anatomical sites of infections are incorporated. And again, I feel that the authors did not adequately address this comment in the manuscript. The model simply distribute the infections randomly to the three atomic locations, but does not incorporate oral sex (or different condom use percentage for this type of sex as mentioned by a previous reviewer), or differences in clearance rates per sites or different transmission probabilities of CT/NG per site. This is again trying to incorporate something complex in the model in a simplified way, but not capturing the transmission dynamics accurately.

We thank the reviewer for raising this point. Once again, we agree with the reviewer that the lack of specific detail regarding the anatomical site of infection is a limitation of our approach – one made primarily due to data limitations. Reliable, population-representative data on the relative frequency of oral-only versus oral-plus-anal versus anal-only sex are not available in Baltimore and, to our knowledge, are not available in other settings either. Similarly, data on the relative transmissibility of NG/CT from/to different anatomical sites are unreliable. All models are simplifications of reality, but simplifications relating to anatomical site of infection are at least in line with those of other published models (see, for example, Jenness S, et al., Clin Infect Dis 2017; 65:712-718, which also modeled only urogenital and rectal infection and transmission).

Given that we do not have the data necessary to explicitly incorporate transmission from one site to the next, we adopted a simplified approach that – as noted by the reviewer – does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infection at each anatomical site. Since the goal of this model is not to comprehensively represent the dynamics of NG/CT transmission but rather to estimate the impact of PrEP strategies for HIV that incorporate NG/CT screening and treatment, we feel that it is more appropriate to adopt this simplified approach (which may get some of the specific transmission dynamics wrong but should result in the appropriate marginal distributions of infection by each anatomical site) than to incorporate data-free assumptions about the relative frequency of oral-only versus oral-plus-genital sex and the relative transmissibility of NG/CT from each anatomical site to the other.

We note this simplification as a limitation in our Discussion section (p. 9, line 266-clean version) and have noted the probability of NG/CT infection at each anatomic site in Table S7 in the Supplementary Material.

3. Since the authors used an individual based model, it is difficult to grasp how the model really works and how much of the results are a result of the assumptions in the model. The authors did a good job by providing an extensive supplementary document describing the model. However, many details are missing. First, the percentage of MSM in each of the 3 activity classes and the number of partners in each activity class (by age) is lacking. A comparison of data and model regarding sexual behavior data would improve the credibility of the model. The authors tried to do this in Figure S5 (where, by the way, model and data are not that similar), but I would like to see this Figure for each activity class separately and a Figure for casual partnerships (per activity class).

We thank the reviewer for their careful consideration of modeling details as presented in the Supplementary Material and have expanded this document to reflect the requested changes.

As now more fully described in Section S1.3.1, we have modeled the heterogeneous level of sexual activity among MSM by assuming three sexual activity classes, each corresponding to a lifetime level of engagement in casual partnerships. As now explained in this section, the use of three sexual activity classes is a previously published* modeling construct, not an explicitly measurable feature of an individual. We use this construct to more accurately represent "tails" in the observed distribution of (self-reported) sexual activity in data from Baltimore** that are potentially important drivers of STI transmission dynamics but not capturable assuming a simple Poisson process of sexual partnership formation. We therefore arbitrarily assign equal numbers of individuals to these three sexual activity classes, and then calibrate the relative frequency of casual partnership formation in each of these classes to most closely fit the observed distribution among MSM in Baltimore. We apologize for the omission of these relative frequency parameters from the supplementary material and now include them in Table S7.

In response to this comment, we have also constructed a figure to describe the frequency of annual partnerships (and annual casual partnerships) for MSM in each sexual activity class (Figure S7, section 2.3.1). Since these three sexual activity classes are a modeling construct, there are no corresponding data according to "sexual activity class" per se, but we have calibrated the coefficients governing these classes to represent the overall distribution of partnerships at a population level as shown in Figure S4 and Figure S5.

*Kasaie P, Pennington J, Shah MS, Berry SA, German D, Flynn CP, Beyrer C, Dowdy DW. The Impact of Preexposure Prophylaxis Among Men Who Have Sex With Men: An Individual-Based Model. Journal of acquired immune deficiency syndromes (1999). 2017 Jun;75(2):175-83.

** Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS). 2015.

Limitations....

4. Furthermore, it would be informative to see how the number of partners change per age(group). Second, it is important to know what the HIV prevalence in each activity class is in the model. Without knowing this, a reduction in HIV incidence can also be caused by a saturation effect in which (almost all) MSM in a certain activity class are HIV infected.

We agree with the reviewer that network characteristics can strongly shape the epidemiological impact of PrEP; indeed, our sensitivity analysis in Figure S14-17 illustrates that a more segregated network (i.e., more individuals in the highest sexual activity class) results in greater impact for PrEP. In response to this important comment, we have extended the supplementary material to include additional figures displaying the frequency of partnerships by age and sexual activity class (Figure S6 and S7, section 2.3.1), as well as the distribution of HIV and NG/CT incidence by age and sexual activity class (Figure S10, Sec 2.4.2) .

5. Third, it is important to understand the mixing in the model. From the supplementary material it is unclear how this is incorporated, i.e. is mixing only based on age and race and not on activity class? If not, than mixing is random across activity classes, which can have major consequences on HIV transmission dynamics (if one group has high HIV prevalence). Furthermore, is serosorting incorporated in the model? If not, again, this can have major implications for HIV transmission.

In response to this comment, we now clarify that we currently model mixing as assortative by age and race only, as supported by available data through the BESURE study*. Since sexual activity class is a modeling construct rather than a measurable feature of an individual (as explained above), there are no data to describe assortative mixing by activity class per se. Similarly, lacking data on serosorting among primary and casual partnerships, we did not explicitly incorporate this into the model. We now note the lack of data on assortative mixing by sexual frequency and by HIV status (independent of sexual frequency) as a limitation of the model in our discussion section (Page 9, line 270-clean version). Moreover, we have we have generated additional figures to report the simulated frequency of sexual partnerships by sexual activity classes (e.g., High-High, High-Med, etc.) and also HIV serostatus (See Figure S11 and Figure S12, section 2.6 in Supplementary Material).

* Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS). 2015.

6. Fourth, it is important to know whether the model captures the HIV and CT/NG co-infection rates accurately. If the CT/NG infections are mainly concentrated in people without HIV in the model, a strategy of providing PrEP to those diagnosed with CT/NG is more effective than when all CT/NG infections are in HIV positive MSM. Therefore, I suggest the authors to compare model output and data on co-infection rates. If data is not available, please provide co-infection rates from the model only. Last, please provide a Figure with the PrEP uptake percentage over time in each risk class under each of the 3 studied interventions.

While we agree with the reviewer that the level of coinfection between NG/CT and HIV is important, we lack data on these coinfection levels among MSM in Baltimore. Unpublished results from analysis of SSuN data from 2008 to 2013 in 12 jurisdictions suggest that about 8% of patients diagnosed with NG had a previous HIV diagnosis, and among the remaining, 69% received a subsequent HIV test within the first 30 days after STI diagnosis; however, the subsequent proportion of patients diagnosed with HIV coinfection is not clear. We therefore took a conservative approach, assuming that the only correlations between these infections would be induced by age- and race-specific assortative mixing, plus differentiation of individuals into different sexual activity classes. To the extent that HIV and CT/NG co-locate among similar populations beyond these characteristics, one would expect that CT/NG-targeted PrEP strategies would have even greater impact than projected in this model.

In response to this appropriate concern, we now explicitly report that, in the absence of PrEP, 20% [18 – 22.0%] of incident NG/CT cases in our simulation were coinfected with HIV (Page 7, line 195) – somewhat lower than the overall HIV prevalence of 22% (reported HIV prevalence by MDHMH*). These results suggest that our underlying assumptions for overlapping the network of sexual contacts may not impose a high rate of correlation between the two diseases, and if anything, our estimates of the impact of STI-based PrEP may be conservative.

We now also provide a Figure (Figure S13) illustrating the percentage of individuals on PrEP who fall into each of the three sexual activity classes and age-groups under each intervention strategy. As expected, targeting PrEP at MSM diagnosed with STIs provides an efficient approach for providing PrEP to high-risk individuals in the high sexual activity class and younger age groups (Figure S13-Panels A & D)

* Maryland Department of Health and Mental Hygiene, MDHMH. 2016 Baltimore City Annual HIV Epidemiological Profile. Baltimore: 2016.
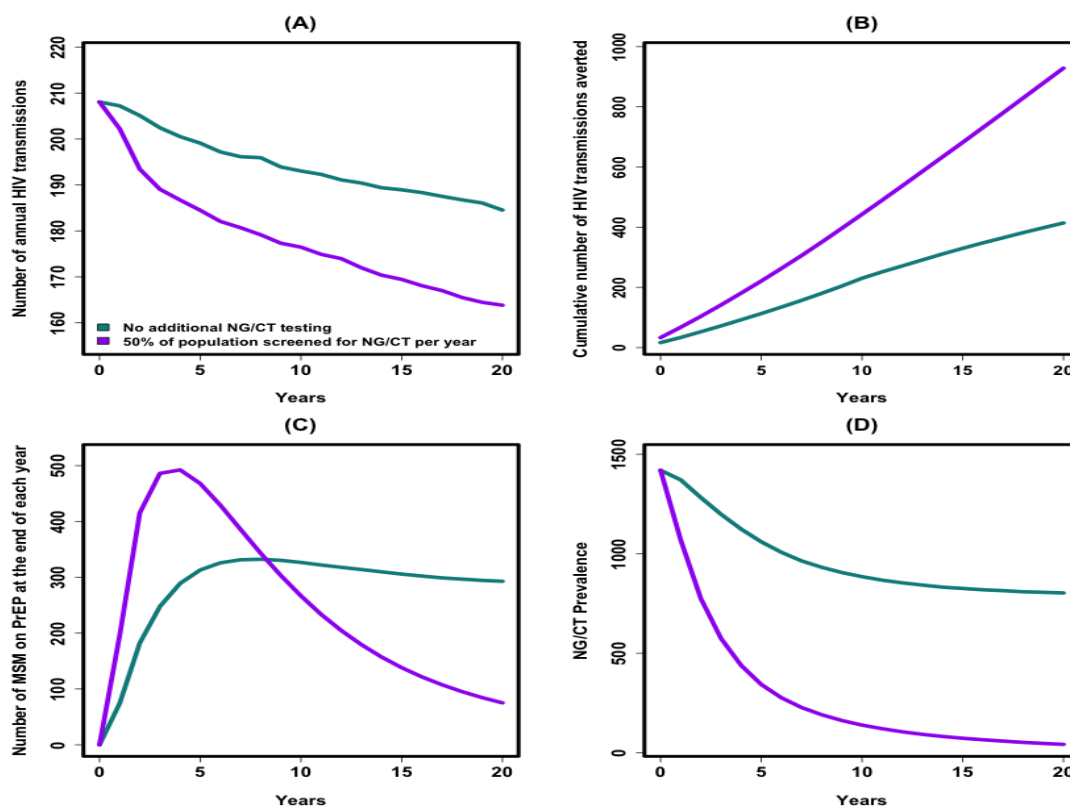
Other comments:
1) From the supplementary material it looks like most of the behavioral data that is used in the model comes from the BESURE study. Looking at Table S2, the participants in this study have very high prevalence of HIV infection, suggesting that this **reflects a high risk group**. So how generalizable are the results from this model to the entire MSM population?

As the reviewer has correctly pointed out, the BESURE study is our main source of data for calibrating the sexual risks and the contact network components, and its venue-based sampling approach does result in capture of a higher-risk group, particularly according to age (i.e., sampled population is younger than the overall population of MSM). As we have reported previously*, we discussed this concern specifically with the BESURE investigators, who felt that the BESURE data were representative of the sexual activity patterns of younger MSM. We therefore incorporated a function of decreasing sexual activity with age, which allowed for a better (though still not perfect) fit to the observed data. Importantly, the model most accurately reflects sexual frequency and HIV incidence in the 15-29 year age stratum – the same age stratum in which NG/CT dynamics are likely to have their greatest effect on HIV incidence. We feel that a full discussion of this issue is beyond the scope of the present manuscript – having been published before – but we have included it in Section 2.3.1 of the Supplementary Material.

* Kasaie P, Pennington J, Shah MS, Berry SA, German D, Flynn CP, Beyrer C, Dowdy DW. *The Impact of Preexposure Prophylaxis Among Men Who Have Sex With Men: An Individual-Based Model. Journal of acquired immune deficiency syndromes (1999). 2017 Jun;75(2):175-83*

2) It is striking that after about 10 years the percentage of total MSM on PrEP is less than 1% (2C), but an enormous amount of HIV infections are averted (2B). Please explain. Is this real or is this a result of the assumptions in the model and the network it's creating?

We thank the reviewer for noticing this issue and apologize for the confusion. We have corrected a minor error in the labels for each figure panel to now reflect A. Annual number of HIV transmissions, and B. Cumulative number of HIV transmissions averted.

(A) Number of annual HIV transmissions vs Years

(B) Cumulative number of HIV transmissions averted vs Years

(C) Number of MSM on PrEP at the end of each year vs Years

(D) NG/CT Prevalence vs Years

Legend:
- No additional NG/CT testing
- 50% of population screened for NG/CT per year

In response to the reviewer's comment on the low number of MSM receiving PrEP (Figure 2c), our results suggest that at baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on PrEP (i.e., uptake = 60%), around 216 MSM will start PrEP each year (some of whom will discontinue and/or restart at future timepoints, as PrEP eligibility is assessed on a three-month basis). Under these assumptions and the baseline level of NG/CT diagnosis (green line), the number of MSM receiving PrEP is projected to increase through the first 8 years of the program, reaching a total of 332 [327 – 338] MSM on PrEP, and to fall afterward as the incidence of NG/CT slowly declines (Figure 2C). This decline is much faster in the additional NG/CT screening scenario (purple line). Assuming an adherence of 60% among those on PrEP, HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 2A). This corresponds to averting 318 [253 – 385] potential HIV transmissions (Figure 2B). The reason for the continued increase in cumulative HIV infections averted – particularly in the expanded-screening scenario – despite relatively fewer individuals on PrEP is a reduction in secondary and tertiary HIV infections (i.e., HIV infections averted by PrEP in years 0-10 then lead to averted second- and third-generation HIV infections in years 10-20).

1) Last lines of the last paragraph of the results section: this belongs to the discussion section.

We have moved the last lines of the results section on additional sensitivity analysis on the role of behavioral disinhibition to the Discussion section (see page 9. Line 276-clean version)

2) Discussion: please add as a limitation that all MSM are "born" in a risk class and stay there their entire life.

We have noted this as a limitation of our model in the discussion (see page 9. Line 271-clean version)

3) Discussion: please expand the limitation section and describe how each limitation influences the results.

We have expanded the limitation section to include additional simplifying assumptions used in development of our simulation model and have discussed the potential implications of these assumptions on our results.

6) Figures: I assume that this is the result of multiple runs, please provide credible intervals (or inter quartile ranges) around each line.

We thank the reviewer for raising this point. The reviewer is correct in that each line is the result of multiple runs. However, we feel that showing uncertainty around these lines may be misleading to the average reader because the uncertainty from one run to the next is much greater than the uncertainty in the comparison of two different PrEP scenarios within the same run. Thus, credible intervals around each line may overlap tremendously, but the corresponding credible interval around the *difference* between impact of different PrEP scenarios (the main purpose of this figure) does not approach zero. It is also difficult to visually represent data where credible intervals are wide and apparently overlapping. To address the reviewer's concern, we have included a copy of the main figures with inclusion of 95% uncertainty ranges in section 4 of the supplementary material (Figure S20 & S21), but we have retained the original figures in the primary manuscript.

7) Figure S6A: this is what the model is calibrated too, so it is logic that it looks identical to the data. Please remove.

The goal of this figure was to illustrate the effectiveness of our calibration procedure. While one of course always hopes that a model will replicate the data to which it is calibrated, it is an important assessment of any model that it actually do so. As such, we think it is important to show to readers that our calibration process actually accomplished the goal that it was intended to.

To address the reviewer's concern, we have added language to highlight that this graph is only meant to show the closeness between model's projections and the data to which it is calibrated, not to suggest that the underlying data are therefore more likely to be correct, nor that this is an external validation of the model.

8) Figure S7: please use more informative labeling than "pStartStbPart+" and enlarge the figures to improve readability.

We apologize for the confusion caused by previous labeling. We have now revised the figures with more clear description of each parameter and have separated each panel into a separate figure with enlarged fonts for better readability (Figure S14 to S17).

Reviewer: 2
Reviewer Name: Randolph D. Hubach, PhD, MPH
Institution and Country: Oklahoma State University--Center for Health Sciences, USA
Please state any competing interests or state 'None declared': None

The authors have gone to great lengths to address the comments presented from the original reviewers. By doing so the manuscript is greatly improved and is ready for publication.

VERSION 2 – REVIEW

REVIEWER	Janneke Heijne National Institute for Public Health and the Environment (RIVM), the Netherlands
REVIEW RETURNED	30-Oct-2018

GENERAL COMMENTS	Thank you for giving me the opportunity to see a revised version of the manuscript. I appreciate the comprehensive responses from the authors to the comments and the manuscript improved substantially. Especially the appendix improved which now provides a clearer overview of the partnership network that the

| | model creates and the distribution of the infections over the network.

Although I believe that the use of NG/CT as one entity remains a weakness of the study, I agree with the authors that it is not necessarily the goal of the study to precisely characterize transmission dynamics of CT and NG in the population, but rather use this as an entry point for starting PrEP. Figure S10 is very important in this, and it I suggest the authors to move this figure to the main text.

Last, it looks like something went wrong when adding the labels to the Figures S15 to S17 since the values seem different for some parameters compared to the previous version. |

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Janneke Heijne
Institution and Country: National Institute for Public Health and the Environment (RIVM), the Netherlands
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Thank you for giving me the opportunity to see a revised version of the manuscript. I appreciate the comprehensive responses from the authors to the comments and the manuscript improved substantially. Especially the appendix improved which now provides a clearer overview of the partnership network that the model creates and the distribution of the infections over the network.

Thank you for taking the time to review this manuscript again and considering our responses to your previous comments.
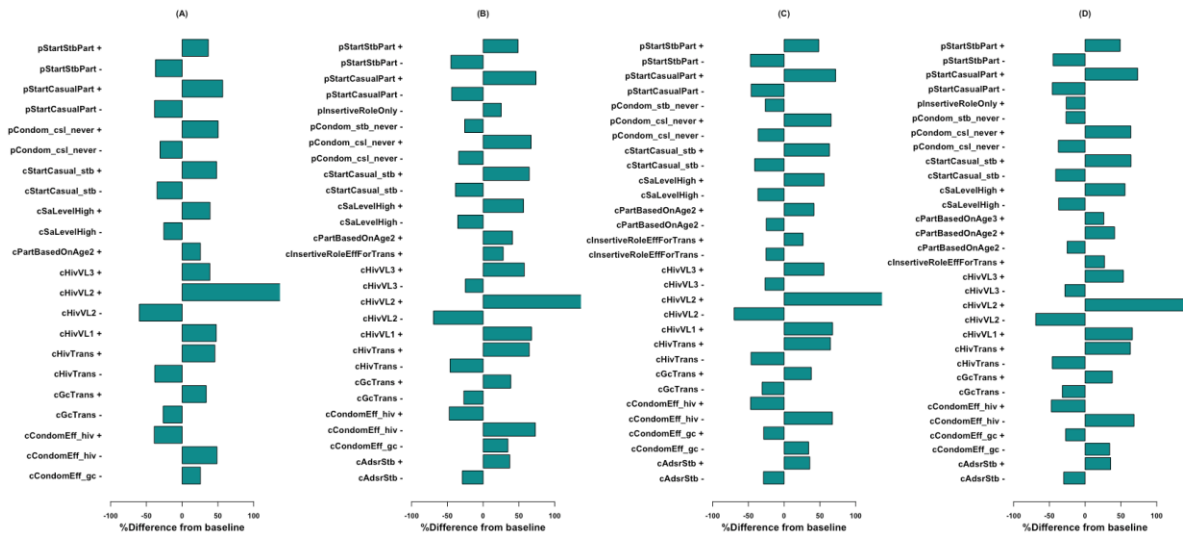
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Thank you for this suggestion. We have moved figure S10 to the main manuscript and included it as Figure 2 in the revised version.

Last, it looks like something went wrong when adding the labels to the Figures S15 to S17 since the values seem different for some parameters compared to the previous version.

Based on your suggestion, we have renamed the parameters appearing in the first figure (below) to be more descriptive, and have changed the order of parameters based on name. No values for any parameters have changed; the visual difference is due to the different layout and order of parameters.

Original figure:

New Figures: