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Title page

Potential effect of antibacterial mouthwash on the incidence of *Neisseria gonorrhoeae* among men who have sex with men: a mathematical modelling study

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ABSTRACT

Objectives: The incidence of gonorrhoea is rising in many countries, and the antimicrobial resistance of *Neisseria gonorrhoeae* is increasing. Mouthwash is a potential new intervention for reducing gonorrhoea transmission without using antibiotics. We modelled the effect that antibacterial mouthwash may have on the incidence of gonorrhoea.

Design: We developed a mathematical model to analysis the transmission of gonorrhoea between each anatomical site (oropharynx, urethra and anorectum) in MSM. We constructed four scenarios: (1) mouthwash had no effect; (2) mouthwash increased the susceptibility of the oropharynx; (3) mouthwash reduced the transmissibility from the oropharynx; (4) the combined effect of mouthwash from scenarios 2 and 3.

Setting: We used gonorrhoea diagnosis data at three anatomical sites from 4873 MSM attending Melbourne Sexual Health Centre in 2018 and 2019 to calibrate our models. We also used data USA, Dutch and Thailand for sensitivity analysis.

Participants: Publicly available data on MSM with multi-site infections of gonorrhoea.

Primary and secondary outcome measures: Incidence of gonorrhoea.

Results: Under scenario 1, the overall incidence of gonorrhoea was 44 (95% CI: 37-50)/100 person-years. Under scenario 2, with 20-80% mouthwash coverage in the MSM population, the incidence increased at all three anatomical sites by between 7.4% (5.9-60.8%) and 136.6% (108.1-177.5%). Under scenario 3, with the same coverage, the incidence decreased at all anatomical sites by between 11.6% (10.2-13.5%) and 99.8% (99.2-100%). Under scenario 4, changes in the incidence depended on the

efficacy of mouthwash on the susceptibility and transmissibility with a broad overall effect from large increases of nearly 130% to large declines of almost 100%.

Conclusions: The effect of mouthwash on gonorrhoea incidence is largely predictable depending on whether it increases susceptibility to or reduces the transmissibility of gonorrhoea, highlighting an urgent need for further empirical investigation given the rapid rises that are occurring throughout the world.

Strengths and limitations of this study

- To our knowledge, this is the first study to model the effect that mouthwash may have on gonorrhoea incidence at a population level if the model assumes that mouthwash increases susceptibility or decreases its transmissibility.
- When assuming mouthwash coverage of 20%, 50%, and 80%, the incremental reduction in the susceptibility and incremental increase in transmissibility from 5% to 25% results in both increases and decreases in new gonorrhoea infections from a decrease of 100% or to an increase 130%.
- Our findings suggest that mouthwash has a predictable effect on the rates of gonorrhoea depending on whether mouthwash increases the susceptibility or reduces the transmissibility.
- We have made several assumptions about mouthwash use in our study because no data was available for these estimates.

INTRODUCTION

The world is experiencing increasing trends in both the rates of gonorrhoea and its antimicrobial resistance [1-4] that have prompted *Neisseria gonorrhoeae* to be deemed a significant global health threat [5 6]. Unfortunately, effective interventions to reduce rates of gonorrhoea have been challenging to identify. Recently researchers have suggested that oropharyngeal gonorrhoea may be critical to the persistence of infection at a population level [7] and that infection may be transmitted by kissing and saliva exchange during sex [8-10]. [11] [12]. To address the potential transmission associated with the oropharynx, researchers have been investigating mouthwash as an intervention for gonorrhoea prevention [12-17].

Three randomised controlled trials have explored the effect of antibacterial mouthwash on gonorrhoea infection [18-20]. The first study of 58 MSM in Australia suggested that antibacterial mouthwash reduced the ability to culture gonorrhoea from the oropharynx and, therefore, may potentially reduce gonorrhoea transmission [18]. Men in this study who used Listerine mouthwash were less likely to test positive for gonorrhoea at the tonsillar fossae (OR=0.14, 95% CI 0.03 to 0.77) compared with those who used saline. The second study of 530 MSM in Australia reported no significant risk difference in gonorrhoea positivity between the Listerine mouthwash group and the control (Biotène) group of 2.5% [-1.8 to 6.8%] for oropharyngeal infection or at other sites(-4.4% [-7.4% to -1.3%] for urethral infection, and 2.5% [-2.0 to 7.0%] for anorectal infection) [19].

The third RCT of 343 MSM in Belgium was stopped early because of the COVID-19 pandemic. It reported similar findings to the larger RCT with a non-significant increase in gonorrhea at the oropharyngeal and no significant changes at other anatomical sites in the adjusted analysis [20]. While the adjusted analysis showed no increase in oropharyngeal gonorrhoea the un-adjusted analysis suggested Listerine increased the risk of oropharyngeal gonorrhoea and hence raise the possibility that Listerine mouthwash may actually increase the risk of oropharyngeal gonorrhoea rather than reduce it. Taken together, the results of the three clinical trials raise the possibility that antibacterial mouthwash may either increase the susceptibility of the oropharynx to *Neisseria gonorrhoeae* or potentially decrease its transmissibility.

The WHO's "Global Action Plan to Control the Spread and Impact of Antimicrobial-Resistance in *N. gonorrhoeae*" recommends the use of mathematical models to analyse new interventions [21]. Zhang et al. assumed that mouthwash could reduce the duration of gonorrhoea at the oropharynx and found that widespread use may significantly reduce the prevalence of gonorrhoea in the population [8]. Based on the newly emerging evidence on mouthwash and gonorrhoea transmission, from the randomized studies we used a susceptible-infected-susceptible compartmental model to examine the potential effect of antibacterial mouthwash on gonorrhoea incidence in MSM.

METHODS

Study design

We employed a population-level susceptible-infected-susceptible compartmental model to evaluate the potential effects of antibacterial mouthwash on the incidence of gonorrhoea in MSM. The Forest plot shows the effect of antibacterial mouthwash on the incidence of gonorrhoea (Supplementary Figure S1). The model was based on our previously published multi-site infection model [22] (Supplementary Figure S2).

Data resources

We used gonorrhoea diagnosis data of 4873 MSM attending Melbourne Sexual Health Centre (MSHC) using Nucleic Acid Amplification Test (NAAT) in 2018 and 2019 to calibrate our models [22]. The percentage of positivity was 'oropharynx infection only' (2.96%), 'urethra infection only' (0.31%), 'anorectum infection only' (3.16%), 'oropharynx and urethra co-infection' (0.21%), 'oropharynx and anorectum co-infection' (2.46%), 'urethra and anorectum co-infection' (1.19%), and 'oropharynx, urethra and anorectum co-infection' (0.72%). (see Supplementary Table S1).

Neisseria gonorrhoeae transmission routes

We simulated gonorrhoea transmission through (1) anal sex; (2) penile–oral sex; (3) rimming; (4) kissing; (5) oral sex followed by anal sex (or vice versa) (penis acts as

a mediator and carries *Neisseria gonorrhoeae* to the oropharynx or anorectum); (6) using saliva as a lubricant for anal sex (pass *Neisseria gonorrhoeae* from his oropharynx to his urethra); (7) oral sex followed by oral-anal sex (rimming) or vice versa (oropharynx acts as a mediator and carries *Neisseria gonorrhoeae* to the urethra or anorectum) [22].

Model parameterisation and calibration

We collected behavioural and gonorrhoea progression data in the assumption for our models' parameters /to inform parameter values for the models. (see Supplementary Table S2). We used MATLAB R2019a to conduct numerical simulations and perform the statistical analysis. We sampled the parameter space using Latin Hypercube Sampling within the parameter uncertainty bounds ranges and generated a pool of 1000 parameter sets. Using each sampled set of parameters as the initial points, we simulated the transmission model. We used the 'trust-region-reflective' method ('fmincon' in MATLAB [23]) for the optimisation process to search for the parameter sets that is best fitted to the empirical prevalence of the infections. We then calibrated the model-simulated site-specific gonorrhoea prevalence at equilibrium to empirical gonorrhoea diagnosis data at each anatomical site (i.e., oropharynx, urethra, and anorectum), as well as multi-site infection (oropharynx and urethra together, oropharynx and anorectum together, urethra and anorectum together, oropharynx and urethra and

anorectum together. We define the goodness-of-fit as the sum square error between the prevalence levels based on model simulations and empirical data for each simulation. We then ranked the goodness-of-fit in ascending order (the best-fitted simulations on the top) and selected the top 10% of 1000 simulations. We regarded the selected 10% simulations as the pool of parameter sets that were best calibrated to the empirical data and used these simulations to estimate the 95% confidence intervals of the output indicators. The study methods have been reported previously [8 22].

Scenarios for the modelled effect of mouthwash on gonorrhoea incidence

Following model calibration, we established four scenarios to evaluate antibacterial mouthwash's effectiveness on the incidence of gonorrhoea. We estimated the number of new infections at any given time and calculated the incidence as the ratio between the number of new infections and the number of susceptible [8 22 24]. The effect of antibacterial mouthwash on transmissibility and susceptibility between two men is shown in Figure 1. We constructed the following four scenarios: (1) mouthwash had no effect on *Neisseria gonorrhoeae*; (2) mouthwash increased the susceptibility of acquiring oropharyngeal gonorrhoea, during sexual practices including penile–oral sex (from the urethra to oropharynx), rimming (from the anorectum to oropharynx), and kissing (from the oropharynx to oropharynx); (3) mouthwash reduced the transmissibility from an infected oropharynx, during sexual practices including penile–oral sex (from the oropharynx to urethra), rimming (from the oropharynx to anorectum),

kissing (from the oropharynx to oropharynx), using saliva as a lubricant for anal sex (from own oropharynx to own urethra), oral sex followed by oral-anal sex (rimming) or vice versa (oropharynx acts as a mediator and carries *Neisseria gonorrhoeae* from the oropharynx to the anorectum); (4) mouthwash reduced transmissibility from the oropharynx and increased susceptibility to acquiring oropharyngeal gonorrhoea, that is, a combined scenario of (2) and (3).

In our simulations, we examined scenarios for the potential efficacy of mouthwash that would increase the susceptibility and reduce the transmissibility by 5%, 10%, 15%, 20% and 25% for using mouthwash shortly before or immediately after each sexual act. Like previous studies [19 20], we defined the population coverage of mouthwash as the proportion of MSM who used mouthwash daily.

Sensitivity analysis

We identified five similar studies that reported multi-site infections of gonorrhoea using NAAT, including (1) 3,049 MSM, attending a health centre in Boston, Massachusetts, during 2012-2016 [10]; (2) 393 MSM attending STD & HIV care clinics in the USA during 2018-2019 [25]; (3) 179 MSM living with HIV in Birmingham, Alabama, during 2014-2016 [26]; (4) MSM surveillance data (271,242 consultations) from nation-wide Dutch STI clinics during 2008-2017 [27]; and (5) 1,610 MSM attending

a community-led test and treat cohort in Thailand during 2015-2016 [28]. (see Supplementary Table S1). We also modelled the potential effects of antibacterial mouthwash on the gonorrhoea incidence using the above five additional datasets.

Patient and public involvement

Our study was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or to interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Figures 1 show the potential effects of mouthwash on the incidence of gonorrhoea at any anatomical site and also the effect at individual anatomical sites: oropharynx, anorectum and urethra. In the absence of any effect of mouthwash (scenario 1), the incidence of gonorrhoea at all three anatomical sites was 44 (95% CI: 37 to 50) /100 person-years (PY): 26 (95% CI: 22 to 31) /100 PY at the oropharynx, 9 (95% CI: 8 to 11) /100 PY at the anorectum and 8 (95%CI: 5 to 12) /100 PY at the urethra. (details in Supplementary Table S3-8).

If mouthwash increased the oropharynx's susceptibility to *Neisseria gonorrhoeae* (scenario 2), then the incidence would increase at all three sites. The magnitude of the increase would depend on the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20% the incidence at the oropharynx, percentage changed between 7.5% (95% CI: 5.9 to 61.6 %) to 37.3% (95% CI: 29.3 to 85.4%), at the anorectum percentage changed between 7.3% (95% CI: 5.7 to 59.2%) to 36.0% (95% CI: 28.0 to 81.6 %), and at the urethral it increased by between 7.4% (95% CI: 5.8 to 60.3 %) to 36.5% (95% CI: 28.6 to 83.4 %) when the susceptibility increased from between 5% and 25%. When the population coverage of mouthwash uses increased, the magnitude of the incidence also increased. (Figure 2, 3; Supplementary S3-8).

If mouthwash were to reduce the transmissibility of *Neisseria gonorrhoeae* from the oropharynx (scenario 3), then the incidence of gonorrhoea would reduce at all three sites. As for scenario 3, the magnitude of the decrease would depend on the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20% the percentage change in incidence at the oropharynx from -11.5% (95% CI: -13.5 to -10.1%) to -54.1% (95% CI: -62.0 to -48.6%) at the anorectum from -11.9% (95% CI: -13.9 to -10.5%) to -54.5% (95% CI: -62.3 to -48.9%) and at the urethral from -11.6% (95% CI: -13.6 to -10.2%) to -55.4% (95% CI: -62.9 to -49.8%) when the susceptibility increased from between 5% and 25%. When the population coverage of mouthwash uses increased, the magnitude of the fall in incidence also increased. (Figure 2, 3; Supplementary Table S3-8).

If mouthwash increased the susceptibility of the oropharynx to *Neisseria gonorrhoeae* and to reduce the transmissibility of *Neisseria gonorrhoeae* from the oropharynx (scenario 4), the combined effect of mouthwash on incidence depends on the varying efficacy of both transmissibility and susceptibility and the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20%, mouthwash could result in negative percentage change in incidence of -0.8% (95% CI: -10.7 to 42.5%) to -48.4% (95% CI: -56.8 to -12.2%) at the oropharynx, -1.8% (95% CI: -12.0 to 38.8%) to -48.8% (95% CI: -57.2 to -13.8%) at the anorectum, and -2.8% (95% CI: -12.7 to 38.5%) to -49.8% (95% CI: -57.9 to -15.1%) at the urethra, in areas below the

zero-threshold curve (Figure 3). Mouthwash also could result in positive percentage change in incidence of 2.7% (95% CI: -1.1 to 53.1%) to 11.6% (95% CI: 2.8 to 56.1%) at the oropharynx, 2.3% (95% CI: -1.6 to 50.5%) to 23.2% (95% CI: 14.8 to 67.1%) at the urethra, and 2.0% (95% CI: -1.8 to 51.0%) to 23.2% (95% CI: 14.8 to 68.0%) at the urethra, in areas above the zero-threshold curve (Figure 1). When the coverage increased, so did the magnitude of the percentage increases. If the incremental reduction in the transmissibility is the same as the incremental increase in susceptibility (scenario 4), the combined effect of mouthwash was projected to reduce gonorrhoea incidence (Figure 2, 3; Supplementary Table S3-8).

We conducted the sensitivity analyses using five different studies with multi-site infection data, and the conclusions were similar. The supplementary material includes the model calibrated for the other five datasets. (Supplementary Figure s3a, 3b, 4a, 4b, 5a, 5b, 6a, 6b, 7a, 7b).

DISCUSSION

To our knowledge, this is the first study to model the effect that mouthwash may have on gonorrhoea incidence at a population level if mouthwash were to increase the susceptibility or decrease the transmissibility of gonorrhoea infection. We found substantial changes in the incidence of gonorrhoea occurred in all scenarios but that reductions in the transmissibility of gonorrhoea were more potent than the increases in the susceptibility if the incremental reduction in the transmissibility is the same as the

incremental increase in susceptibility. To date, only one other study has modelled the effect of mouthwash on gonorrhoea incidence [8], but this study only looked at the effect on duration. There has been very little empirical data at present on the effect of mouthwash both on the transmissibility of gonorrhoea in infected men or susceptibility in uninfected men. We hope this work encourages more researchers to explore the effect of mouthwash on the susceptibility and transmissibility of *Neisseria gonorrhoeae* to potentially design an intervention if further studies were to show it was beneficial.

Our study shows that if mouthwash increases the oropharynx's susceptibility in uninfected individuals, it will increase the incidence in the MSM population. Van Dijck et al. [20] reported in their randomised trial that mouthwash did not significantly increase urethral or oropharyngeal gonorrhoea incidence. Van Dijck et al. study was stopped early and they suggested that the non-significant increase could possibly be explained if Listerine damaged the oropharyngeal mucosa or microbiome. Van Dijck et al. also proposed that Listerine mouthwash may eliminate the beneficial effects on the carriage of pathogenic *Neisseria*, and that this effect was potentially mediated through inhibition of some commensal *Neisseria* species that normally act to limit the growth or carriage of *Neisseria gonorrhoeae* or *Neisseria meningitidis* [29 30]. More research will be needed to investigate the benefits and harms of using mouthwash as an intervention for gonorrhoea prevention. Further study is required to explore how mouthwash changes the oral microbiome and resistome and inhibit commensal Neisseria species' growth.

Our study shows that if mouthwash reduced the transmissibility from the oropharynx in the infected individuals, then widespread use of mouthwash would reduce the incidence of gonorrhoea at all sites in MSM at a population level. Mouthwash may reduce transmissibility by reducing the load of viable *Neisseria gonorrhoeae* bacteria at the oropharynx. Indeed, the first randomised trial undertaken by Chow so substantial and significant reductions in culture positive gonorrhoea following a minute use of mouthwash. Chow et al. further examined the effectiveness of antiseptic mouthwash compared to standard of care antibiotics for the treatment of oropharyngeal gonorrhoea and found that mouthwash was not effective albeit in a small RCT among 12 men. The authors concluded from this study and their first randomised study that mouthwash might have a temporary effect on the load of viable organisms but may not have a prolonged effect [31]. The OMEGA (oral mouthwash use to eradicate gonorrhoea) trial examined the effect of mouthwash on the incidence of gonorrhoea by comparing an intervention mouthwash (Listerine) versus a control mouthwash (Biotène) among 530 men using daily mouthwash for three months. Findings from the OMEGA trial suggested that men who use the intervention mouthwash (Listerine) had a 4.4% lower positivity of urethral gonorrhoea compared to the control mouthwash group and one possible explanation for this is that mouthwash reduced transmission from the oropharynx to their own penis [19].

Understanding the effect of mouthwash on the incidence of gonorrhoea could provide additional potential interventions for controlling the increasing gonorrhoea incidence [32] if it were to be widely used [11 12]. There are a number of issues that need to be clarified in relation to mouthwash. Firstly, the duration of any potential effect of antiseptic mouthwash on the transmissibility of *Neisseria gonorrhoeae* at the oropharynx should be quantified because it determines when mouthwash should be used in relation to sexual activities. Secondly, although two randomised controlled trials did not demonstrate a decline in the incidence of overall gonorrhoea [19 20], one study showed a decline in the incidence of urethral gonorrhoea [20]. However, it does not mean mouthwash did not reduce the bacterial load in infected individuals. Thirdly, the incidence measured by the RCT has its limitations. Although it measures the protective effects of mouthwash in these selected individuals, the RCT did not measure the transmissibility of infected individuals in the next generation of gonorrhoea transmission in the whole MSM population since sexual partners were not tested for gonorrhoea.

This modelling study has some limitations. First, we estimated of the effect of mouthwash on susceptibility or transmissibility, we choose equal estimates with only moderate effect sizes of 0-25% effects. If mouthwash had a more potent effect on either susceptibility or transmissibility, the effect on the incidence would be considerably greater. We did, however, show a moderate effect on the incidence of infection with the estimates we chose. Second, we have made several assumptions about mouthwash

use in our study because no data was available for these estimates. These assumptions included the duration of the potential 'treatment' effect of mouthwash, how mouthwash would be used by men (e.g. oral rinse, oral gargle and oral spray) when they used mouthwash (we assumed it was used before sex) and the effect of different ways of using it [33]. Third, the diagnosed gonorrhoea data in our model is at a single time point, and we could not calibrate our model to a temporal trend of the epidemic. Fourth, the transmission of gonorrhoea may be largely biased towards high-risk MSM, and we did not separate the transmission by risk groups in our model. Finally, we acknowledge that sexual practices involved saliva may be more complex, and our model may not capture all sexual practices involving saliva.

CONCLUSIONS

In conclusion, our finding suggests that mouthwash could either increase or decrease the incidence of gonorrhoea at a population level depending on whether it increases susceptibility or decreases transmissibility. Our study highlights the need for more empirical data about the potential effect of mouthwash and the magnitude of this effect.

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Footnotes

Contributors: XX, CKF and LZ conceived and designed the study. EPFC contributed to the study design. XX, and LZ established the model; XX, and LZ did the

analysis. MWS contributed in modelling and gave overall feedback to the analysis. XX wrote the first draft. EPFC, ZZ, CW, JJO, CKF and LZ participated in the interpretation of results. All authors reviewed the manuscript and approved the final version.

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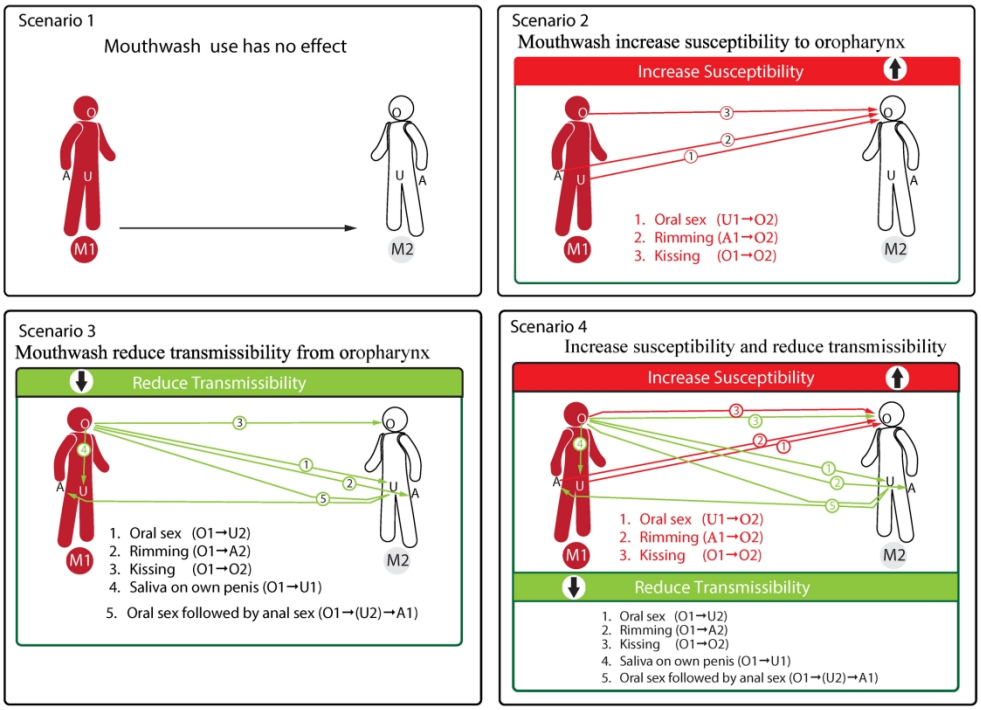
Figure legends

Figure 1. The effect of antibacterial mouthwash on transmissibility and susceptibility between man 1 and man 2 in the one sexual episode

Figure 2. Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM.

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

Figure 3. Contour plots for the effect of antibacterial mouthwash on the percentage change (%) of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx. The black solid isoclines indicate the threshold that the percentage change of incidence is zero.



Man1 is infected and Man 2 is suscetible. U=urethara, A=anorectum, O=oroharynx. The numerical subscript number (1 or 2) refers to Man1 or Man 2 (e.g. A1 = annnorectum of man 1)

Figure 1. The effect of antibacterial mouthwash on transmissibility and susceptibility between man 1 and man 2 in the one sexual episode

202x184mm (300 x 300 DPI)

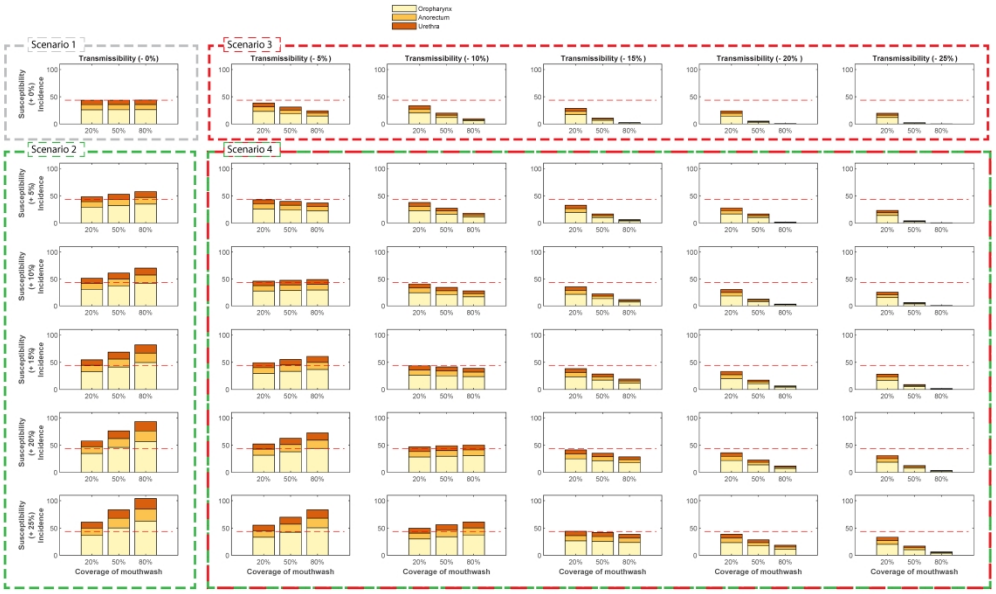


Figure 2. Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

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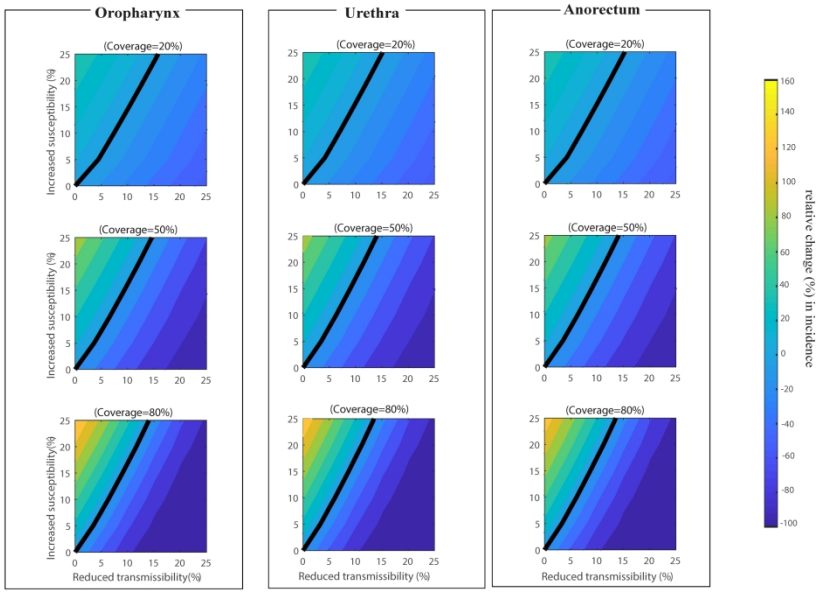

Figure 3. Contour plots for the effect of antibacterial mouthwash on the percentage change (%) of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx. The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

325x211mm (300 x 300 DPI)

Appendix: Potential effect of antibacterial mouthwash on the incidence of *Neisseria gonorrhoeae* among men who have sex with men: a mathematical modelling study

Literature review

We searched PubMed, up to March 5, 2021, for reports of studies assessing the effect of mouthwash on the prevalence or incidence of gonorrhoea. We used the search terms ("gonorrh*" OR "sexual") AND "mouthwash" and found 27 studies. We were also aware of two articles in The Lancet Infectious Disease. Of the 29 identified sources, 4 randomized controlled trials were observed. One of four studies examined the effectiveness of antiseptic mouthwash for the treatment of oropharyngeal gonorrhoea [1], and another study examined whether Listerine could be used to inhibit the growth of *Neisseria gonorrhoeae*. This study concluded that Listerine could significantly reduce the amount of *Neisseria gonorrhoeae* on the pharyngeal surface[2]. Finally, so we only analysed 2 RCT reported incidence [3 4]. The findings of these two studies may lead to the potential of mouthwash to transmissibility and susceptibility. The Forest plot shows the effect of antibacterial mouthwash on the incidence of gonorrhoea (Supplementary Figure S1).

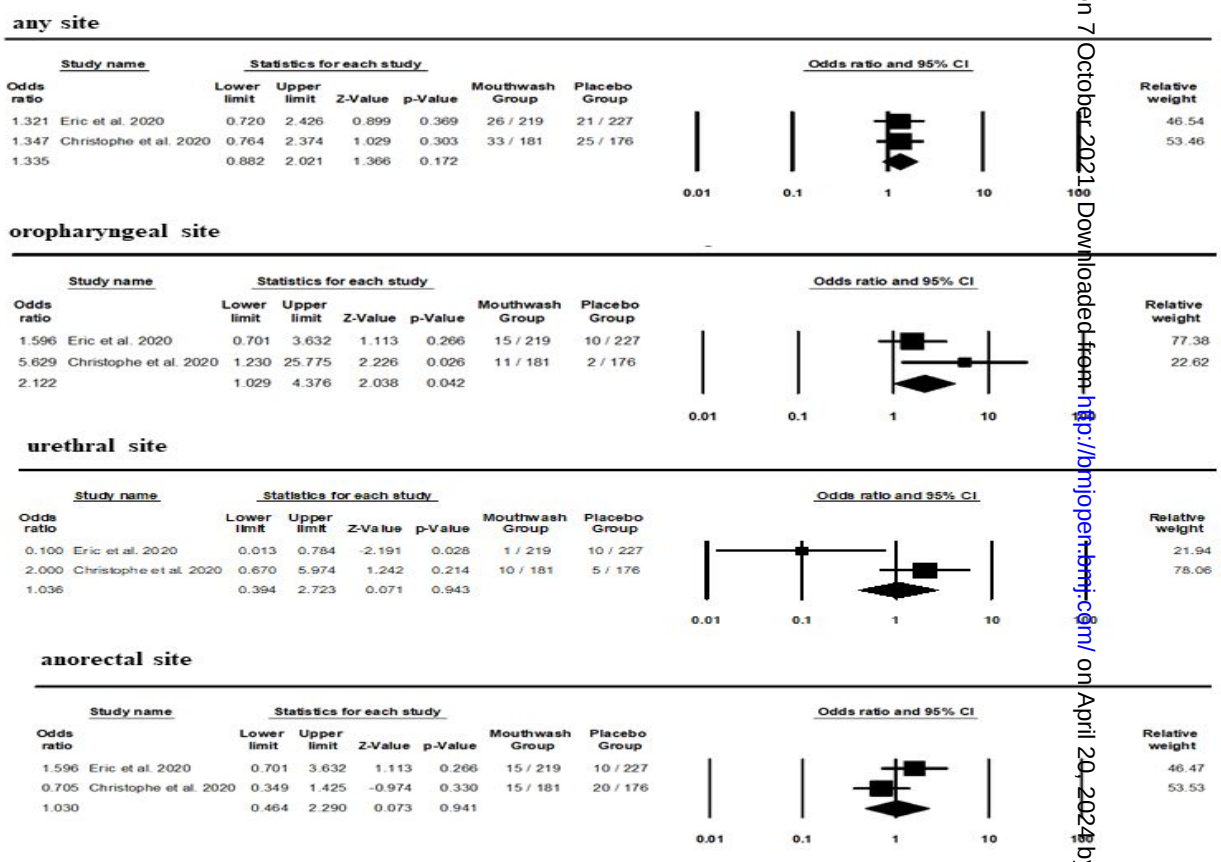

Figure S1. Forest plot for random effects meta-analysis of the effect of antibacterial mouthwash on the incidence of gonorrhoea at any site, oropharyngeal site, urethral site, and anorectal site.

Study design

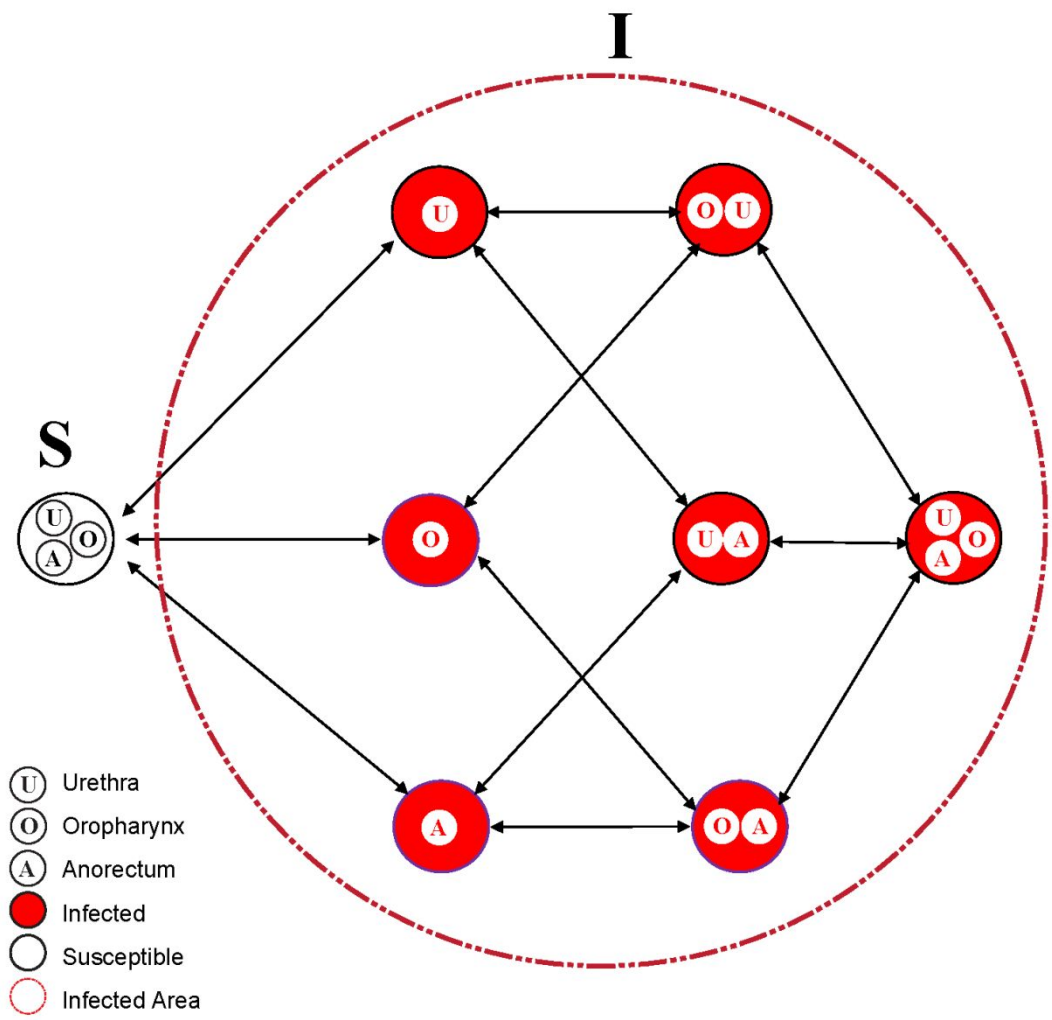

***Figure S2**. A compartmental model for the transmission dynamics of Neisseria gonorrhoeae in men who have sex with men.*

U: only urethral infections; O: only oropharyngeal infections; A: only anorectal infections; Anorectum (A); OU: only oropharyngeal and urethral infections; UA: only urethral and anorectal infections; OA: only oropharyngeal and anorectal infections; OUA: oropharyngeal, urethral and anorectal infections; arrow signifies the direction of infection and clearance.

Differential equations

Force of infection

The force of infection Λ takes the following form[5]:

$$\Lambda = \lambda \cdot P$$

$$\lambda = (1 - (1 - \beta \cdot (1 - \varepsilon_c \cdot C))^{\frac{f}{2}})$$

P represents the prevalence of *Neisseria gonorrhoeae*;

β represents the per-act transmission;

C is the percentage of condom use in anal intercourse;

ε_c is the efficacy of condom in preventing transmission of sexually transmitted infections and

f is the frequency of sexual acts that may facilitate transmission.

f is calculated based on the frequency of sexual acts data[5].

S = S(t) is the number of susceptible MSM;

I = I(t) is the number of infected MSM;

I_o is the number of MSM with oropharyngeal infection only;

I_u is the number of MSM with urethral infection only;

I_a is the number of MSM with rectal infection only;

I_{ou} is the number of MSM with oropharyngeal and urethral infection only;

I_{ua} is the number of MSM with rectal, and urethral infection only;

I_{oa} is the number of MSM with oropharyngeal and rectal infection only;

I_{oua} is the number MSM with oropharyngeal, rectal, and urethral infection;

$$N = S + I_o + I_u + I_a + I_{ou} + I_{ua} + I_{oa} + I_{oua}$$

Based on assumptions, the transmission of *Neisseria gonorrhoeae* infection was governed by the following differential equations.

$$\frac{dS}{dt} = -(\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot S + \gamma_o \cdot I_o - (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot S + \gamma_a \cdot I_a - (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot S + \gamma_u \cdot I_u$$

$$\frac{dI_o}{dt} = (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot S - \gamma_o \cdot I_o - (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_o + \gamma_a \cdot I_{oa} - (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_o + \gamma_u \cdot I_{ou} - \lambda_{ooa} \cdot I_o - \lambda_{oou} \cdot I_o$$

$$\frac{dI_u}{dt} = (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot S - \gamma_u \cdot I_u - (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_u + \gamma_o \cdot I_{ou} - (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_u + \gamma_a \cdot I_{ua} - \lambda_{uua} \cdot I_u - \lambda_{ua2} \cdot I_o$$

$$\frac{dI_a}{dt} = (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot S - \gamma_a \cdot I_a - (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_a + \gamma_o \cdot I_{oa} - (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_a + \gamma_u \cdot I_{ua} - \lambda_{aoa} \cdot I_a - \lambda_{aua} \cdot I_a + \lambda_{ua2} \cdot I_o$$

$$\frac{dI_{ou}}{dt} = (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_u - \gamma_o \cdot I_{ou} + (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_o - \gamma_u \cdot I_{ou} - (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_{ou} + \gamma_a \cdot I_{oua} + \lambda_{oou} \cdot I_o$$

$$\frac{dI_{oa}}{dt} = (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_o - \gamma_a \cdot I_{oa} + (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_a - \gamma_o \cdot I_{oa} - (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_{oa} + \gamma_u \cdot I_{oua} + \lambda_{ooa} \cdot I_o + \lambda_{aoa} \cdot I_a$$

$$\frac{dI_{ua}}{dt} = (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_u - \gamma_a \cdot I_{ua} + (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_a - \gamma_u \cdot I_{ua} - (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_{ua} + \gamma_o \cdot I_{oua} + \lambda_{uua} \cdot I_u + \lambda_{aua} \cdot I_a$$

$$\frac{dI_{oua}}{dt} = (\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}) \cdot I_{ou} - \gamma_a \cdot I_{oua} + (\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}) \cdot I_{ua} - \gamma_o \cdot I_{oua} + (\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}) \cdot I_{oa} - \gamma_u \cdot I_{oua}$$

Data source

Site-specific prevalence data

We used data of 4873 MSM attending Melbourne Sexual Health Centre MSHC in 2018 and 2019 to calibrate our models [6]. We also used five other similar studies with multi-site infection data using NAAT, including (1) 3,049 MSM, attending a health center in Boston, Massachusetts, during 2012-2016 [7]; (2) 393 MSM attending STD & HIV care clinics in the USA during 2018-2019 [8]; (3) 179 MSM living with HIV in Birmingham, Alabama, during 2014-2016 [9]; (4) MSM surveillance data (271,242 consultations) from nation-wide Dutch STI clinics during 2008-2017 [10]; and (5) 1,610 MSM attending a community-led test and treat cohort in Thailand during 2015-2016 [11].

Table S1. *Site-specific prevalence of gonorrhoea* [12]

		Prevalence/ Mean value (95%CI)						
	Sample size	Oropharyngeal only	Urethral only	Rectal only	Oropharyngeal and urethra	Oropharyngeal and rectum	Urethra and rectum both	Oropharyngeal and urethra and rectum
Xu [12]	4,873 (First time visiting	2.96 (2.51-3.49)	Empirical data: 0.31 (0.18-0.52)	3.16 (2.70-3.70)	Empirical data: 0.21	2.46 (2.05-2.94)	Empirical data: 1.19 (0.91-1.55)	Empirical data: 0.72 (0.51-1.01)

	MSHC)				(0.11-0.40)			
			Calibrated to community level data:0.01 (0.00-0.02)		Calibrated to community level data: 0.01 (0.00-0.02)		Calibrated to community level data: 0.02 (0.02-0.08)	Calibrated to community level data: 0.03 (0.01-0.05)
Spicknall [7] .	3,049		Empirical data:2.09 (1.63-2.69)		Empirical data:0.98 (0.67- 1.42)		Empirical data: 1.21 (0.86-1.68)	Empirical data:0.75 (0.49-1.14)
		8.50 (7.54-9.55)	Calibrated to community level data:0.20 (0.07-0.32)	6.80 (5.93-7.76)	Calibrated to community level data:0.10 (0.03-0.16)	3.40 (2.81-4.13)	Calibrated to community level data:0.11 (0.04-0.19)	Calibrated to community level data:0.07 (0.02-0.12)
Pol [8]	393		Empirical data:2.54 (1.29-4.78)		Empirical data:1.53 (0.62-3.47)		Empirical data: 0.76 (0.20-2.40)	Empirical data: 0.25 (0.01-1.63)
		2.04 (0.95-4.14)	Calibrated to community level data:0.10 (0.04-0.16)	3.56 (2.04-6.04)	Calibrated to community level data:0.06 (0.02-0.10)	1.53 (0.62-3.47)	Calibrated to community level data:0.02 (0.01-0.05)	Calibrated to community level data:0.01 (0.00-0.02)

Footman [9]	179		Empirical data:0 (0-0)		Empirical data:0.56 (0.03-3.55)		Empirical data:0(0-0)	Empirical data:0(0-0)
		0.56 (0.03-3.55)	Calibrated to community level data:0(0-0)	3.91 (1.72-8.21)	Calibrated to community level data:0.02 (0.01-0.04)	2.23 (0.72- 5.98)	Calibrated to community level data:0(0-0)	Calibrated to community level data:0(0-0)
van Liere [10]	271,242 consultations		Empirical data: 0.85 (0.81-0.89)		Empirical data: 0.33 (0.31-0.36)		Empirical l data: 0.95 (0.91-0.99)	Empirical data: 0.73 (0.69-0.77)
		3.02 (2.95-3.09)	Calibrated to community level data:0.03 (0.01-0.06)	10.17 (10.05-10.30)	Calibrated to community level data:0.01 (0.00-0.02)	1.69 (1.64-1.75)	Calibrated to community level data:0.0 (0.01-0.06)	Calibrated to community level data:0.03 (0.01-0.05)
Hiransuthikul [11]	1,610	3.91 (3.04-5.01)	1.93 (1.34-2.76)	5.84 (4.77-7.13)	0.31 (0.11-0.77)	2.24 (1.60-3.12)	0.87 (0.50-1.49)	0.37 (0.15-0.85)

Note: MSHC did not test for urethral NG among asymptomatic MSM before 2018, so multi-site infections would be biased towards symptomatic patients. Hence, we used NG data for 2018-19. We calculated the confidence interval for each parameter using this method [13-15]. Empirical data: The prevalence of urethral gonorrhoea infection in the community at a given point in time will be much lower than STI clinics. Asymptomatic urethral gonorrhoea is uncommon (7.69%) [16], but when it occurs, it is likely to be infectious for 3 to 5 months before the natural clearance. Therefore, the proportion of urethral gonorrhoea cases that are potentially infectious will be the prevalence of urethral gonorrhoea infection in STI clinics multiplied by 1/52 (infectious

for one week till treatment) plus an additional asymptomatic 7.69% of cases who will be infectious for 3 to 5 months. Based on this information, we used previously published methods [5] to calibrate the prevalence of individuals with urethral infection in the community assuming about 92.3% will present symptoms shortly after a successful infection.

Model parameters

Table S2. *Biological and behavioural data of Neisseria gonorrhoeae for model parameterization and calibration* [5,12]

Parameters	Values (95%95% uncertainty bounds)	Reference/ Notes
Proportion of men using condoms for anal sex in the past 12 months with casual partners (%)	46.90(34.50- 59.30)	[5]
Efficacy of condoms for preventing *N. gonorrhoeae* transmission when used for anal sex (%)	87.50(80.00-95.00)	[5]
Frequency of kissing (days)	6.31(0.00-13.12)	[5]
Frequency of oral sex (days)	13.53(0.00-28.11)	[5]
Frequency of rimming (days)	38.57(0.00-80.15)	[5]

Frequency of anal sex (days)	26.44(0.00-54.94)	[5]
Duration of untreated *N. gonorrhoeae* at the oropharynx (asymptomatic infection) (weeks)	12.00(10.00-14.00)	[5]
Duration of *N. gonorrhoeae* at the urethra (symptomatic infection) (weeks)	1.00(0.90-1.10)	[5]
Duration of untreated *N. gonorrhoeae* at the urethra (asymptomatic infection) (weeks)	12.00(10.00- 14.00)	[5]
Duration of untreated *N. gonorrhoeae* at the anorectum (weeks)	49.43(48.00- 52.00)	[5]
Proportion of urethral infections that are asymptomatic (%)	7.69(4.09-13.67)	[16]
Proportion of MSM received throat swab in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of MSM received anal swab in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of MSM received urine test in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of ' oral sex and anal sex' in the same sex episode (%)	29.41(24.82-34.00)	Footnote *b*, [18].
Proportion of 'oral sex and rimming' in the same sex episode (%)	70.5 (67.94-72.94)	Footnote *c*, [18 19].
Proportion of men using saliva as a lubricant during anal sex, the saliva is coming from the insertive (top) partner (%)	68.52(65.92-71.01)	[19]
Proportion of men having oral sex and then anal sex when they have both oral sex and anal sex (%)	80.00(80.00-80.00)	Footnote *d* [20 21].

Proportion of men having oral sex and then rimming their partner when they perform both oral sex and rimming (%)	80.00(80.00-80.00)	Footnote e

Footnote:

a. The proportion of gay and bisexual men attending sexual health clinics tested for *N. gonorrhoeae* in 2017 was 95.6%. The proportion of gay and bisexual men attending general practice clinics tested for *N. gonorrhoeae* in 2017 was 63.7%. We used the proportion of gay and bisexual men attending sexual health clinics tested as the lower bound. We used the proportion of gay and bisexual men attending general practice clinics tested as the upper bound. We used the mean value of the upper bound and lower as value.

b. The proportion of men who had receptive oral sex in their last sexual encounter that we used was 73.0%, and the proportion who had insertive anal sex was 34.0%. To determine proportion who had both oral sex and anal sex in the same encounter we used the proportion of anal sex (34.0%) as upper bound, and the value of the proportion of anal sex (34.0%) multiply the proportion of oral sex (73.0%) as the lower bound. The mean value is the average of the upper bound and lower bound.

c. The proportion of men who had insertive rimming in their last sexual encounter that we used was 70.5%, and the proportion of insertive oral sex was 75.0% To determine proportion who had both oral sex and anal sex in the same encounter we used the value of the proportion of oral sex multiply prevalence of rimming as lower bound and proportion of rimming behavior as upper bound. The mean value is the average of the upper bound and lower bound.

d. We estimated that the proportion of men who had oral sex followed by anal sex to be 80% based on expert opinion and published data.

e. This was calculated by subtracting 100% from the estimate in d.

Supplementary Results

1) 4873 MSM attending Melbourne Sexual Health Centre in 2018 and 2019[6]

Table S3. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 20% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 20%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI)			Oropharynx (95%CI)			Anorectum (95%CI)			Urethra (95%CI)		
1	0%	0%	44	37	50	26	22	31	9	8	11	8	5	12
2	0%	5%	47	39	72	28	23	46	10	9	17	9	6	13
2	0%	10%	51	42	74	30	25	47	11	9	17	9	6	14
2	0%	15%	54	45	76	32	26	49	11	10	18	10	7	15
2	0%	20%	57	47	79	34	28	51	12	11	18	10	7	16
2	0%	25%	60	49	82	36	30	53	13	11	19	11	7	17
3	5%	0%	39	32	45	23	19	28	8	7	10	7	5	10
4	5%	5%	42	34	66	25	20	42	9	8	15	8	5	12

4	5%	10%	46	37	68	27	22	43	9	16	8	6	13	
4	5%	15%	49	40	70	29	24	45	10	16	9	6	13	
4	5%	20%	52	42	73	31	25	47	11	17	9	6	14	
4	5%	25%	55	44	77	33	27	49	12	17	10	6	15	
3	10%	0%	34	27	39	20	16	24	7	9	6	4	9	
4	10%	5%	37	30	60	22	18	37	8	14	7	4	10	
4	10%	10%	40	32	62	24	19	39	8	14	7	5	11	
4	10%	15%	43	35	64	26	20	41	9	15	8	5	12	
4	10%	20%	46	37	67	28	22	43	10	15	8	5	13	
4	10%	25%	49	39	70	29	24	44	10	16	9	6	14	
3	15%	0%	29	23	34	17	13	22	6	8	5	3	8	
4	15%	5%	32	25	53	19	15	33	7	12	6	4	9	
4	15%	10%	35	28	55	21	16	35	7	13	6	4	10	
4	15%	15%	38	30	58	23	18	37	8	13	7	4	11	
4	15%	20%	41	32	61	24	19	38	9	14	7	5	11	
4	15%	25%	43	34	63	26	20	40	9	14	8	5	12	
3	20%	0%	24	19	29	14	11	19	5	6	4	3	7	
4	20%	5%	27	21	46	16	12	29	6	11	5	3	8	

4	20%	10%	30	23	49	18	13	31	6	4	11	5	3	9
4	20%	15%	32	25	51	20	15	32	7	4	12	6	4	9
4	20%	20%	35	27	54	21	16	34	7	4	12	6	4	10
4	20%	25%	38	29	56	23	17	36	8	4	13	7	4	11
3	25%	0%	20	15	24	12	9	16	4	3	5	3	2	5
4	25%	5%	22	16	41	13	10	25	5	4	9	4	2	7
4	25%	10%	25	18	43	15	11	26	5	4	10	4	3	7
4	25%	15%	27	20	45	16	12	28	6	4	10	5	3	8
4	25%	20%	30	22	47	18	13	30	6	4	11	5	3	9
4	25%	25%	32	24	49	20	14	31	7	4	11	6	3	9

Table S4. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 20% coverage*

Estimated effect of antibacterial mouthwash on percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM (%). 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 20%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	7.4	5.9	60.8	7.5	5.9	61.6	7.3	5.7	59.2	7.4	5.8	60.3
2	0%	10%	14.8	11.7	66.7	15.0	11.8	67.6	14.6	11.4	64.9	14.7	11.6	66.1
2	0%	15%	22.3	17.5	72.6	22.5	17.7	73.6	21.8	17.0	70.5	22.1	17.3	71.9
2	0%	20%	29.6	23.2	78.4	29.9	23.5	79.5	29.0	22.5	76.1	29.4	23.0	77.7
2	0%	25%	36.9	28.9	84.2	37.3	29.3	85.4	36.0	28.0	81.6	36.5	28.6	83.4
3	5%	0%	-11.6	-13.5	-10.2	-11.5	-13.5	-10.1	-11.6	-13.6	-10.2	-11.9	-13.9	-10.5
4	5%	5%	-4.5	-7.0	46.4	-4.3	-6.9	47.2	-4.6	-7.2	44.9	-4.9	-7.5	45.2
4	5%	10%	-4.5	-7.0	46.4	2.7	-1.1	53.1	2.3	-1.6	50.5	2.0	-1.8	51.0
4	5%	15%	9.5	4.4	58.0	9.8	4.7	59.0	9.2	3.9	56.1	8.9	3.8	56.7
4	5%	20%	16.9	10.0	63.7	17.3	10.4	64.9	16.3	9.4	61.6	16.2	9.3	62.3
4	5%	25%	24.0	15.6	69.5	24.5	16.1	70.7	23.2	14.8	67.1	23.2	14.8	68.0
3	10%	0%	-23.0	-26.9	-20.3	-22.9	-26.7	-20.2	-23.0	-26.9	-20.3	-23.6	-27.5	-20.9
4	10%	5%	-16.0	-20.4	31.7	-15.7	-20.2	32.5	-16.1	-20.6	30.4	-16.6	-21.2	30.1
4	10%	10%	-9.3	-14.4	37.4	-9.0	-14.1	38.3	-9.5	-14.7	35.9	-10.1	-15.3	35.7

4	10%	15%	-2.4	-8.8	43.1	-2.0	-8.4	44.1	-2.8	-9.2	41.4	-3.4	-9.8	41.3
4	10%	20%	4.1	-3.4	48.8	4.6	-2.9	49.9	3.7	-3.9	46.9	3.1	-4.3	46.9
4	10%	25%	11.1	2.2	54.6	11.6	2.8	56.1	10.5	1.4	52.3	9.9	1.0	52.5
3	15%	0%	-34.1	-39.6	-30.3	-33.9	-39.3	-30.1	-34.1	-39.6	-30.3	-34.9	-40.2	-31.0
4	15%	5%	-27.5	-33.4	16.8	-27.2	-33.1	17.7	-27.6	-33.6	15.7	-28.3	-34.3	14.9
4	15%	10%	-20.7	-27.8	22.4	-20.4	-27.5	23.3	-20.9	-28.1	21.1	-21.7	-28.8	20.4
4	15%	15%	-14.5	-22.1	28.0	-14.0	-21.7	29.0	-14.7	-22.5	26.5	-15.6	-23.3	25.9
4	15%	20%	-8.0	-16.6	33.5	-7.5	-16.1	34.7	-8.3	-17.2	31.9	-9.2	-17.9	31.3
4	15%	25%	-1.4	-11.3	41.0	-0.8	-10.7	42.5	-1.8	-12.0	38.8	-2.8	-12.7	38.5
3	20%	0%	-44.7	-51.3	-39.9	-44.5	-51.1	-39.6	-44.7	-51.4	-39.9	-45.4	-52.1	-40.7
4	20%	5%	-38.4	-45.7	1.8	-38.1	-45.4	2.7	-38.6	-45.8	0.9	-39.4	-46.6	-0.2
4	20%	10%	-32.1	-40.6	7.3	-31.8	-40.3	8.2	-32.2	-40.9	6.2	-33.2	-41.7	5.1
4	20%	15%	-25.9	-35.3	12.7	-25.4	-34.9	13.7	-26.1	-35.4	11.4	-27.2	-36.3	10.4
4	20%	20%	-19.9	-30.0	18.1	-19.3	-29.5	19.3	-20.2	-30.4	16.7	-21.3	-31.3	15.7
4	20%	25%	-13.8	-24.7	27.1	-13.1	-24.1	28.6	-14.1	-25.3	25.2	-15.2	-26.2	24.4
3	25%	0%	-54.4	-62.2	-48.9	-54.1	-62.0	-48.6	-54.5	-62.3	-48.9	-55.4	-62.9	-49.8
4	25%	5%	-48.7	-57.0	-13.0	-48.4	-56.8	-12.2	-48.8	-57.2	-13.8	-49.8	-57.9	-15.1
4	25%	10%	-43.0	-52.5	-7.6	-42.6	-52.2	-6.7	-43.0	-52.6	-8.7	-44.0	-53.4	-10.0

4	25%	15%	-37.0	-47.9	-1.0	-36.6	-47.6	0.0	-37.2	-48.2	-2.3	-38.2	-49.1	-3.7
4	25%	20%	-31.5	-42.6	5.6	-30.9	-42.2	6.7	-31.7	-43.0	4.0	-32.9	-44.0	2.7
4	25%	25%	-25.7	-37.8	13.2	-25.1	-37.3	14.7	-26.0	-38.3	11.5	-27.3	-39.3	10.4

Table S5. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 50% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 50%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI)			oropharynx(95%CI)			anorectum (95%CI)			urethra (95%CI)		
1	0%	0%	44	36	50	26	21	31	9	8	11	8	5	12
2	0%	5%	53	43	75	31	25	48	12	10	18	10	6	14
2	0%	10%	60	49	82	36	30	53	13	11	19	11	7	17
2	0%	15%	68	55	90	41	33	57	14	12	19	12	8	19
2	0%	20%	76	61	97	46	37	60	15	13	20	13	9	21
2	0%	25%	83	67	102	51	40	62	17	15	22	15	10	23
3	5%	0%	31	25	37	19	15	23	7	6	8	6	4	8
4	5%	5%	39	31	60	23	18	38	8	7	14	7	5	11
4	5%	10%	47	37	67	28	22	43	9	8	15	8	5	13
4	5%	15%	55	43	74	33	26	47	11	10	17	10	6	15
4	5%	20%	62	48	81	38	29	51	13	11	18	11	7	18
4	5%	25%	70	54	88	42	33	55	15	12	19	12	8	20
3	10%	0%	20	15	24	12	9	16	4	4	5	3	2	5

4	10%	5%	26	20	45	16	11	28	8	5	10	5	3	8
4	10%	10%	33	25	51	20	15	32	7	6	11	6	4	10
4	10%	15%	41	30	58	25	18	37	8	7	13	7	4	12
4	10%	20%	48	36	65	30	22	41	7	8	14	8	5	14
4	10%	25%	55	41	74	34	25	45	7	9	16	10	6	16
3	15%	0%	11	7	15	7	4	9	2	2	3	2	1	3
4	15%	5%	16	10	30	10	6	18	6	2	7	3	1	5
4	15%	10%	22	14	36	13	8	22	6	3	8	4	2	7
4	15%	15%	28	18	44	17	11	27	6	4	10	5	3	9
4	15%	20%	35	23	53	21	14	33	7	5	11	6	3	11
4	15%	25%	41	29	62	25	17	38	7	6	13	7	4	13
3	20%	0%	5	3	8	3	2	5	1	1	2	1	0	2
4	20%	5%	8	4	19	5	3	12	4	1	4	1	1	3
4	20%	10%	12	7	26	7	4	16	5	2	5	2	1	4
4	20%	15%	17	9	33	10	6	21	4	2	7	3	1	6
4	20%	20%	23	12	41	13	8	26	5	3	8	4	2	7
4	20%	25%	29	16	50	17	10	31	5	4	10	5	2	9
3	25%	0%	2	1	4	1	1	2	0	0	1	0	0	1

4	25%	5%	4	2	10	2	1	7	1	0	2	1	0	2
4	25%	10%	6	2	15	3	2	10	1	1	3	1	0	2
4	25%	15%	9	4	22	5	2	15	1	1	4	1	1	3
4	25%	20%	12	5	29	7	3	19	1	1	6	2	1	5
4	25%	25%	17	8	37	10	5	24	2	2	7	3	1	6

Table S6. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 50% coverage*

Estimated effect of antibacterial mouthwash on Percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 50%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	18.5	14.6	70.8	18.7	14.7	71.7	18.2	14.1	68.8	18.4	14.4	70.1
2	0%	10%	36.9	28.9	85.2	37.3	29.2	86.4	36.0	28.0	82.5	36.5	28.6	84.3
2	0%	15%	54.7	42.9	99.3	55.5	43.5	100.8	53.3	41.4	96.0	54.2	42.4	98.2
2	0%	20%	72.2	56.6	113.1	73.4	57.5	115.0	70.0	54.4	109.1	71.3	55.9	111.8
2	0%	25%	89.3	70.0	131.8	90.9	71.2	134.4	86.2	67.0	126.8	88.1	69.0	130.2
3	5%	0%	-28.5	-33.3	-25.3	-28.3	-33.1	-25.1	-28.4	-33.3	-25.3	-29.1	-34.0	-25.9
4	5%	5%	-11.3	-17.6	34.5	-10.9	-17.2	35.5	-11.5	-18.0	33.0	-12.3	-18.6	32.6
4	5%	10%	-11.3	-17.6	34.5	6.4	-2.9	51.3	5.3	-4.3	47.5	4.5	-4.8	47.4
4	5%	15%	23.1	10.3	63.2	24.0	11.2	65.0	22.3	9.1	60.7	21.5	8.7	60.7
4	5%	20%	40.9	24.0	78.3	42.2	25.1	80.2	39.1	22.1	74.5	38.7	22.0	75.2

4	5%	25%	57.3	37.4	96.3	58.9	38.8	99.0	54.8	35.0	92.2	54.7	35.0	93.0
3	10%	0%	-54.3	-62.3	-48.8	-54.0	-62.1	-48.4	-54.3	-62.3	-48.8	-55.2	-63.0	-49.6
4	10%	5%	-39.1	-48.9	-2.4	-38.7	-48.5	-1.4	-39.3	-49.1	-3.6	-40.4	-50.0	-4.9
4	10%	10%	-23.7	-35.8	15.9	-23.0	-35.2	17.4	-24.1	-36.4	14.2	-25.3	-37.4	13.0
4	10%	15%	-7.4	-22.1	31.5	-6.4	-21.3	33.0	-8.1	-23.1	28.9	-9.5	-24.2	27.7
4	10%	20%	8.8	-9.3	45.5	10.0	-8.1	47.6	7.7	-10.7	43.2	6.2	-11.8	41.9
4	10%	25%	25.3	4.0	67.1	26.9	5.4	69.7	23.7	2.0	62.3	21.9	1.0	61.8
3	15%	0%	-74.8	-82.4	-68.2	-74.6	-82.3	-67.9	-74.9	-82.6	-68.2	-75.4	-82.9	-68.9
4	15%	5%	-63.4	-73.9	-32.4	-63.1	-73.7	-31.5	-63.6	-74.0	-33.3	-64.5	-74.6	-34.9
4	15%	10%	-50.5	-63.8	-16.4	-49.9	-63.4	-15.2	-50.7	-64.2	-17.7	-51.9	-65.0	-19.6
4	15%	15%	-36.9	-53.5	-4.2	-36.0	-52.9	-2.5	-37.5	-54.1	-5.6	-39.0	-55.1	-7.6
4	15%	20%	-22.1	-41.4	11.9	-21.0	-40.6	12.9	-22.8	-42.4	10.7	-24.7	-43.7	9.5
4	15%	25%	-6.9	-29.3	36.6	-5.5	-28.1	39.3	-7.9	-30.7	31.3	-10.1	-32.2	30.5
3	20%	0%	-88.1	-93.7	-82.3	-87.9	-93.6	-82.1	-88.2	-93.8	-82.4	-88.5	-93.9	-82.8
4	20%	5%	-81.5	-89.2	-59.1	-81.3	-89.0	-58.6	-81.6	-89.3	-59.4	-82.2	-89.6	-60.2
4	20%	10%	-72.6	-83.8	-45.4	-72.2	-83.6	-44.9	-72.9	-84.0	-45.9	-73.7	-84.4	-47.4
4	20%	15%	-61.7	-76.7	-29.7	-61.1	-76.4	-29.0	-62.0	-77.1	-30.4	-63.3	-77.7	-32.1
4	20%	20%	-50.2	-69.0	-12.6	-49.3	-68.5	-11.6	-50.8	-69.6	-13.7	-52.5	-70.5	-15.9

4	20%	25%	-37.5	-60.0	5.5	-36.3	-59.3	6.7	-38.3	-60.9	3.3	-40.3	-62.0	0.7
3	25%	0%	-95.0	-98.1	-91.1	-94.9	-98.0	-91.0	-95.1	-98.1	-91.2	-95.2	-98.1	-91.4
4	25%	5%	-91.8	-96.3	-78.2	-91.7	-96.2	-77.8	-91.9	-96.3	-78.6	-92.1	-96.4	-79.3
4	25%	10%	-87.3	-94.1	-67.8	-87.1	-94.0	-67.2	-87.5	-94.2	-68.5	-87.9	-94.4	-69.5
4	25%	15%	-80.8	-90.9	-54.9	-80.4	-90.8	-54.1	-81.0	-91.1	-55.9	-81.7	-91.4	-57.4
4	25%	20%	-72.4	-86.5	-39.9	-71.8	-86.3	-38.7	-72.8	-86.8	-41.5	-73.9	-87.2	-43.5
4	25%	25%	-63.1	-81.4	-23.5	-62.3	-81.0	-21.9	-63.7	-81.9	-25.7	-65.1	-82.4	-28.2

Table S7. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 80% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 80%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI), 100 person-years			Incidence at the oropharynx(95%CI), 100 person-years			Incidence at the anorectum (95%CI), 100 person-years			Incidence at the urethra (95%CI), 100 person-years		
1	0%	0%	44	37	50	26	21	31	9	8	11	8	5	12
2	0%	5%	58	47	79	34	28	51	12	10	18	10	7	16
2	0%	10%	69	56	92	42	34	58	15	12	19	12	8	19
2	0%	15%	82	65	102	50	39	62	17	14	22	14	10	23
2	0%	20%	93	74	113	57	45	68	19	16	25	16	11	26
2	0%	25%	104	83	127	63	50	77	22	18	27	18	12	30
3	5%	0%	24	19	29	14	11	19	5	4	6	4	3	7
4	5%	5%	36	28	55	22	17	35	8	6	13	7	4	10
4	5%	10%	48	37	66	29	22	43	10	8	15	9	5	14
4	5%	15%	60	46	78	37	28	49	13	10	17	11	6	17
4	5%	20%	71	55	91	44	33	55	15	12	19	12	8	21

4	5%	25%	83	63	105	51	39	64	17	14	22	14	9	24
3	10%	0%	10	6	14	6	4	8	2	1	3	2	1	3
4	10%	5%	18	11	31	11	7	19	4	3	7	3	2	5
4	10%	10%	28	17	44	17	11	28	6	4	9	5	2	9
4	10%	15%	39	26	59	24	16	36	8	6	12	7	3	12
4	10%	20%	49	34	71	30	21	43	10	7	15	8	5	15
4	10%	25%	60	42	83	37	26	50	13	9	17	10	6	18
3	15%	0%	3	1	5	2	1	3	1	0	1	0	0	1
4	15%	5%	6	3	15	4	2	10	1	1	3	1	0	2
4	15%	10%	11	5	26	7	3	17	2	1	5	2	1	4
4	15%	15%	19	9	39	12	6	25	4	2	8	3	1	7
4	15%	20%	29	15	51	17	9	31	6	3	10	5	2	10
4	15%	25%	38	22	59	23	14	36	8	5	13	6	3	13
3	20%	0%	1	0	1	0	0	1	0	0	0	0	0	0
4	20%	5%	1	0	5	1	0	3	0	0	1	0	0	1
4	20%	10%	3	1	10	2	1	7	1	0	2	1	0	2
4	20%	15%	6	2	19	4	1	13	1	0	4	1	0	3
4	20%	20%	11	3	30	7	2	20	2	1	6	2	0	5

4	20%	25%	18	6	37	11	4	24	4	1	7	3	1	8
3	25%	0%	0	0	0	0	0	0	0	0	0	0	0	0
4	25%	5%	0	0	1	0	0	1	0	0	0	0	0	0
4	25%	10%	1	0	3	0	0	2	0	0	1	0	0	1
4	25%	15%	1	0	7	1	0	4	0	0	1	0	0	1
4	25%	20%	3	0	12	2	0	8	1	0	2	0	0	2
4	25%	25%	5	1	19	3	1	12	1	0	4	1	0	3

Table S8. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 80% coverage*

Estimated effect of antibacterial mouthwash on Percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM (%). 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 80%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	29.4	23.1	80.1	29.8	23.4	81.2	28.7	22.4	77.7	29.1	22.9	79.3
2	0%	10%	58.1	45.6	102.5	58.9	46.2	104.1	56.4	43.9	99.1	57.5	45.0	101.4
2	0%	15%	85.6	67.2	128.5	87.0	68.4	131.1	82.8	64.5	121.4	84.5	66.3	125.9
2	0%	20%	111.5	88.1	148.1	113.5	89.7	151.4	107.5	84.0	142.5	110.1	86.7	145.2
2	0%	25%	136.6	108.1	177.5	139.2	110.4	181.7	131.0	102.6	169.2	134.6	106.4	174.6
3	5%	0%	-44.4	-51.2	-39.7	-44.1	-51.0	-39.4	-44.3	-51.3	-39.7	-45.1	-52.0	-40.4
4	5%	5%	-18.0	-28.2	21.8	-17.4	-27.6	23.0	-18.4	-28.7	20.3	-19.5	-29.6	19.3
4	5%	10%	-18.0	-28.2	21.8	9.9	-5.1	49.5	7.8	-7.3	45.0	6.5	-8.1	44.4
4	5%	15%	35.6	15.7	75.5	37.1	17.0	78.1	33.9	13.6	70.5	32.7	12.9	70.8
4	5%	20%	62.4	36.8	103.7	64.7	38.7	106.9	59.2	33.7	97.8	58.4	33.3	98.1

4	5%	25%	87.7	57.4	130.7	90.8	60.0	134.8	83.5	53.1	122.5	82.7	53.2	123.6
3	10%	0%	-77.9	-85.4	-71.3	-77.6	-85.3	-71.0	-77.9	-85.5	-71.4	-78.4	-85.8	-71.9
4	10%	5%	-59.8	-72.1	-28.2	-59.2	-71.8	-27.2	-60.1	-72.4	-29.3	-61.1	-73.0	-31.1
4	10%	10%	-38.1	-55.8	-6.2	-37.3	-55.2	-4.6	-38.7	-56.4	-7.2	-40.3	-57.5	-8.3
4	10%	15%	-13.5	-36.2	24.2	-12.1	-35.1	26.5	-14.6	-37.5	22.6	-16.8	-38.9	21.1
4	10%	20%	12.0	-16.4	58.9	14.0	-14.8	62.0	10.1	-18.5	53.5	7.5	-20.1	52.2
4	10%	25%	37.4	4.1	85.4	40.0	6.3	88.0	34.8	1.0	78.9	31.8	-0.7	76.8
3	15%	0%	-94.0	-97.5	-89.6	-93.9	-97.5	-89.4	-94.1	-97.6	-89.7	-94.2	-97.6	-89.9
4	15%	5%	-86.9	-93.7	-67.6	-86.7	-93.6	-67.1	-87.0	-93.8	-68.3	-87.4	-93.9	-69.2
4	15%	10%	-74.4	-87.3	-45.3	-73.9	-87.1	-44.3	-74.6	-87.5	-46.5	-75.6	-87.9	-48.2
4	15%	15%	-58.1	-77.8	-18.3	-57.2	-77.4	-16.7	-58.5	-78.4	-20.5	-60.2	-79.0	-23.0
4	15%	20%	-37.3	-64.7	10.6	-35.9	-63.9	13.0	-38.3	-65.7	7.2	-40.8	-66.9	4.1
4	15%	25%	-14.5	-48.5	33.7	-12.3	-47.1	37.5	-16.3	-50.2	30.5	-19.4	-51.9	26.0
3	20%	0%	-98.7	-99.7	-97.0	-98.7	-99.7	-96.9	-98.8	-99.7	-97.0	-98.8	-99.7	-97.1
4	20%	5%	-96.9	-99.0	-89.4	-96.9	-99.0	-89.2	-97.0	-99.1	-89.7	-97.1	-99.1	-90.0
4	20%	10%	-93.1	-97.9	-78.1	-93.0	-97.8	-77.6	-93.3	-97.9	-78.7	-93.5	-98.0	-79.5
4	20%	15%	-86.3	-95.9	-59.9	-85.9	-95.8	-59.0	-86.6	-96.0	-61.1	-87.2	-96.1	-62.7
4	20%	20%	-75.8	-92.2	-36.3	-75.1	-92.0	-34.5	-76.2	-92.5	-38.7	-77.4	-92.8	-41.4

4	20%	25%	-61.3	-85.6	-14.5	-60.2	-85.1	-11.9	-62.0	-86.1	-17.4	-64.0	-86.7	-20.0
3	25%	0%	-99.8	-100.0	-99.2	-99.8	-100.0	-99.2	-99.8	-100.0	-99.3	-99.8	-100.0	-99.3
4	25%	5%	-99.4	-99.9	-97.1	-99.4	-99.9	-97.0	-99.4	-99.9	-97.2	-99.5	-99.9	-97.2
4	25%	10%	-98.7	-99.8	-93.4	-98.6	-99.8	-93.3	-98.7	-99.8	-93.6	-98.7	-99.8	-93.8
4	25%	15%	-97.1	-99.5	-86.0	-97.0	-99.5	-85.6	-97.1	-99.6	-86.5	-97.3	-99.6	-87.0
4	25%	20%	-93.8	-99.0	-74.4	-93.6	-99.0	-73.5	-94.0	-99.1	-75.5	-94.2	-99.1	-76.8
4	25%	25%	-88.2	-97.9	-57.2	-87.8	-97.8	-55.7	-88.6	-98.0	-59.1	-89.2	-98.1	-61.4

2) Results based on 3,049 MSM attending a health center in the USA[7]

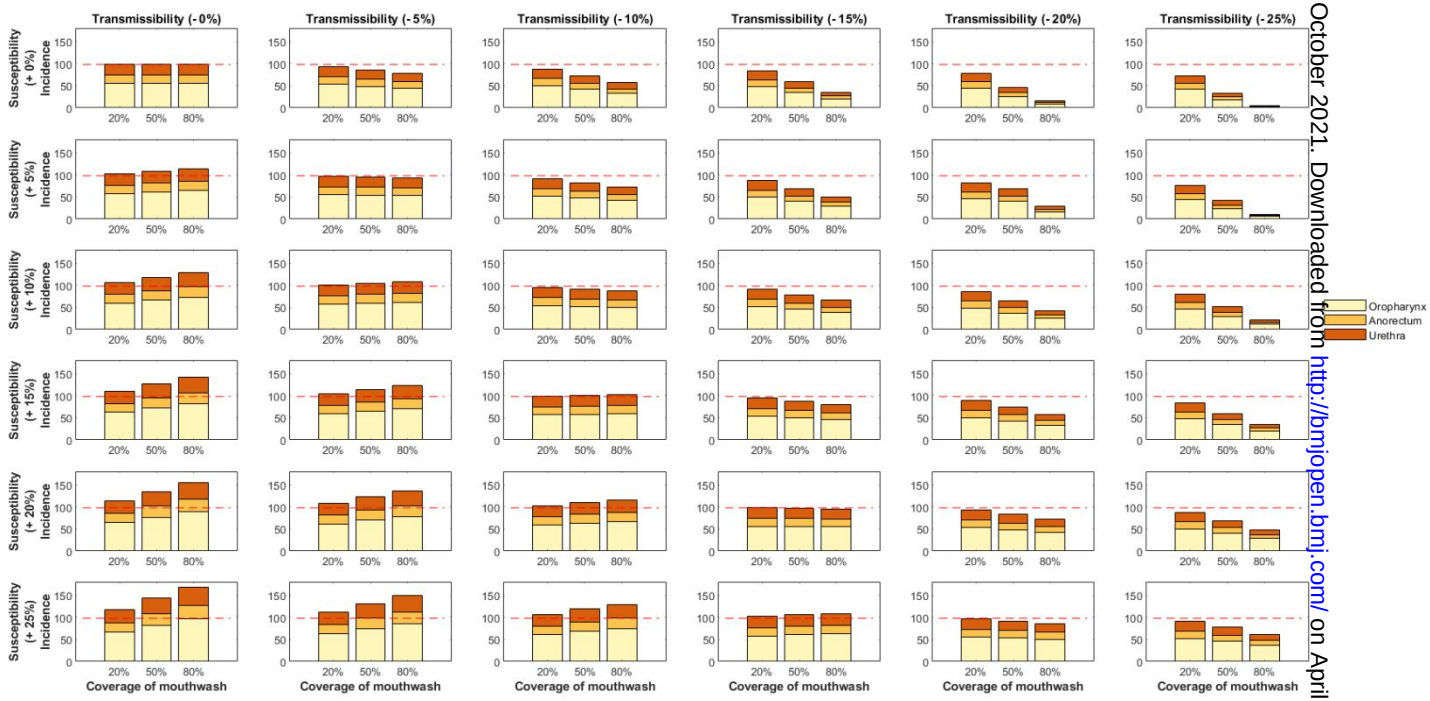

Figure 3a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

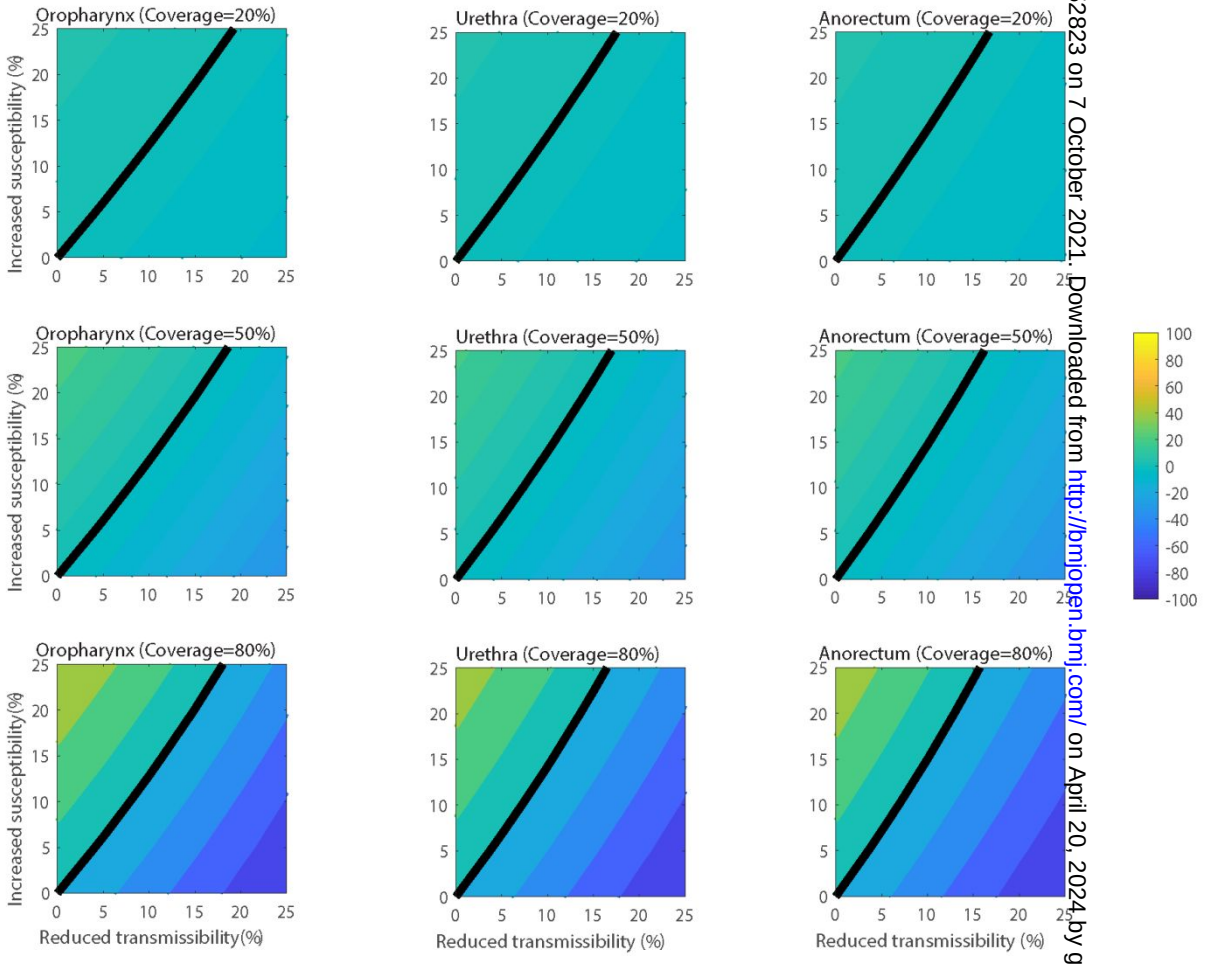

Figure 3b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

3）Results based on 393 MSM attending STD & HIV care clinics in the USA[8]

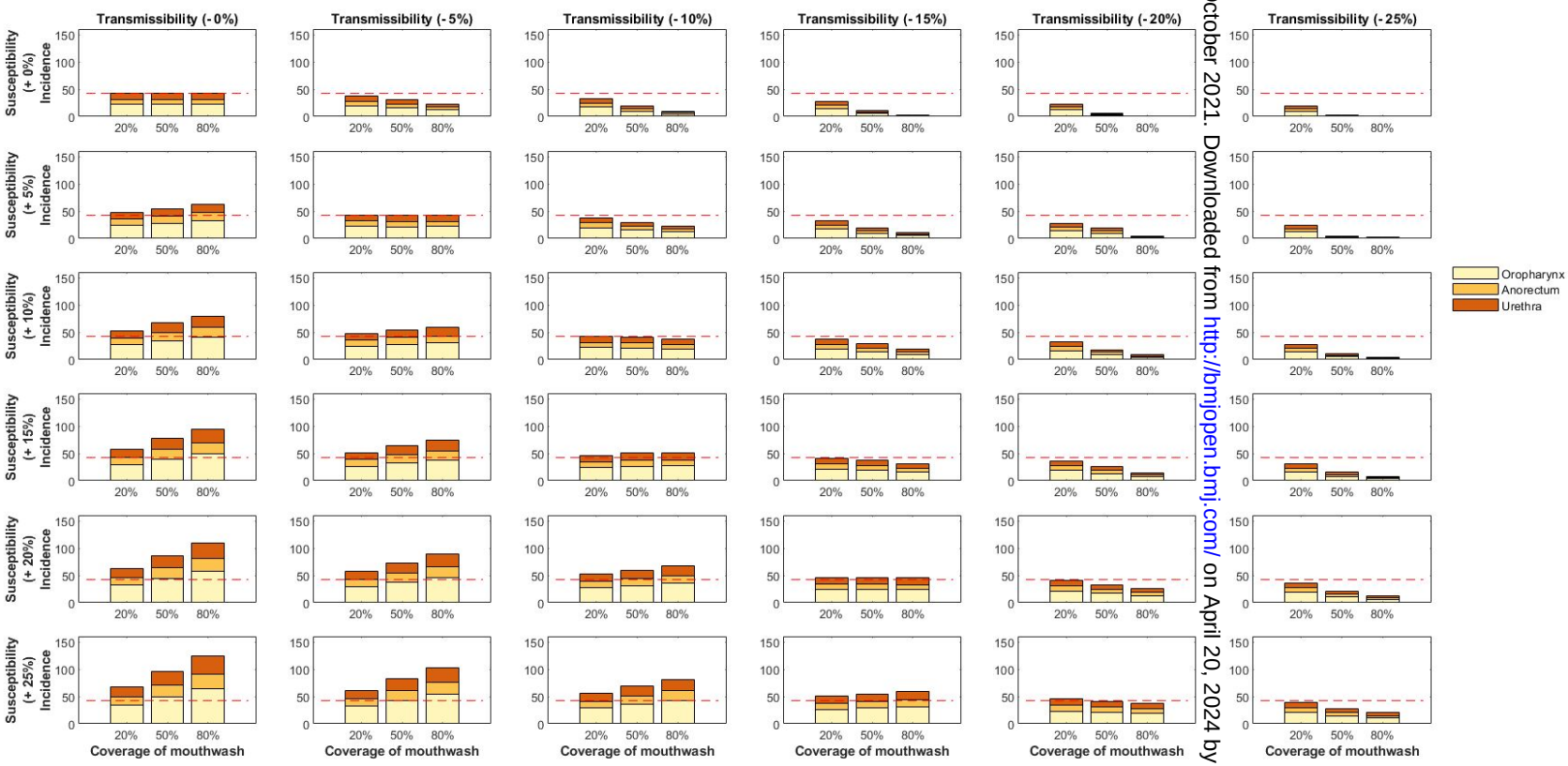

Figure 4a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

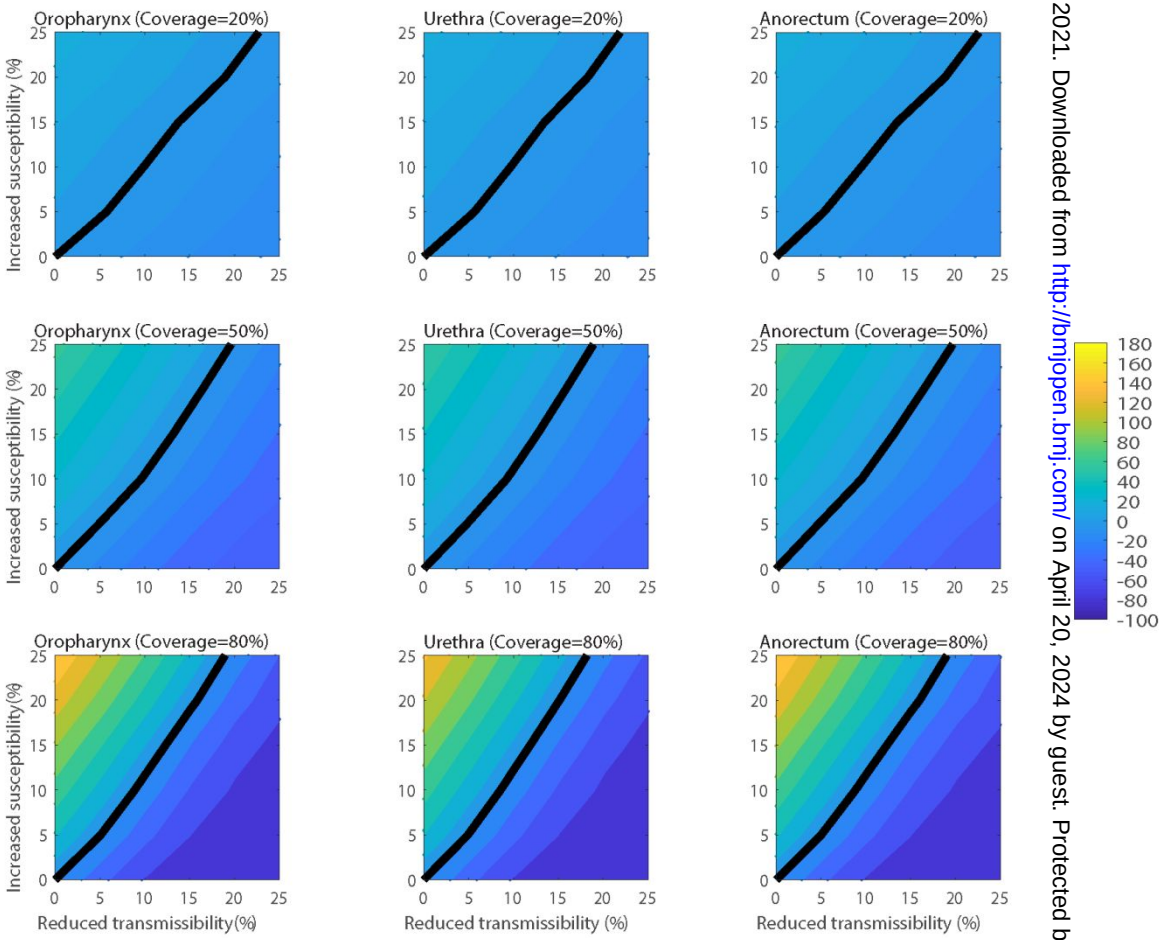

Figure 4b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

4) Results based on 179 MSM with HIV in the USA[9]

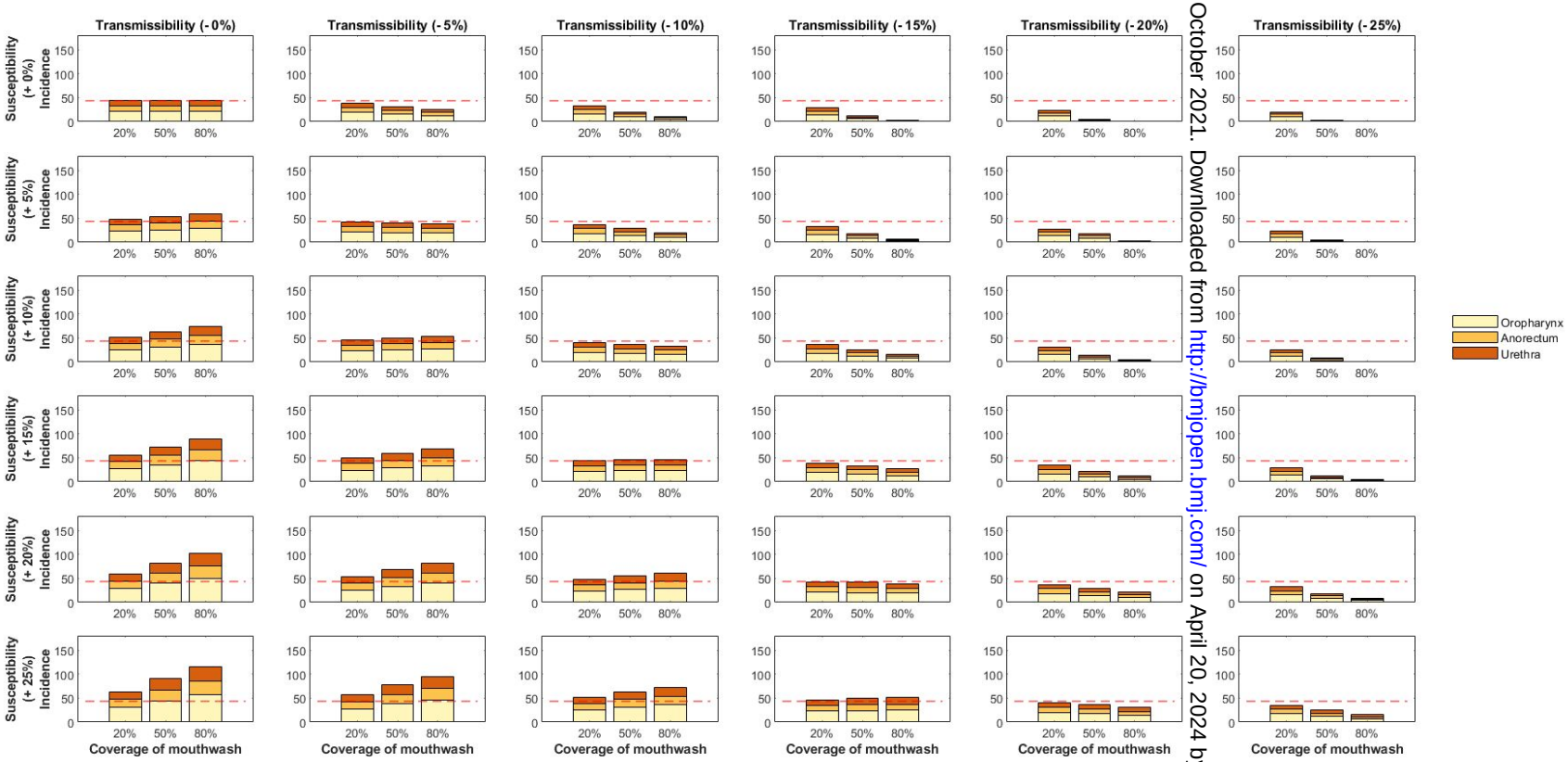

Figure 5a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

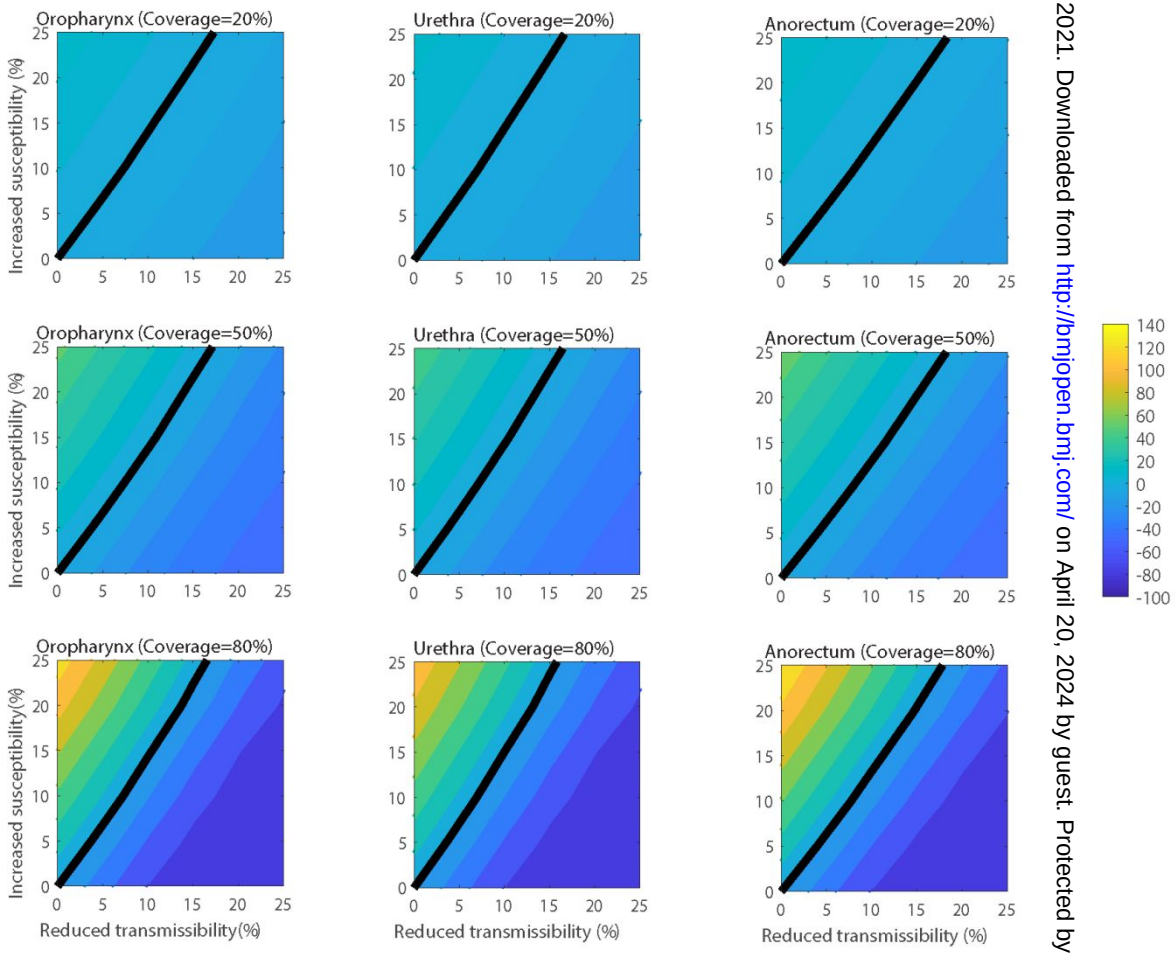

Figure 5b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

5) Results based on MSM surveillance data (271, 242 consultations) from all Dutch STI clinics[10]

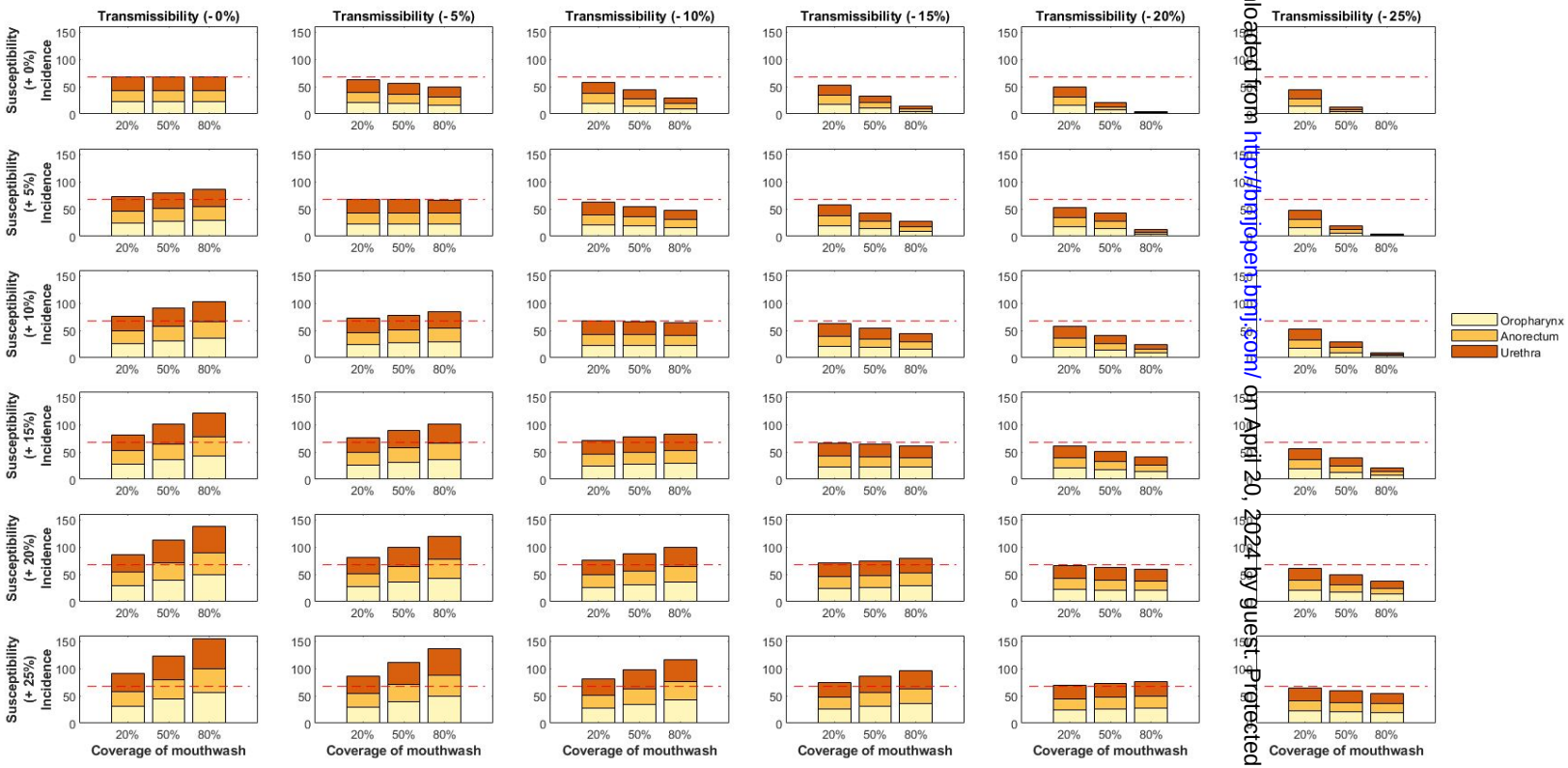

Figure 6a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

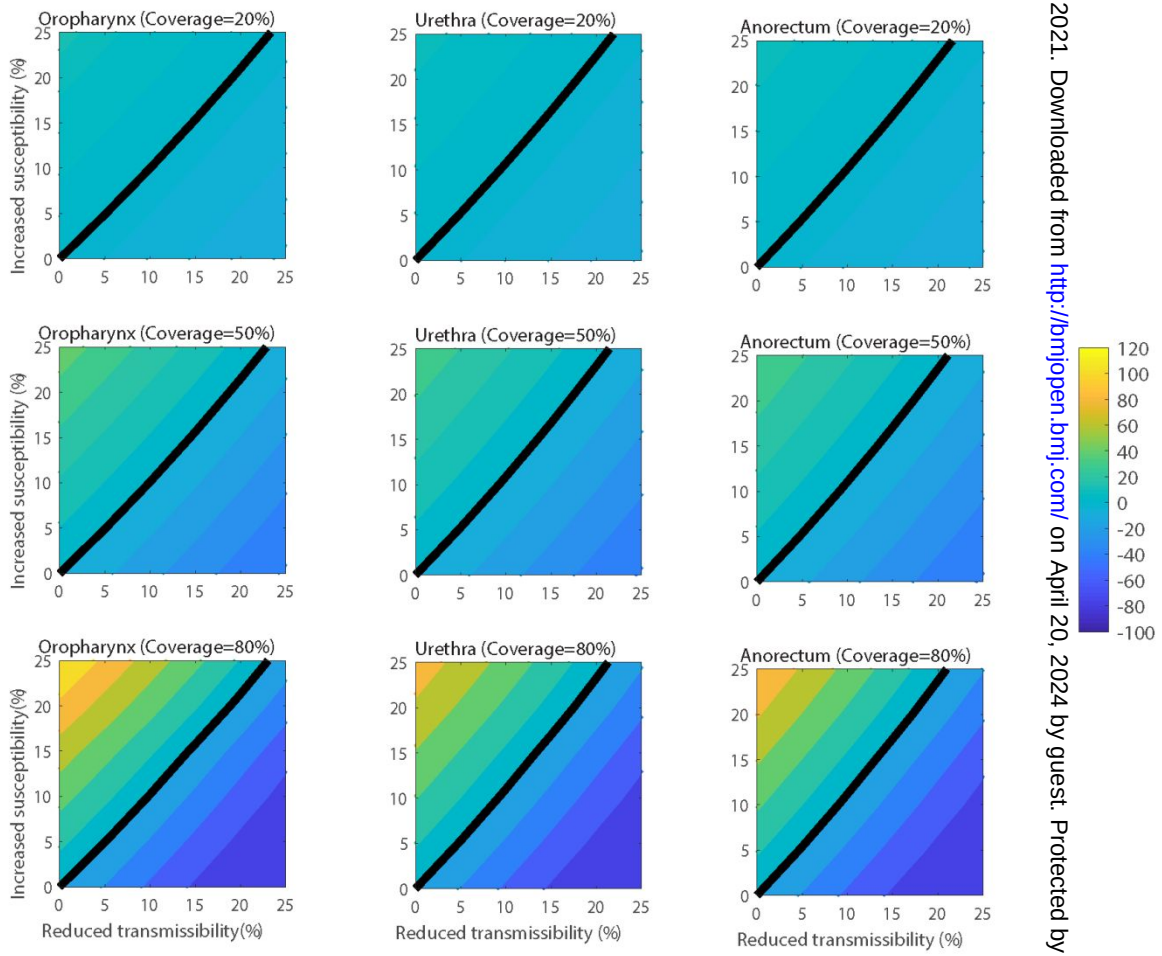

Figure 6b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

6) Results based on 1,610 community samples of MSM in Thailand[11]

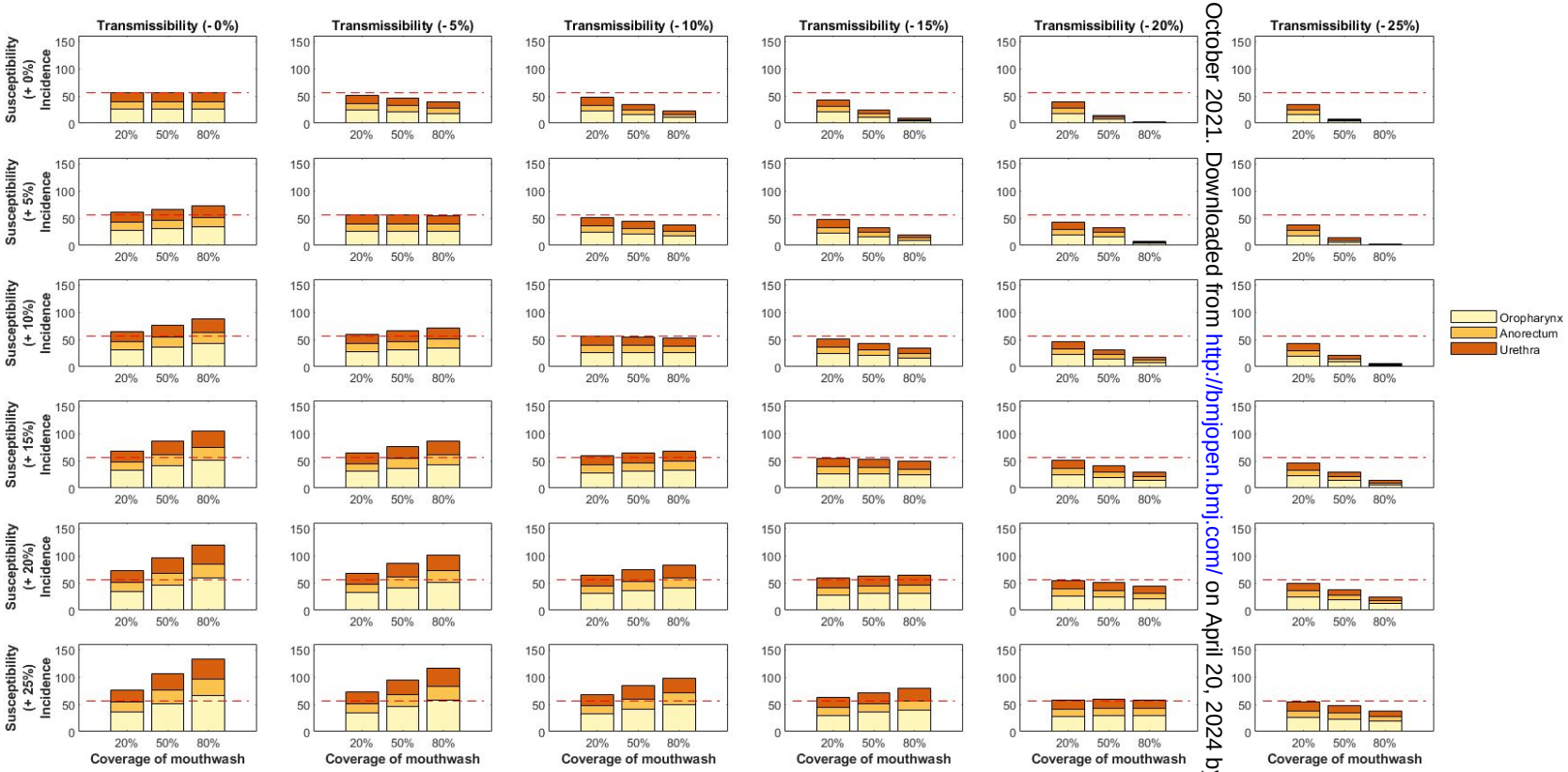

Figure 7a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

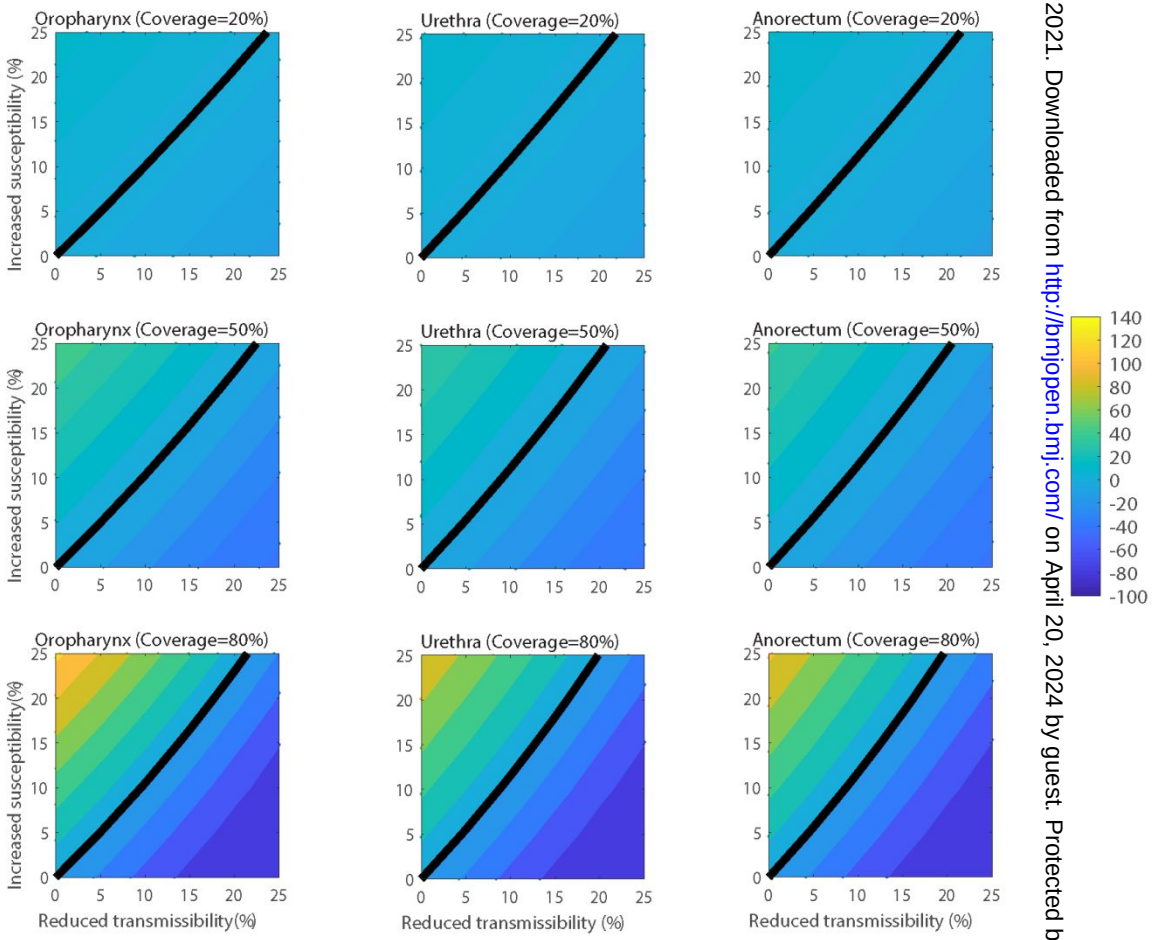

Figure 7b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

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Potential effect of antiseptic mouthwash on the incidence of Neisseria gonorrhoeae among men who have sex with men: a mathematical modelling study

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Title page

Potential effect of antiseptic mouthwash on the incidence of *Neisseria gonorrhoeae* among men who have sex with men: a mathematical modelling study

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ABSTRACT

Objectives: The incidence of *Neisseria gonorrhoeae* and its antimicrobial resistance is increasing in many countries. Antibacterial mouthwash may reduce gonorrhoea transmission without using antibiotics. We modelled the effect that antiseptic mouthwash may have on the incidence of gonorrhoea.

Design: We developed a mathematical model of the transmission of gonorrhoea between each anatomical site (oropharynx, urethra and anorectum) in men who have sex with men (MSM). We constructed four scenarios: (1) mouthwash had no effect; (2) mouthwash increased the susceptibility of the oropharynx; (3) mouthwash reduced the transmissibility from the oropharynx; (4) the combined effect of mouthwash from scenarios 2 and 3.

Setting: We used data at three anatomical sites from 4873 MSM attending Melbourne Sexual Health Centre in 2018 and 2019 to calibrate our models and data from the USA, Netherlands and Thailand for sensitivity analyses.

Participants: Published available data on MSM with multi-site infections of gonorrhoea.

Primary and secondary outcome measures: Incidence of gonorrhoea.

Results: The overall incidence of gonorrhoea was 44 (95% CI: 37 to 50)/100 person-years (PY) in scenario 1. Under scenario 2 (20-80% mouthwash coverage), the total incidence increased (47- 60/100 person-years) and at all three anatomical sites by between 7.4% (5.9- 60.8%) and 136.6% (108.1-177.5%). Under scenario 3, with the same coverage, the total incidence decreased (20-39/100 PY) and at all anatomical sites

by between 11.6% (10.2-13.5%) and 99.8% (99.2-100%). Under scenario 4, changes in the incidence depended on the efficacy of mouthwash on the susceptibility or transmissibility. The effect on the total incidence varied (22-55/100 PY), and at all anatomical sites, there were increases of nearly 130% and large declines of almost 100%.

Conclusions: The effect of mouthwash on gonorrhoea incidence is largely predictable depending on whether it increases susceptibility to or reduces the transmissibility of gonorrhoea.

Strengths and limitations of this study

- Our model is the first to include infection occurring at multiple anatomical sites in the same person and include complex sequential sexual practices to evaluate the potential effect of antiseptic mouthwash on the incidence of gonorrhoea at a population level.
- Our model is the first to assess the effect that antiseptic mouthwash would have on gonorrhoea incidence if it were to increase the susceptibility of the oropharynx to gonorrhoea or/and reduce transmission of gonorrhoea from the oropharynx at a population level.
- There were limited data on the effect of mouthwash on susceptibility or transmissibility, so we had to make assumptions about the magnitude of these effects.

- There were limited data on some variables in our model, including the duration of mouthwash's potential 'treatment' effect, how men would use mouthwash (e.g., oral rinse, oral gargle and oral spray), and when they used mouthwash in relation to sexual exposure.
- Our model included the main sexual practices that involved the use of saliva when men have sex together but not all of the many possible combinations.

INTRODUCTION

The world is experiencing increasing trends in both the rates of gonorrhoea and its antimicrobial resistance that have prompted *Neisseria gonorrhoeae* to be deemed a significant global health threat, particularly among men who have sex with men (MSM) [1-5]. Unfortunately, effective interventions to reduce rates of gonorrhoea have been challenging to identify. Recently researchers have suggested that oropharyngeal gonorrhoea may be critical to the persistence of infection at a population level [6] and that infection may be transmitted by kissing and saliva exchange during sex [7-12]. To address the potential transmission associated with the oropharynx, researchers have been investigating mouthwash as an intervention for gonorrhoea prevention without using antibiotics [13-17].

Three randomised controlled trials have explored the effect of antiseptic mouthwash on gonorrhoea infection [18-20]. The first study of 58 MSM in Australia

suggested that antiseptic mouthwash reduced the ability to culture gonorrhoea from the oropharynx and, therefore, may potentially reduce gonorrhoea transmission [18]. Men in this study who used Listerine mouthwash were less likely to test positive for gonorrhoea at the tonsillar fossae (OR=0.14, 95% CI 0.03 to 0.77) compared with those who used saline. The second study of 530 MSM in Australia assessed whether mouthwash would prevent infection among men who used mouthwash for three months. This study reported no significant risk difference in gonorrhoea positivity between the Listerine mouthwash group and the control (Biotène) group of 2.5% (-1.8 to 6.8%) for oropharyngeal infection or at other sites of -4.4% (-7.4% to -1.3%) for urethral infection and 2.5% (-2.0 to 7.0%) for anorectal infection [19].

The third RCT of 343 MSM in Belgium was stopped early because of the COVID-19 pandemic. It reported some similar findings to the larger RCT with a significant increase in gonorrhea at the oropharyngeal and no significant changes at other anatomical sites in the adjusted analysis [20]. This suggested that Listerine mouthwash increased the risk of oropharyngeal gonorrhoea and raised the possibility that it may increase the risk of oropharyngeal gonorrhoea rather than reduce it. Taken together, the results of the three clinical trials raise the possibility that antiseptic mouthwash may either increase the susceptibility of the oropharynx to *Neisseria gonorrhoeae* or potentially decrease its transmissibility.

The WHO's "Global Action Plan to Control the Spread and Impact of Antimicrobial-Resistance in *Neisseria gonorrhoeae*" recommends the use of mathematical models to analyse new interventions [21]. Zhang et al. assumed that mouthwash could reduce the duration of gonorrhoea at the oropharynx and found that widespread use may significantly reduce the prevalence of gonorrhoea in the population [7]. Based on the newly emerging evidence on mouthwash and gonorrhoea transmission and the mouthwash randomized controlled trials, we used a susceptible-infected-susceptible compartmental model to examine the potential effect of antiseptic mouthwash on gonorrhoea incidence in MSM.

METHODS

Study design

We employed a population-level susceptible-infected-susceptible compartmental model to evaluate the potential effects of antiseptic mouthwash on the incidence of gonorrhoea in MSM. The model structure was based on our previously published multi-site infection model [7 22]. (online supplemental figure S1). Differential equations are provided in the online supplemental information.

Data resources

We used gonorrhoea diagnosis data of 4873 MSM attending Melbourne Sexual Health Centre (MSHC) using Nucleic Acid Amplification Test (NAAT) in 2018 and 2019 to calibrate our models [22]. The percentage of positivity was 'oropharynx infection only' (2.96%), 'urethra infection only' (0.31%), 'anorectum infection only' (3.16%), 'oropharynx and urethra co-infection' (0.21%), 'oropharynx and anorectum co-infection' (2.46%), 'urethra and anorectum co-infection' (1.19%), and 'oropharynx, urethra and anorectum co-infection' (0.72%). (online supplemental information, Data source, online supplemental table S1).

Neisseria gonorrhoeae transmission routes

We simulated gonorrhoea transmission through (1) anal sex; (2) penile–oral sex; (3) rimming; (4) kissing; (5) oral sex followed by anal sex (or vice versa) (penis acts as a mediator and carries *Neisseria gonorrhoeae* to the oropharynx or anorectum); (6) using saliva as a lubricant for anal sex (pass *Neisseria gonorrhoeae* from his oropharynx to his urethra); (7) oral sex followed by oral-anal sex (rimming) or vice versa (oropharynx acts as a mediator and carries *Neisseria gonorrhoeae* to the urethra or anorectum) [22].

Model parameterisation and calibration

We collected behavioural and gonorrhoea progression data in the assumption for

our models' parameters /to inform parameter values for the models. (online supplemental information, Data source, online supplemental table S2). We used MATLAB R2019a to conduct numerical simulations and perform the statistical analysis. We sampled the parameter space using Latin Hypercube Sampling [23 24] within the parameter uncertainty bounds ranges and generated a pool of 1000 parameter sets. Using each sampled set of parameters as the initial points, we simulated the transmission model. We used the 'trust-region-reflective' method ('fmincon' in MATLAB [25]) for the optimisation process to search for the parameter sets that is best fitted to the empirical prevalence of the infections. We then calibrated the model-simulated site-specific gonorrhoea prevalence at equilibrium to empirical gonorrhoea diagnosis data at each anatomical site (i.e., oropharynx, urethra, and anorectum), as well as multi-site infection (oropharynx and urethra together, oropharynx and anorectum together, urethra and anorectum together, oropharynx and urethra and anorectum together. We define the goodness-of-fit as the sum square error between the prevalence levels based on model simulations and empirical data for each simulation. We then ranked the goodness-of-fit in ascending order (the best-fitted simulations on the top) and selected the top 10% of 1000 simulations. We regarded the selected 10% simulations as the pool of parameter sets that were best calibrated to the empirical data and used these simulations to estimate the 95% confidence intervals of the output indicators. The study methods and goodness-of-fit of model have been reported previously [22].

Scenarios for the modelled effect of mouthwash on gonorrhoea incidence

Following model calibration, we established four scenarios to evaluate antiseptic mouthwash's effectiveness on the incidence of gonorrhoea. We estimated the number of new infections at any given time and calculated the incidence as the ratio between the number of new infections and the number of susceptible [7 22 26]. The effect of antiseptic mouthwash on transmissibility and susceptibility between two men is shown in Figure 1. We constructed the following four scenarios: (1) mouthwash had no effect on *Neisseria gonorrhoeae*; (2) mouthwash increased the susceptibility of acquiring oropharyngeal gonorrhoea, during sexual practices including penile–oral sex (from the urethra to oropharynx), rimming (from the anorectum to oropharynx), and kissing (from the oropharynx to oropharynx); (3) mouthwash reduced the transmissibility from an infected oropharynx, during sexual practices including penile–oral sex (from the oropharynx to urethra), rimming (from the oropharynx to anorectum), kissing (from the oropharynx to oropharynx), using saliva as a lubricant for anal sex (from own oropharynx to own urethra), oral sex followed by oral-anal sex (rimming) or vice versa (oropharynx acts as a mediator and carries *Neisseria gonorrhoeae* from the oropharynx to the anorectum); (4) mouthwash reduced transmissibility from the oropharynx and increased susceptibility to acquiring oropharyngeal gonorrhoea, that is, a combined scenario of (2) and (3).

In our simulations, we examined scenarios for the potential efficacy of mouthwash that would increase the susceptibility and reduce the transmissibility by 5%, 10%, 15%, 20% and 25% for using mouthwash shortly before or immediately after each sexual act. Like previous studies [19 20], we defined the population coverage of mouthwash as the proportion of MSM who used mouthwash daily.

Sensitivity analysis

We identified five similar studies that reported multi-site infections of gonorrhoea using NAAT, including (1) 3,049 MSM, attending a health centre in Boston, Massachusetts, during 2012-2016 [9]; (2) 393 MSM attending STD & HIV care clinics in the USA during 2018-2019 [27]; (3) 179 MSM living with HIV in Birmingham, Alabama, during 2014-2016 [28]; (4) MSM surveillance data (271,242 consultations) from nation-wide Dutch STI clinics during 2008-2017 [29]; and (5) 1,610 MSM attending a community-led test and treat cohort in Thailand during 2015-2016 [30]. (online supplemental information, Data source, online supplemental table S1). We also modelled the potential effects of antiseptic mouthwash on the gonorrhoea incidence using the above five additional datasets.

Patient and public involvement

Our study was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or to interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Figure 1 shows the potential effects of mouthwash on the incidence of gonorrhoea at any anatomical site and also the effect at individual anatomical sites: oropharynx, anorectum and urethra. In the absence of any effect of mouthwash (scenario 1), the incidence of gonorrhoea at all three anatomical sites was 44 (95% CI: 37 to 50) /100 person-years (PY): 26 (95% CI: 22 to 31) /100 PY at the oropharynx, 9 (95% CI: 8 to 11) /100 PY at the anorectum and 8 (95%CI: 5 to 12) /100 PY at the urethra. (online supplemental information, Supplementary Results, online supplementaltable S3-8).

If mouthwash increased the oropharynx's susceptibility to *Neisseria gonorrhoeae* (scenario 2), then the incidence would increase at all three sites. The magnitude of the increase would depend on the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20% the incidence at the oropharynx, percentage changed between 7.5% (95% CI: 5.9 to 61.6 %) to 37.3% (95% CI: 29.3 to 85.4%), at the anorectum percentage changed between 7.3% (95% CI: 5.7 to 59.2%) to 36.0% (95% CI: 28.0 to 81.6 %), and at the urethral it increased by between 7.4% (95% CI: 5.8 to 60.3 %) to 36.5% (95% CI: 28.6 to 83.4 %) when the susceptibility increased from

between 5% and 25%. When the population coverage of mouthwash uses increased, the magnitude of the incidence also increased. (Figure 2, 3).

If mouthwash were to reduce the transmissibility of *Neisseria gonorrhoeae* from the oropharynx (scenario 3), then the incidence of gonorrhoea would reduce at all three sites. As for scenario 3, the magnitude of the decrease would depend on the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20% the percentage change in incidence at the oropharynx from -11.5% (95% CI: -13.5 to -10.1%) to -54.1% (95% CI: -62.0 to -48.6%) at the anorectum from -11.9% (95% CI: -13.9 to -10.5%) to -54.5% (95% CI: -62.3 to -48.9%) and at the urethral from -11.6% (95% CI: -13.6 to -10.2%) to -55.4% (95% CI: -62.9 to -49.8%) when the susceptibility increased from between 5% and 25%. When the population coverage of mouthwash uses increased, the magnitude of the fall in incidence also increased. (Figure 2, 3). (online supplemental information, Supplementary Results, online supplemental table S2-7).

If mouthwash increased the susceptibility of the oropharynx to *Neisseria gonorrhoeae* and reduce the transmissibility of *Neisseria gonorrhoeae* from the oropharynx (scenario 4), the combined effect of mouthwash on incidence depends on the varying efficacy of both transmissibility and susceptibility and the coverage of mouthwash in the MSM population. With a mouthwash coverage of 20%, mouthwash

could result in negative percentage change in incidence of -0.8% (95% CI: -10.7 to 42.5%) to -48.4% (95% CI: -56.8 to -12.2%) at the oropharynx, -1.8% (95% CI: -12.0 to 38.8%) to -48.8% (95% CI: -57.2 to -13.8%) at the anorectum, and -2.8% (95% CI: -12.7 to 38.5%) to -49.8% (95% CI: -57.9 to -15.1%) at the urethra, in areas below the zero-threshold curve (Figure 3). Mouthwash also could result in positive percentage change in incidence of 2.7% (95% CI: -1.1 to 53.1%) to 11.6% (95% CI: 2.8 to 56.1%) at the oropharynx, 2.3% (95% CI: -1.6 to 50.5%) to 23.2% (95% CI: 14.8 to 67.1%) at the urethra, and 2.0% (95% CI: -1.8 to 51.0%) to 23.2% (95% CI: 14.8 to 68.0%) at the urethra, in areas above the zero-threshold curve (Figure 1). When the coverage increased, so did the magnitude of the percentage increase. If the incremental reduction in the transmissibility is the same as the incremental increase in susceptibility (scenario 4), the combined effect of mouthwash was projected to reduce gonorrhoea incidence (Figure 2, 3).

We conducted the sensitivity analyses using five different studies with multi-site infection data, and the conclusions were similar. Details in the supplemental materials (online supplemental information, Supplementary Results, online supplemental figure 2-6).

DISCUSSION

To our knowledge, this is the first study to model the effect that mouthwash may have on gonorrhoea incidence at a population level if mouthwash were to increase the

susceptibility or decrease the transmissibility of gonorrhoea infection. We found substantial changes in the incidence of gonorrhoea occurred in all scenarios but that reductions in the transmissibility of gonorrhoea were more potent than increases in the susceptibility if the incremental reduction in the transmissibility is the same as the incremental increase in susceptibility. To date, only one other study has modelled the effect of mouthwash on gonorrhoea incidence [7], but this study only looked at the effect on duration. There has been very little empirical data at present on the effect of mouthwash both on the transmissibility of gonorrhoea in infected men or susceptibility in uninfected men. We hope this work encourages more researchers to explore the effect of mouthwash on the susceptibility and transmissibility of *Neisseria gonorrhoeae* to potentially design an intervention if further studies were to show it was beneficial.

Our study shows that if mouthwash increases the oropharynx's susceptibility in uninfected individuals, it will increase the incidence in the MSM population. Van Dijck et al. [20] reported that mouthwash significantly increase oropharyngeal gonorrhoea incidence in their randomised trial. Van Dijck et al. study was stopped early, and they suggested that the non-significant increase could possibly be explained if Listerine damaged the oropharyngeal mucosa or microbiome. Van Dijck et al. also proposed that Listerine mouthwash may eliminate the beneficial effects on the carriage of pathogenic *Neisseria*, and that this effect was potentially mediated through inhibition of some commensal *Neisseria* species that normally act to limit the growth or carriage of

Neisseria gonorrhoeae or *Neisseria meningitidis* [31 32]. More research will be needed to investigate the benefits and harms of using mouthwash as an intervention for gonorrhoea prevention. Further study is required to explore how mouthwash changes the oral microbiome and resistome and inhibits the growth of commensal *Neisseria* species.

Our study shows that if mouthwash reduced the transmissibility from the oropharynx in the infected individuals, then widespread use of mouthwash would reduce the incidence of gonorrhoea at all sites in MSM at a population level. Mouthwash may reduce transmissibility by reducing the load of viable *Neisseria gonorrhoeae* bacteria at the oropharynx. Indeed, the first randomised trial undertaken by Chow so substantial and significant reductions in culture-positive gonorrhoea following a minute use of mouthwash [33 34]. Chow et al. further examined the effectiveness of antiseptic mouthwash compared to standard of care antibiotics for the treatment of oropharyngeal gonorrhoea and found that mouthwash was not effective albeit in a small RCT among 12 men. The authors concluded from this study and their first randomised study that mouthwash might have a temporary effect on the load of viable organisms but may not have a prolonged effect [35]. The OMEGA (oral mouthwash use to eradicate gonorrhoea) trial examined the effect of mouthwash on the incidence of gonorrhoea by comparing an intervention mouthwash (Listerine) versus a control mouthwash (Biotène) among 530 men using daily mouthwash for three months. Findings from the OMEGA trial found that men who use the intervention mouthwash

(Listerine) had a 4.4% lower positivity of urethral gonorrhoea compared to the control mouthwash group and one possible explanation for this is that mouthwash reduced transmission from the oropharynx to their own penis [19].

Understanding the effect of mouthwash on the incidence of gonorrhoea could provide additional potential interventions for controlling the increasing gonorrhoea incidence [36], if it were to be widely used [10 13]. There are several issues that need to be clarified in relation to mouthwash. First, the duration of any potential effect of antiseptic mouthwash on the transmissibility of *Neisseria gonorrhoeae* at the oropharynx should be quantified because it determines when mouthwash should be used in relation to sexual activities. Second, although two randomised controlled trials did not demonstrate a decline in the incidence of overall gonorrhoea [19 20], one study showed a decline in the incidence of urethral gonorrhoea [20]. However, it does not mean mouthwash did not reduce the bacterial load in infected individuals. Third, the incidence measured by the RCT has its limitations. Although it measures the protective effects of mouthwash in these selected individuals, the RCT did not measure the transmissibility of infected individuals in the next generation of gonorrhoea transmission in the whole MSM population since sexual partners were not tested for gonorrhoea.

This modelling study has some limitations. First, we assumed the effect of mouthwash on susceptibility or transmissibility, and we choose equal estimates with

only moderate effect sizes of 0-25% effects. If mouthwash had a more potent effect on either susceptibility or transmissibility, the effect on the incidence would be considerably greater. We did, however, show a moderate effect on the incidence of infection with the estimates we chose. Second, we have made several assumptions about mouthwash use in our study because no data was available for these estimates. These assumptions included the duration of the potential 'treatment' effect of mouthwash, how mouthwash would be used by men (e.g. oral rinse, oral gargle and oral spray) when they used mouthwash (we assumed it was used before sex) and the effect of different ways of using it [37]. Third, the diagnosed gonorrhoea data in our model was at a single time point, and we could not calibrate our model to a temporal trend of the epidemic. Fourth, the transmission of gonorrhoea may be largely biased towards high-risk MSM, and we did not separate the transmission by risk groups in our model. Finally, we acknowledge that sexual practices involved saliva may be more complex, and our model may not capture all sexual practices involving saliva. However, our gonorrhoea model does provide a good fit single-site and multi-site infection at the oropharynx, urethra and anorectum [22]. The good fit indicated an accurate reflection of the actual transmission of gonorrhoea among MSM.

CONCLUSIONS

In conclusion, our finding suggests that mouthwash could either increase or decrease the incidence of gonorrhoea at a population level depending on whether it increases susceptibility or decreases transmissibility. Our study highlights the need for

more empirical data about the potential effect of mouthwash and the magnitude of this effect.

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Footnotes

Contributors: XX, CKF and LZ conceived and designed the study. EPFC contributed to the study design. XX, and LZ established the model; XX, and LZ did the analysis. MWS contributed in modelling and gave overall feedback to the analysis. XX wrote the first draft. EPFC, ZZ, CW, JJO, CKF and LZ participated in the interpretation of results. All authors reviewed the manuscript and approved the final version.

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Data availability statement: Technical appendix and all data relevant to the study are included in the article or uploaded as supplementary information.

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Figure legends

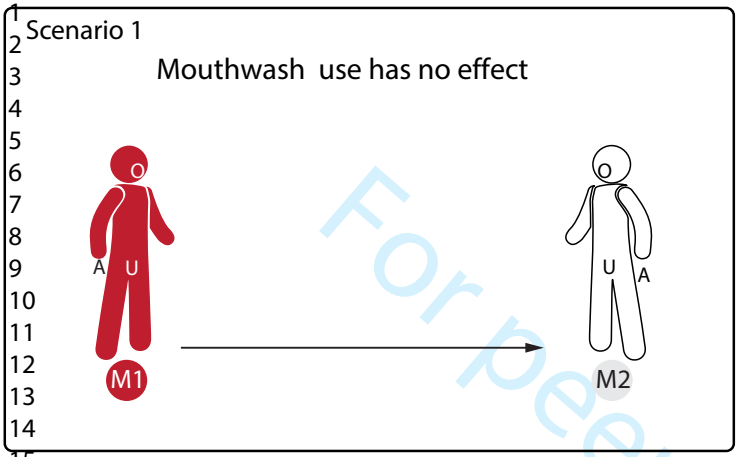
Figure 1. The effect of antiseptic mouthwash on transmissibility and susceptibility between man 1 and man 2 in the one sexual episode

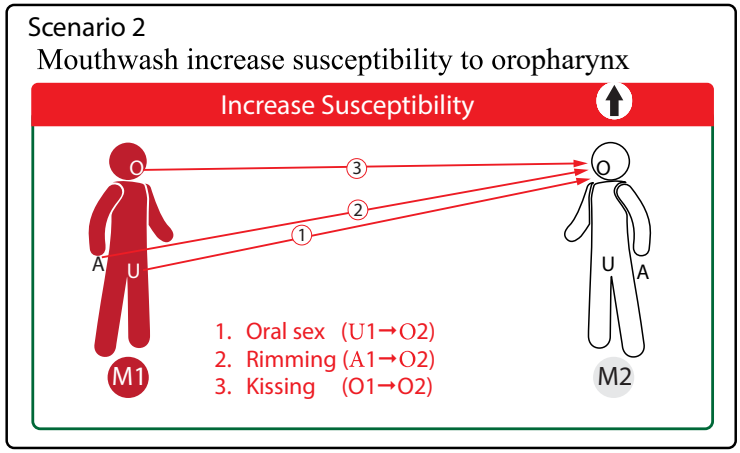
Figure 2. Estimated effect of antiseptic mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM.

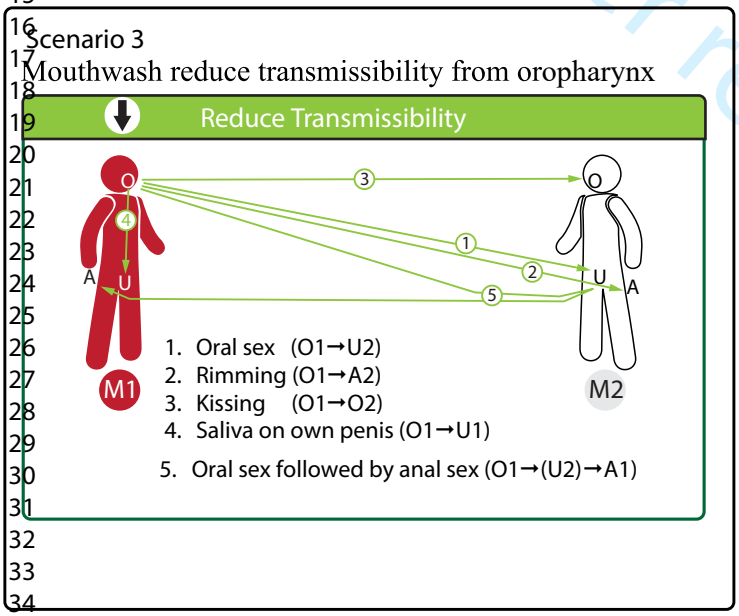
1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

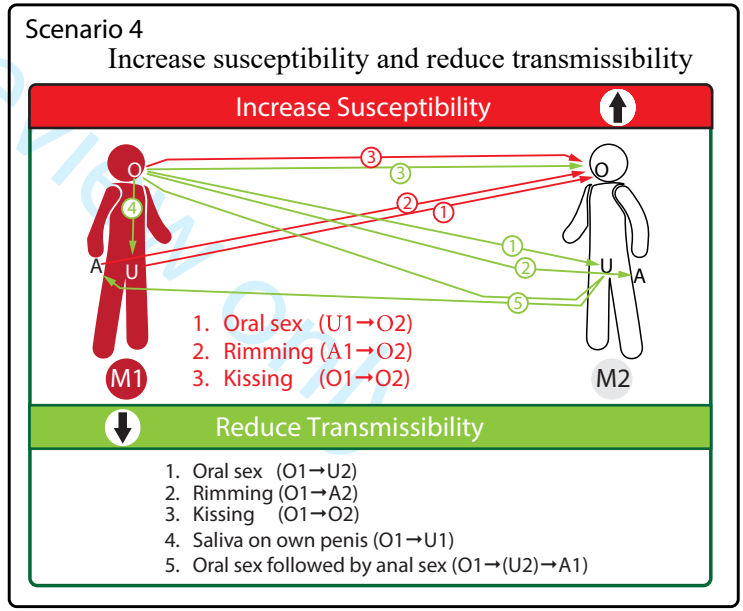
Figure 3. Contour plots for the effect of antiseptic mouthwash on the percentage change (%) of incidence at the oropharynx, anorectum or urethra by increasing susceptibility

of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx. The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

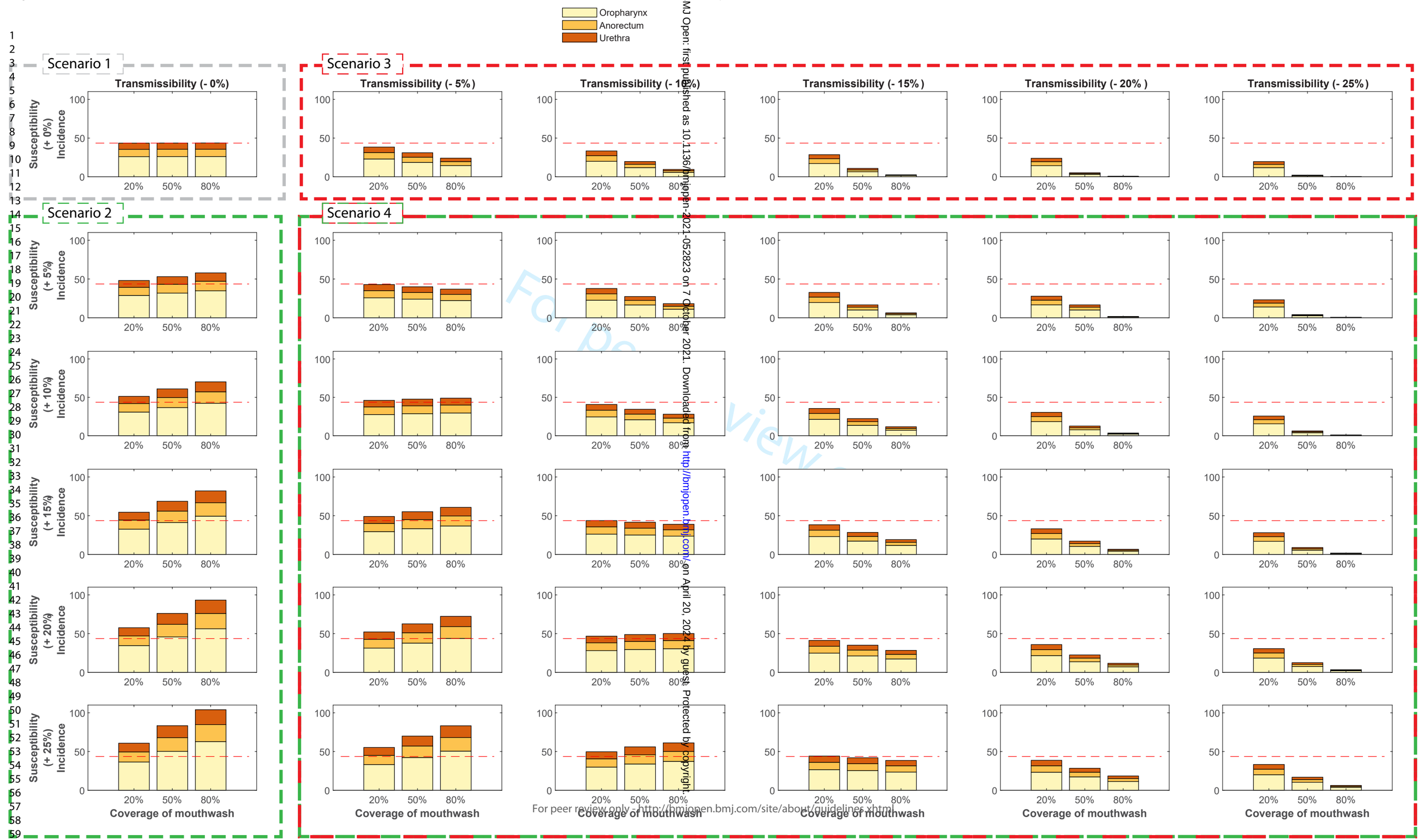


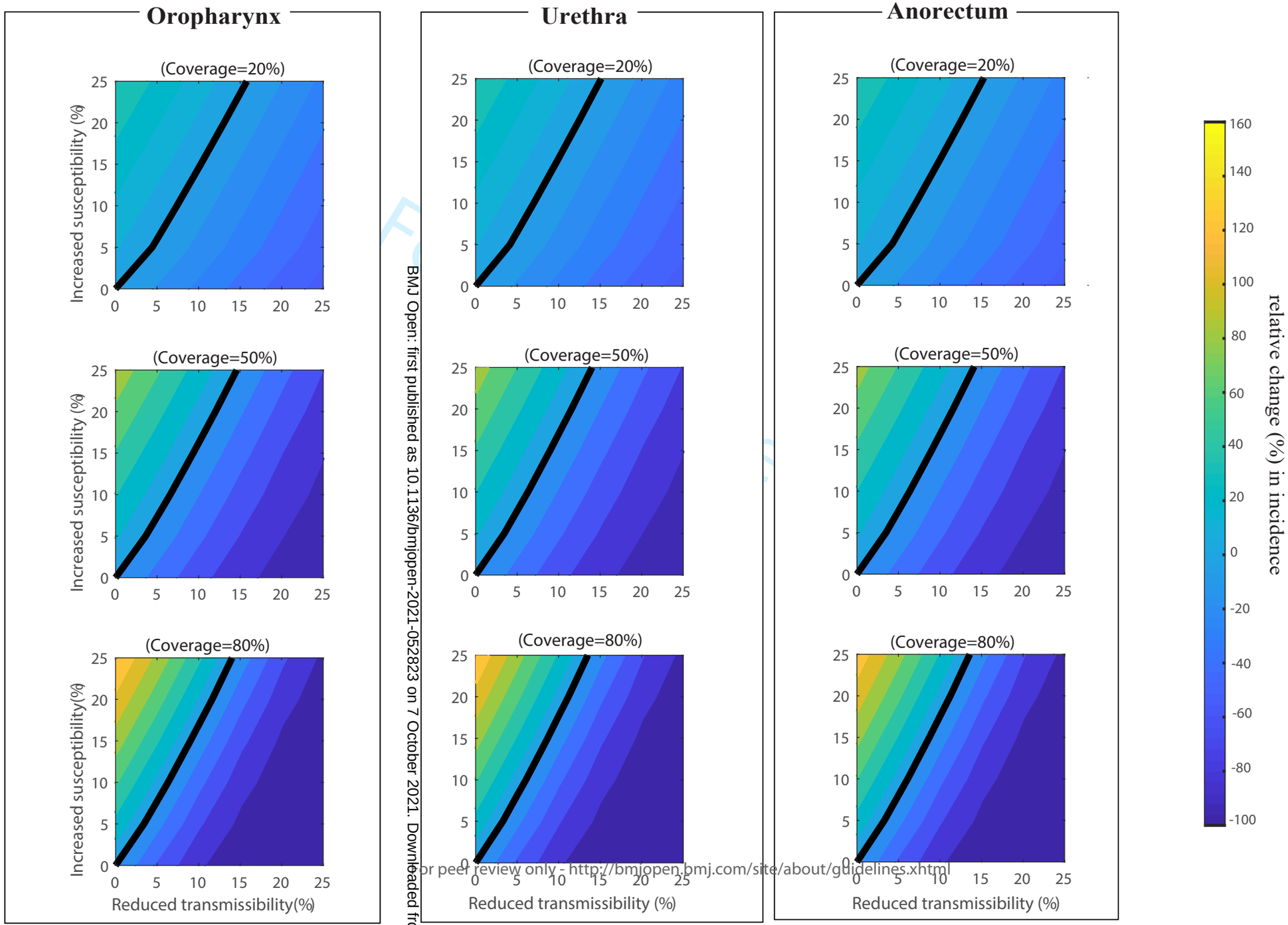






Man1 is infected and Man 2 is suscetible. U=urethra, A=anorectum, O=oropharynx. The numerical subscript number (1 or 2) refers to Man1 or Man 2 (e.g. A1 = anorectum of man 1)





Appendix: Potential effect of antibacterial mouthwash on the incidence of *Neisseria gonorrhoeae* among men who have sex with men: a mathematical modelling study

Literature review

We searched PubMed, up to March 5, 2021, for reports of studies assessing the effect of mouthwash on the prevalence or incidence of gonorrhoea. We used the search terms ("gonorrh*" OR "sexual") AND "mouthwash" and found 27 studies. We were also aware of two articles in The Lancet Infectious Disease. Of the 29 identified sources, 4 randomized controlled trials were observed. One of four studies examined the effectiveness of antiseptic mouthwash for the treatment of oropharyngeal gonorrhoea [1], and another study examined whether Listerine could be used to inhibit the growth of *Neisseria gonorrhoeae*. This study concluded that Listerine could significantly reduce the amount of *Neisseria gonorrhoeae* on the pharyngeal surface[2]. Finally, so we only analysed 2 RCT reported incidence [3 4]. The findings of these two studies may lead to the potential of mouthwash to transmissibility and susceptibility.

Study design

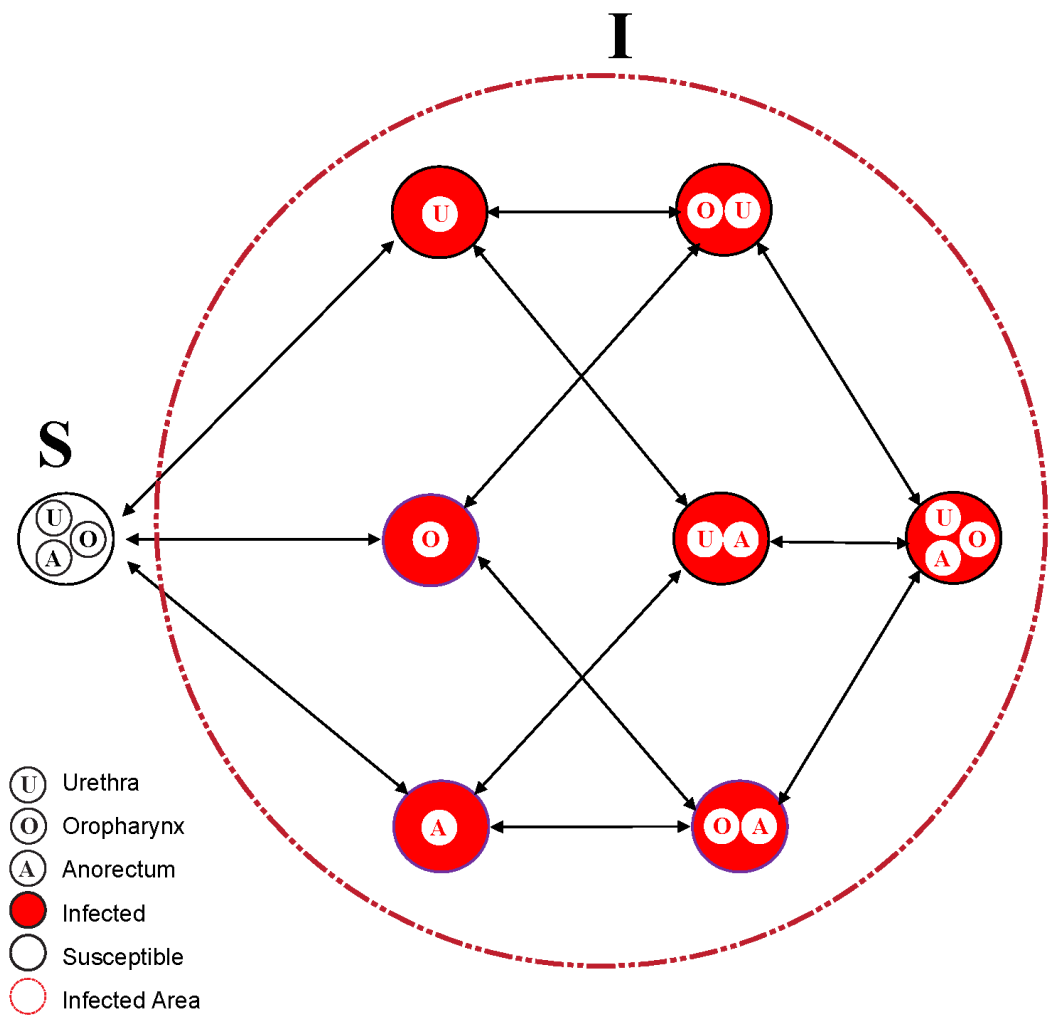


Figure S1. *A compartmental model for the transmission dynamics of Neisseria gonorrhoeae in men who have sex with men.*

U: only urethral infections; O: only oropharyngeal infections; A: only anorectal infections; Anorectum (A); OU: only oropharyngeal and urethral infections; UA: only urethral and anorectal infections; OA: only oropharyngeal and anorectal infections; OUA: oropharyngeal, urethral and anorectal infections; arrow signifies the direction of infection and clearance.

Differential equations

Force of infection

The force of infection Λ takes the following form[5]:

$$\Lambda = \lambda \cdot P$$

$$\lambda = (1 - (1 - \beta \cdot (1 - \varepsilon_c \cdot C))^{\frac{f}{2}})$$

P represents the prevalence of *Neisseria gonorrhoeae*;

β represents the per-act transmission;

C is the percentage of condom use in anal intercourse;

ε_c is the efficacy of condom in preventing transmission of sexually transmitted infections and

f is the frequency of sexual acts that may facilitate transmission.

f is calculated based on the frequency of sexual acts data[5].

S = S(t) is the number of susceptible MSM;

I = I(t) is the number of infected MSM;

I_o is the number of MSM with oropharyngeal infection only;

I_u is the number of MSM with urethral infection only;

I_a is the number of MSM with rectal infection only;

I_{ou} is the number of MSM with oropharyngeal and urethral infection only;

I_{ua} is the number of MSM with rectal, and urethral infection only;

I_{oa} is the number of MSM with oropharyngeal and rectal infection only;

I_{oua} is the number MSM with oropharyngeal, rectal, and urethral infection;

$$N = S + I_o + I_u + I_a + I_{ou} + I_{ua} + I_{oa} + I_{oua}$$

Based on assumptions, the transmission of *Neisseria gonorrhoeae* infection was governed by the following differential equations.

$$\frac{dS}{dt} = -\left(\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}\right)\cdot S + \gamma_o \cdot I_o - \left(\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}\right)\cdot S + \gamma_a \cdot I_a - \left(\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}\right)\cdot S + \gamma_u \cdot I_u$$

$$\frac{dI_o}{dt} = \left(\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}\right)\cdot S - \gamma_o \cdot I_o - \left(\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}\right)\cdot I_o + \gamma_a \cdot I_{oa} - \left(\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}\right)\cdot I_o + \gamma_u \cdot I_{ou} - \lambda_{ooa}\cdot I_o - \lambda_{oou}\cdot I_o$$

$$\frac{dI_u}{dt} = \left(\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}\right)\cdot S - \gamma_u \cdot I_u - \left(\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}\right)\cdot I_u + \gamma_o \cdot I_{ou} - \left(\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}\right)\cdot I_u + \gamma_a \cdot I_{ua} - \lambda_{uua}\cdot I_u - \lambda_{ua2}\cdot I_o$$

$$\frac{dI_a}{dt} = \left(\lambda_{oa}P_{o\_all} + \lambda_{ua}P_{u\_all}\right)\cdot S - \gamma_a \cdot I_a - \left(\lambda_{oo}P_{o\_all} + \lambda_{ao}P_{a\_all} + \lambda_{uo}P_{u\_all}\right)\cdot I_a + \gamma_o \cdot I_{oa} - \left(\lambda_{ou}P_{o\_all} + \lambda_{au}P_{a\_all}\right)\cdot I_a + \gamma_u \cdot I_{ua} - \lambda_{aoa}\cdot I_a - \lambda_{aua}\cdot I_a + \lambda_{ua2} \cdot I_o$$

$$\frac{dI_{ou}}{dt} = \left(\lambda_{oo}P_{o\_\mathrm{all}} + \lambda_{ao}P_{a\_\mathrm{all}} + \lambda_{uo}P_{u\_\mathrm{all}}\right)\cdot I_u - \gamma_o \cdot I_{ou} + \left(\lambda_{ou}P_{o\_\mathrm{all}} + \lambda_{au}P_{a\_\mathrm{all}}\right)\cdot I_o - \gamma_u \cdot I_{ou} - \left(\lambda_{oa}P_{o\_\mathrm{all}} + \lambda_{ua}P_{u\_\mathrm{all}}\right)\cdot I_{ou} + \gamma_a \cdot I_{oua} + \lambda_{oou}\cdot I_o$$

$$\frac{dI_{oa}}{dt} = \left(\lambda_{oa}P_{o\_\mathrm{all}} + \lambda_{ua}P_{u\_\mathrm{all}}\right)\cdot I_o - \gamma_a \cdot I_{oa} + \left(\lambda_{oo}P_{o\_\mathrm{all}} + \lambda_{ao}P_{a\_\mathrm{all}} + \lambda_{uo}P_{u\_\mathrm{all}}\right)\cdot I_a - \gamma_o \cdot I_{oa} - \left(\lambda_{ou}P_{o\_\mathrm{all}} + \lambda_{au}P_{a\_\mathrm{all}}\right)\cdot I_{oa} + \gamma_u \cdot I_{oua} + \lambda_{ooa}\cdot I_o + \lambda_{aoa}\cdot I_a$$

$$\frac{dI_{ua}}{dt} = \left(\lambda_{oa}P_{o\_\mathrm{all}} + \lambda_{ua}P_{u\_\mathrm{all}}\right)\cdot I_u - \gamma_a \cdot I_{ua} + \left(\lambda_{ou}P_{o\_\mathrm{all}} + \lambda_{au}P_{a\_\mathrm{all}}\right)\cdot I_a - \gamma_u \cdot I_{ua} - \left(\lambda_{oo}P_{o\_\mathrm{all}} + \lambda_{ao}P_{a\_\mathrm{all}} + \lambda_{uo}P_{u\_\mathrm{all}}\right)\cdot I_{ua} + \gamma_o \cdot I_{oua} + \lambda_{uua}\cdot I_u + \lambda_{aua} \cdot I_a$$

$$\frac{dI_{oua}}{dt} = \left(\lambda_{oa}P_{o\_\mathrm{all}} + \lambda_{ua}P_{u\_\mathrm{all}}\right)\cdot I_{ou} - \gamma_a \cdot I_{oua} + \left(\lambda_{oo}P_{o\_\mathrm{all}} + \lambda_{ao}P_{a\_\mathrm{all}} + \lambda_{uo}P_{u\_\mathrm{all}}\right)\cdot I_{ua} - \gamma_o \cdot I_{oua} + \left(\lambda_{ou}P_{o\_\mathrm{all}} + \lambda_{au}P_{a\_\mathrm{all}}\right)\cdot I_{oa} - \gamma_u \cdot I_{oua}$$

Data source

Site-specific prevalence data

We used data of 4873 MSM attending Melbourne Sexual Health Centre MSHC in 2018 and 2019 to calibrate our models [6]. We also used five other similar studies with multi-site infection data using NAAT, including (1) 3,049 MSM, attending a health center in Boston, Massachusetts, during 2012-2016 [7]; (2) 393 MSM attending STD & HIV care clinics in the USA during 2018-2019 [8]; (3) 179 MSM living with HIV in Birmingham, Alabama, during 2014-2016 [9]; (4) MSM surveillance data (271,242 consultations) from nation-wide Dutch STI clinics during 2008-2017 [10]; and (5) 1,610 MSM attending a community-led test and treat cohort in Thailand during 2015-2016 [11].

Table S1. *Site-specific prevalence of gonorrhoea* [12]

		Prevalence/ Mean value (95%CI)						
	Sample size	Oropharyngeal only	Urethral only	Rectal only	Oropharyngeal and urethra	Oropharyngeal and rectum	Urethra and rectum both	Oropharyngeal and urethra and rectum
Xu [12]	4,873	2.96 (2.51-3.49)	Empirical data: 0.31 (0.18-0.52)	3.16 (2.70-3.70)	Empirical data: 0.21	2.46 (2.05-2.94)	Empirical data: 1.19 (0.91-1.55)	Empirical data: 0.72 (0.51-1.01)

	(First time visiting MSHC)				(0.11-0.40)			
			Calibrated to community level data:0.01 (0.00-0.02)		Calibrated to community level data: 0.01 (0.00-0.02)		Calibrated to community level data: 0.03 (0.02-0.08)	Calibrated to community level data: 0.03 (0.01-0.05)
Spicknall [7] .	3,049		Empirical data:2.09 (1.63-2.69)		Empirical data:0.98 (0.67- 1.42)		Empirical data: 1.21 (0.86-1.68)	Empirical data:0.75 (0.49-1.14)
		8.50 (7.54-9.55)	Calibrated to community level data:0.20 (0.07-0.32)	6.80 (5.93-7.76)	Calibrated to community level data:0.10 (0.03-0.16)	3.40 (2.81-4.13)	Calibrated to community level data:0.10 (0.04-0.19)	Calibrated to community level data:0.07 (0.02-0.12)
Pol [8]	393		Empirical data:2.54 (1.29-4.78)		Empirical data:1.53 (0.62-3.47)		Empirical data: 0.76 (0.20-2.40)	Empirical data: 0.25 (0.01-1.63)
		2.04 (0.95-4.14)	Calibrated to community level data:0.10 (0.04-0.16)	3.56 (2.04-6.04)	Calibrated to community level data:0.06 (0.02-0.10)	1.53 (0.62-3.47)	Calibrated to community level data:0.02 (0.01-0.05)	Calibrated to community level data:0.01 (0.00-0.02)

Footman [9]	179		Empirical data:0 (0-0)		Empirical data:0.56 (0.03-3.55)		Empirical data:0(0-0)	Empirical data:0(0-0)
		0.56 (0.03-3.55)	Calibrated to community level data:0(0-0)	3.91 (1.72-8.21)	Calibrated to community level data:0.02 (0.01-0.04)	2.23 (0.72- 5.98)	Calibrated to community level data:0(0-0)	Calibrated to community level data:0(0-0)
van Liere [10]	271,242 consultations		Empirical data: 0.85 (0.81-0.89)		Empirical data: 0.33 (0.31-0.36)		Empirical l data:0.95 (0.91-0.99)	Empirical data: 0.73 (0.69-0.77)
		3.02 (2.95-3.09)	Calibrated to community level data:0.03 (0.01-0.06)	10.17 (10.05-10.30)	Calibrated to community level data:0.01 (0.00-0.02)	1.69 (1.64-1.75)	Calibrated to community level data:0.0 (0.01-0.06)	Calibrated to community level data:0.03 (0.01-0.05)
Hiransuthikul [11]	1,610	3.91 (3.04-5.01)	1.93 (1.34-2.76)	5.84 (4.77-7.13)	0.31 (0.11-0.77)	2.24 (1.60-3.12)	0.87 (0.50-1.49)	0.37 (0.15-0.85)

Note: MSHC did not test for urethral NG among asymptomatic MSM before 2018, so multi-site infections would be biased towards symptomatic patients. Hence, we used NG data for 2018-19. We calculated the confidence interval for each parameter using this method [13-15]. Empirical data: The prevalence of urethral gonorrhoea infection in the community at a given point in time will be much lower than STI clinics. Asymptomatic urethral gonorrhoea is uncommon (7.69%) [16], but when it occurs, it is likely to be infectious for 3 to 5 months before the natural clearance. Therefore, the proportion of urethral gonorrhoea cases that are potentially infectious will be the prevalence of urethral gonorrhoea infection in STI clinics multiplied by 1/52 (infectious

for one week till treatment) plus an additional asymptomatic 7.69% of cases who will be infectious for 3 to 5 months. Based on this information, we used previously published methods [5] to calibrate the prevalence of individuals with urethral infection in the community assuming about 92.3% will present symptoms shortly after a successful infection.

Model parameters

Table S2. *Biological and behavioural data of Neisseria gonorrhoeae for model parameterization and calibration*[12]

Parameters	**Values (95%95% uncertainty bounds)**	**Reference/ Notes**
Proportion of men using condoms for anal sex in the past 12 months with casual partners (%)	46.90(34.50- 59.30)	[5]
Efficacy of condoms for preventing *N. gonorrhoeae* transmission when used for anal sex (%)	87.50(80.00-95.00)	[5]
Frequency of kissing (days)	6.31(0.00-13.12)	[5]
Frequency of oral sex (days)	13.53(0.00-28.11)	[5]
Frequency of rimming (days)	38.57(0.00-80.15)	[5]

Frequency of anal sex (days)	26.44(0.00-54.94)	[5]
Duration of untreated *N. gonorrhoeae* at the oropharynx (asymptomatic infection) (weeks)	12.00(10.00-14.00)	[5]
Duration of *N. gonorrhoeae* at the urethra (symptomatic infection) (weeks)	1.00(0.90-1.10)	[5]
Duration of untreated *N. gonorrhoeae* at the urethra (asymptomatic infection) (weeks)	12.00(10.00- 14.00)	[5]
Duration of untreated *N. gonorrhoeae* at the anorectum (weeks)	49.43(48.00- 52.00)	[5]
Proportion of urethral infections that are asymptomatic (%)	7.69(4.09-13.67)	[16]
Proportion of MSM received throat swab in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of MSM received anal swab in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of MSM received urine test in the past 12 months (%)	79.65(63.70-95.60)	Footnote *a*, [17]
Proportion of ' oral sex and anal sex' in the same sex episode (%)	29.41(24.82-34.00)	Footnote *b*, [18].
Proportion of 'oral sex and rimming' in the same sex episode (%)	70.5 (67.94-72.94)	Footnote *c*, [18 19].
Proportion of men using saliva as a lubricant during anal sex, the saliva is coming from the insertive (top) partner (%)	68.52(65.92-71.01)	[19]
Proportion of men having oral sex and then anal sex when they have both oral sex and anal sex (%)	80.00(80.00-80.00)	Footnote *d* [20 21].

Proportion of men having oral sex and then rimming their partner when they perform both oral sex and rimming (%)	80.00(80.00-80.00)	Footnote e

Footnote:

a. The proportion of gay and bisexual men attending sexual health clinics tested for *N. gonorrhoeae* in 2017 was 95.6%. The proportion of gay and bisexual men attending general practice clinics tested for *N. gonorrhoeae* in 2017 was 63.7%. We used the proportion of gay and bisexual men attending sexual health clinics tested as the lower bound. We used the proportion of gay and bisexual men attending general practice clinics tested as the upper bound. We used the mean value of the upper bound and lower as value.

b. The proportion of men who had receptive oral sex in their last sexual encounter that we used was 73.0%, and the proportion who had insertive anal sex was 34.0%. To determine proportion who had both oral sex and anal sex in the same encounter we used the proportion of anal sex (34.0%) as upper bound, and the value of the proportion of anal sex (34.0%) multiply the proportion of oral sex (73.0%) as the lower bound. The mean value is the average of the upper bound and lower bound.

c. The proportion of men who had insertive rimming in their last sexual encounter that we used was 70.5%, and the proportion of insertive oral sex was 75.0% To determine proportion who had both oral sex and anal sex in the same encounter we used the value of the proportion of oral sex multiply prevalence of rimming as lower bound and proportion of rimming behavior as upper bound. The mean value is the average of the upper bound and lower bound.

d. We estimated that the proportion of men who had oral sex followed by anal sex to be 80% based on expert opinion and published data.

e. This was calculated by subtracting 100% from the estimate in d.

Supplementary Results

1) 4873 MSM attending Melbourne Sexual Health Centre in 2018 and 2019[6]

Table S3. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 20% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 20%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI)			Oropharynx (95%CI)			Anorectum (95%CI)			Urethra (95%CI)		
1	0%	0%	44	37	50	26	22	31	9	8	11	8	5	12
2	0%	5%	47	39	72	28	23	46	10	9	17	9	6	13
2	0%	10%	51	42	74	30	25	47	11	9	17	9	6	14
2	0%	15%	54	45	76	32	26	49	11	10	18	10	7	15
2	0%	20%	57	47	79	34	28	51	12	10	18	10	7	16
2	0%	25%	60	49	82	36	30	53	13	11	19	11	7	17
3	5%	0%	39	32	45	23	19	28	8	7	10	7	5	10
4	5%	5%	42	34	66	25	20	42	9	8	15	8	5	12

4	5%	10%	46	37	68	27	22	43	9	6	16	8	6	13
4	5%	15%	49	40	70	29	24	45	10	6	16	9	6	13
4	5%	20%	52	42	73	31	25	47	11	6	17	9	6	14
4	5%	25%	55	44	77	33	27	49	12	10	17	10	6	15
3	10%	0%	34	27	39	20	16	24	7	5	9	6	4	9
4	10%	5%	37	30	60	22	18	37	8	6	14	7	4	10
4	10%	10%	40	32	62	24	19	39	8	6	14	7	5	11
4	10%	15%	43	35	64	26	20	41	9	6	15	8	5	12
4	10%	20%	46	37	67	28	22	43	10	6	15	8	5	13
4	10%	25%	49	39	70	29	24	44	10	6	16	9	6	14
3	15%	0%	29	23	34	17	13	22	6	4	8	5	3	8
4	15%	5%	32	25	53	19	15	33	7	5	12	6	4	9
4	15%	10%	35	28	55	21	16	35	7	5	13	6	4	10
4	15%	15%	38	30	58	23	18	37	8	6	13	7	4	11
4	15%	20%	41	32	61	24	19	38	9	6	14	7	5	11
4	15%	25%	43	34	63	26	20	40	9	6	14	8	5	12
3	20%	0%	24	19	29	14	11	19	5	4	6	4	3	7
4	20%	5%	27	21	46	16	12	29	6	5	11	5	3	8

4	20%	10%	30	23	49	18	13	31	6	5	11	5	3	9
4	20%	15%	32	25	51	20	15	32	7	5	12	6	4	9
4	20%	20%	35	27	54	21	16	34	7	6	12	6	4	10
4	20%	25%	38	29	56	23	17	36	8	6	13	7	4	11
3	25%	0%	20	15	24	12	9	16	4	4	5	3	2	5
4	25%	5%	22	16	41	13	10	25	5	4	9	4	2	7
4	25%	10%	25	18	43	15	11	26	5	4	10	4	3	7
4	25%	15%	27	20	45	16	12	28	6	5	10	5	3	8
4	25%	20%	30	22	47	18	13	30	6	5	11	5	3	9
4	25%	25%	32	24	49	20	14	31	7	6	11	6	3	9

Table S4. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 20% coverage*

Estimated effect of antibacterial mouthwash on percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM (%). 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 20%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	7.4	5.9	60.8	7.5	5.9	61.6	7.3	5.7	59.2	7.4	5.8	60.3
2	0%	10%	14.8	11.7	66.7	15.0	11.8	67.6	14.6	11.4	64.9	14.7	11.6	66.1
2	0%	15%	22.3	17.5	72.6	22.5	17.7	73.6	21.8	17.0	70.5	22.1	17.3	71.9
2	0%	20%	29.6	23.2	78.4	29.9	23.5	79.5	29.0	22.5	76.1	29.4	23.0	77.7
2	0%	25%	36.9	28.9	84.2	37.3	29.3	85.4	36.0	28.0	81.6	36.5	28.6	83.4
3	5%	0%	-11.6	-13.5	-10.2	-11.5	-13.5	-10.1	-11.6	-13.6	-10.2	-11.9	-13.9	-10.5
4	5%	5%	-4.5	-7.0	46.4	-4.3	-6.9	47.2	-4.6	-7.2	44.9	-4.9	-7.5	45.2
4	5%	10%	-4.5	-7.0	46.4	2.7	-1.1	53.1	2.3	-1.6	50.5	2.0	-1.8	51.0
4	5%	15%	9.5	4.4	58.0	9.8	4.7	59.0	9.2	3.9	56.1	8.9	3.8	56.7
4	5%	20%	16.9	10.0	63.7	17.3	10.4	64.9	16.3	9.4	61.6	16.2	9.3	62.3
4	5%	25%	24.0	15.6	69.5	24.5	16.1	70.7	23.2	14.8	67.1	23.2	14.8	68.0
3	10%	0%	-23.0	-26.9	-20.3	-22.9	-26.7	-20.2	-23.0	-26.9	-20.3	-23.6	-27.5	-20.9
4	10%	5%	-16.0	-20.4	31.7	-15.7	-20.2	32.5	-16.1	-20.6	30.4	-16.6	-21.2	30.1
4	10%	10%	-9.3	-14.4	37.4	-9.0	-14.1	38.3	-9.5	-14.7	35.9	-10.1	-15.3	35.7

4	10%	15%	-2.4	-8.8	43.1	-2.0	-8.4	44.1	-2.8	-9.2	41.4	-3.4	-9.8	41.3
4	10%	20%	4.1	-3.4	48.8	4.6	-2.9	49.9	3.7	-3.9	46.9	3.1	-4.3	46.9
4	10%	25%	11.1	2.2	54.6	11.6	2.8	56.1	10.5	1.4	52.3	9.9	1.0	52.5
3	15%	0%	-34.1	-39.6	-30.3	-33.9	-39.3	-30.1	-34.1	-39.6	-30.3	-34.9	-40.2	-31.0
4	15%	5%	-27.5	-33.4	16.8	-27.2	-33.1	17.7	-27.6	-33.6	15.7	-28.3	-34.3	14.9
4	15%	10%	-20.7	-27.8	22.4	-20.4	-27.5	23.3	-20.9	-28.1	21.1	-21.7	-28.8	20.4
4	15%	15%	-14.5	-22.1	28.0	-14.0	-21.7	29.0	-14.7	-22.5	26.5	-15.6	-23.3	25.9
4	15%	20%	-8.0	-16.6	33.5	-7.5	-16.1	34.7	-8.3	-17.2	31.9	-9.2	-17.9	31.3
4	15%	25%	-1.4	-11.3	41.0	-0.8	-10.7	42.5	-1.8	-12.0	38.8	-2.8	-12.7	38.5
3	20%	0%	-44.7	-51.3	-39.9	-44.5	-51.1	-39.6	-44.7	-51.4	-39.9	-45.4	-52.1	-40.7
4	20%	5%	-38.4	-45.7	1.8	-38.1	-45.4	2.7	-38.6	-45.8	0.9	-39.4	-46.6	-0.2
4	20%	10%	-32.1	-40.6	7.3	-31.8	-40.3	8.2	-32.2	-40.9	6.2	-33.2	-41.7	5.1
4	20%	15%	-25.9	-35.3	12.7	-25.4	-34.9	13.7	-26.1	-35.4	11.4	-27.2	-36.3	10.4
4	20%	20%	-19.9	-30.0	18.1	-19.3	-29.5	19.3	-20.2	-30.4	16.7	-21.3	-31.3	15.7
4	20%	25%	-13.8	-24.7	27.1	-13.1	-24.1	28.6	-14.1	-25.3	25.2	-15.2	-26.2	24.4
3	25%	0%	-54.4	-62.2	-48.9	-54.1	-62.0	-48.6	-54.5	-62.3	-48.9	-55.4	-62.9	-49.8
4	25%	5%	-48.7	-57.0	-13.0	-48.4	-56.8	-12.2	-48.8	-57.2	-13.8	-49.8	-57.9	-15.1
4	25%	10%	-43.0	-52.5	-7.6	-42.6	-52.2	-6.7	-43.0	-52.6	-8.7	-44.0	-53.4	-10.0

4	25%	15%	-37.0	-47.9	-1.0	-36.6	-47.6	0.0	-37.2	-48.2	-2.3	-38.2	-49.1	-3.7
4	25%	20%	-31.5	-42.6	5.6	-30.9	-42.2	6.7	-31.7	-43.0	4.0	-32.9	-44.0	2.7
4	25%	25%	-25.7	-37.8	13.2	-25.1	-37.3	14.7	-26.0	-38.3	11.5	-27.3	-39.3	10.4

Table S5. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 50% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 50%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI)			oropharynx(95%CI)			anorectum (95%CI)			urethra (95%CI)		
1	0%	0%	44	36	50	26	21	31	8	8	11	8	5	12
2	0%	5%	53	43	75	31	25	48	11	10	18	10	6	14
2	0%	10%	60	49	82	36	30	53	13	11	19	11	7	17
2	0%	15%	68	55	90	41	33	57	14	12	19	12	8	19
2	0%	20%	76	61	97	46	37	60	16	13	20	13	9	21
2	0%	25%	83	67	102	51	40	62	17	15	22	15	10	23
3	5%	0%	31	25	37	19	15	23	7	6	8	6	4	8
4	5%	5%	39	31	60	23	18	38	8	7	14	7	5	11
4	5%	10%	47	37	67	28	22	43	10	8	15	8	5	13
4	5%	15%	55	43	74	33	26	47	11	10	17	10	6	15
4	5%	20%	62	48	81	38	29	51	13	11	18	11	7	18
4	5%	25%	70	54	88	42	33	55	15	12	19	12	8	20
3	10%	0%	20	15	24	12	9	16	4	4	5	3	2	5

4	10%	5%	26	20	45	16	11	28	8	5	10	5	3	8
4	10%	10%	33	25	51	20	15	32	7	6	11	6	4	10
4	10%	15%	41	30	58	25	18	37	8	7	13	7	4	12
4	10%	20%	48	36	65	30	22	41	7	8	14	8	5	14
4	10%	25%	55	41	74	34	25	45	7	9	16	10	6	16
3	15%	0%	11	7	15	7	4	9	2	2	3	2	1	3
4	15%	5%	16	10	30	10	6	18	6	2	7	3	1	5
4	15%	10%	22	14	36	13	8	22	5	3	8	4	2	7
4	15%	15%	28	18	44	17	11	27	6	4	10	5	3	9
4	15%	20%	35	23	53	21	14	33	7	5	11	6	3	11
4	15%	25%	41	29	62	25	17	38	9	6	13	7	4	13
3	20%	0%	5	3	8	3	2	5	1	1	2	1	0	2
4	20%	5%	8	4	19	5	3	12	4	1	4	1	1	3
4	20%	10%	12	7	26	7	4	16	5	2	5	2	1	4
4	20%	15%	17	9	33	10	6	21	4	2	7	3	1	6
4	20%	20%	23	12	41	13	8	26	5	3	8	4	2	7
4	20%	25%	29	16	50	17	10	31	5	4	10	5	2	9
3	25%	0%	2	1	4	1	1	2	0	0	1	0	0	1

4	25%	5%	4	2	10	2	1	7	0	2	1	0	2	
4	25%	10%	6	2	15	3	2	10	1	3	1	0	2	
4	25%	15%	9	4	22	5	2	15	1	4	1	1	3	
4	25%	20%	12	5	29	7	3	19	1	6	2	1	5	
4	25%	25%	17	8	37	10	5	24	2	7	3	1	6	

Table S6. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 50% coverage*

Estimated effect of antibacterial mouthwash on Percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 50%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	18.5	14.6	70.8	18.7	14.7	71.7	18.2	14.1	68.8	18.4	14.4	70.1
2	0%	10%	36.9	28.9	85.2	37.3	29.2	86.4	36.0	28.0	82.5	36.5	28.6	84.3
2	0%	15%	54.7	42.9	99.3	55.5	43.5	100.8	53.3	41.4	96.0	54.2	42.4	98.2
2	0%	20%	72.2	56.6	113.1	73.4	57.5	115.0	70.0	54.4	109.1	71.3	55.9	111.8
2	0%	25%	89.3	70.0	131.8	90.9	71.2	134.4	86.2	67.0	126.8	88.1	69.0	130.2
3	5%	0%	-28.5	-33.3	-25.3	-28.3	-33.1	-25.1	-28.4	-33.3	-25.3	-29.1	-34.0	-25.9
4	5%	5%	-11.3	-17.6	34.5	-10.9	-17.2	35.5	-11.5	-18.0	33.0	-12.3	-18.6	32.6
4	5%	10%	-11.3	-17.6	34.5	6.4	-2.9	51.3	5.3	-4.3	47.5	4.5	-4.8	47.4
4	5%	15%	23.1	10.3	63.2	24.0	11.2	65.0	22.3	9.1	60.7	21.5	8.7	60.7
4	5%	20%	40.9	24.0	78.3	42.2	25.1	80.2	39.1	22.1	74.5	38.7	22.0	75.2

4	5%	25%	57.3	37.4	96.3	58.9	38.8	99.0	54.8	35.0	92.2	54.7	35.0	93.0
3	10%	0%	-54.3	-62.3	-48.8	-54.0	-62.1	-48.4	-54.3	-62.3	-48.8	-55.2	-63.0	-49.6
4	10%	5%	-39.1	-48.9	-2.4	-38.7	-48.5	-1.4	-39.3	-49.1	-3.6	-40.4	-50.0	-4.9
4	10%	10%	-23.7	-35.8	15.9	-23.0	-35.2	17.4	-24.1	-36.4	14.2	-25.3	-37.4	13.0
4	10%	15%	-7.4	-22.1	31.5	-6.4	-21.3	33.0	-8.1	-23.1	28.9	-9.5	-24.2	27.7
4	10%	20%	8.8	-9.3	45.5	10.0	-8.1	47.6	7.7	-10.7	43.2	6.2	-11.8	41.9
4	10%	25%	25.3	4.0	67.1	26.9	5.4	69.7	23.7	2.0	62.3	21.9	1.0	61.8
3	15%	0%	-74.8	-82.4	-68.2	-74.6	-82.3	-67.9	-74.9	-82.6	-68.2	-75.4	-82.9	-68.9
4	15%	5%	-63.4	-73.9	-32.4	-63.1	-73.7	-31.5	-63.6	-74.0	-33.3	-64.5	-74.6	-34.9
4	15%	10%	-50.5	-63.8	-16.4	-49.9	-63.4	-15.2	-50.7	-64.2	-17.7	-51.9	-65.0	-19.6
4	15%	15%	-36.9	-53.5	-4.2	-36.0	-52.9	-2.5	-37.5	-54.1	-5.6	-39.0	-55.1	-7.6
4	15%	20%	-22.1	-41.4	11.9	-21.0	-40.6	12.9	-22.8	-42.4	10.7	-24.7	-43.7	9.5
4	15%	25%	-6.9	-29.3	36.6	-5.5	-28.1	39.3	-7.9	-30.7	31.3	-10.1	-32.2	30.5
3	20%	0%	-88.1	-93.7	-82.3	-87.9	-93.6	-82.1	-88.2	-93.8	-82.4	-88.5	-93.9	-82.8
4	20%	5%	-81.5	-89.2	-59.1	-81.3	-89.0	-58.6	-81.6	-89.3	-59.4	-82.2	-89.6	-60.2
4	20%	10%	-72.6	-83.8	-45.4	-72.2	-83.6	-44.9	-72.9	-84.0	-45.9	-73.7	-84.4	-47.4
4	20%	15%	-61.7	-76.7	-29.7	-61.1	-76.4	-29.0	-62.0	-77.1	-30.4	-63.3	-77.7	-32.1
4	20%	20%	-50.2	-69.0	-12.6	-49.3	-68.5	-11.6	-50.8	-69.6	-13.7	-52.5	-70.5	-15.9

4	20%	25%	-37.5	-60.0	5.5	-36.3	-59.3	6.7	-38.3	-60.9	3.3	-40.3	-62.0	0.7
3	25%	0%	-95.0	-98.1	-91.1	-94.9	-98.0	-91.0	-95.1	-98.1	-91.2	-95.2	-98.1	-91.4
4	25%	5%	-91.8	-96.3	-78.2	-91.7	-96.2	-77.8	-91.9	-96.3	-78.6	-92.1	-96.4	-79.3
4	25%	10%	-87.3	-94.1	-67.8	-87.1	-94.0	-67.2	-87.5	-94.2	-68.5	-87.9	-94.4	-69.5
4	25%	15%	-80.8	-90.9	-54.9	-80.4	-90.8	-54.1	-81.0	-91.1	-55.9	-81.7	-91.4	-57.4
4	25%	20%	-72.4	-86.5	-39.9	-71.8	-86.3	-38.7	-72.8	-86.8	-41.5	-73.9	-87.2	-43.5
4	25%	25%	-63.1	-81.4	-23.5	-62.3	-81.0	-21.9	-63.7	-81.9	-25.7	-65.1	-82.4	-28.2

Table S7. *Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person-years with 80% coverage.*

Estimated effect of antibacterial mouthwash on gonorrhoea incidence rate per 100 person years that occur at the oropharynx, anorectum or urethra in MSM. 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 80%)

Scenarios	Transmissibility	Susceptibility	Total incidence (95%CI), 100 person-years			Incidence at the oropharynx(95%CI), 100 person-years			Incidence at the anorectum (95%CI), 100 person-years			Incidence at the urethra (95%CI), 100 person-years		
1	0%	0%	44	37	50	26	21	31	9	8	11	8	5	12
2	0%	5%	58	47	79	34	28	51	12	10	18	10	7	16
2	0%	10%	69	56	92	42	34	58	15	12	19	12	8	19
2	0%	15%	82	65	102	50	39	62	17	14	22	14	10	23
2	0%	20%	93	74	113	57	45	68	19	16	25	16	11	26
2	0%	25%	104	83	127	63	50	77	22	18	27	18	12	30
3	5%	0%	24	19	29	14	11	19	5	4	6	4	3	7
4	5%	5%	36	28	55	22	17	35	8	6	13	7	4	10
4	5%	10%	48	37	66	29	22	43	10	8	15	9	5	14
4	5%	15%	60	46	78	37	28	49	13	10	17	11	6	17
4	5%	20%	71	55	91	44	33	55	15	12	19	12	8	21

4	5%	25%	83	63	105	51	39	64	17	14	22	14	9	24
3	10%	0%	10	6	14	6	4	8	2	1	3	2	1	3
4	10%	5%	18	11	31	11	7	19	4	3	7	3	2	5
4	10%	10%	28	17	44	17	11	28	6	4	9	5	2	9
4	10%	15%	39	26	59	24	16	36	8	6	12	7	3	12
4	10%	20%	49	34	71	30	21	43	10	7	15	8	5	15
4	10%	25%	60	42	83	37	26	50	13	9	17	10	6	18
3	15%	0%	3	1	5	2	1	3	1	0	1	0	0	1
4	15%	5%	6	3	15	4	2	10	1	1	3	1	0	2
4	15%	10%	11	5	26	7	3	17	2	1	5	2	1	4
4	15%	15%	19	9	39	12	6	25	4	2	8	3	1	7
4	15%	20%	29	15	51	17	9	31	6	3	10	5	2	10
4	15%	25%	38	22	59	23	14	36	8	5	13	6	3	13
3	20%	0%	1	0	1	0	0	1	0	0	0	0	0	0
4	20%	5%	1	0	5	1	0	3	0	0	1	0	0	1
4	20%	10%	3	1	10	2	1	7	1	0	2	1	0	2
4	20%	15%	6	2	19	4	1	13	1	0	4	1	0	3
4	20%	20%	11	3	30	7	2	20	2	1	6	2	0	5

4	20%	25%	18	6	37	11	4	24	4	1	7	3	1	8
3	25%	0%	0	0	0	0	0	0	0	0	0	0	0	0
4	25%	5%	0	0	1	0	0	1	0	0	0	0	0	0
4	25%	10%	1	0	3	0	0	2	0	0	1	0	0	1
4	25%	15%	1	0	7	1	0	4	0	0	1	0	0	1
4	25%	20%	3	0	12	2	0	8	1	0	2	0	0	2
4	25%	25%	5	1	19	3	1	12	1	0	4	1	0	3

Table S8. *Estimated effect of antibacterial mouthwash on percentage change in incidence with 80% coverage*

Estimated effect of antibacterial mouthwash on Percentage change in incidence that occur at the oropharynx, anorectum or urethra in MSM (%). 1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4). (Coverage 80%)

Scenarios	Transmissibility	Susceptibility	Percentage change of total incidence than baseline (95%CI),%			Percentage change at the oropharynx than baseline (95%CI),%			Percentage change at the anorectum than baseline (95%CI),%			Percentage change at the urethra than baseline (95%CI),%		
1	0%	0%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0%	5%	29.4	23.1	80.1	29.8	23.4	81.2	28.7	22.4	77.7	29.1	22.9	79.3
2	0%	10%	58.1	45.6	102.5	58.9	46.2	104.1	56.4	43.9	99.1	57.5	45.0	101.4
2	0%	15%	85.6	67.2	128.5	87.0	68.4	131.1	82.8	64.5	121.4	84.5	66.3	125.9
2	0%	20%	111.5	88.1	148.1	113.5	89.7	151.4	107.5	84.0	142.5	110.1	86.7	145.2
2	0%	25%	136.6	108.1	177.5	139.2	110.4	181.7	131.0	102.6	169.2	134.6	106.4	174.6
3	5%	0%	-44.4	-51.2	-39.7	-44.1	-51.0	-39.4	-44.3	-51.3	-39.7	-45.1	-52.0	-40.4
4	5%	5%	-18.0	-28.2	21.8	-17.4	-27.6	23.0	-18.4	-28.7	20.3	-19.5	-29.6	19.3
4	5%	10%	-18.0	-28.2	21.8	9.9	-5.1	49.5	7.8	-7.3	45.0	6.5	-8.1	44.4
4	5%	15%	35.6	15.7	75.5	37.1	17.0	78.1	33.9	13.6	70.5	32.7	12.9	70.8
4	5%	20%	62.4	36.8	103.7	64.7	38.7	106.9	59.2	33.7	97.8	58.4	33.3	98.1

4	5%	25%	87.7	57.4	130.7	90.8	60.0	134.8	83.5	53.1	122.5	82.7	53.2	123.6
3	10%	0%	-77.9	-85.4	-71.3	-77.6	-85.3	-71.0	-77.9	-85.5	-71.4	-78.4	-85.8	-71.9
4	10%	5%	-59.8	-72.1	-28.2	-59.2	-71.8	-27.2	-60.1	-72.4	-29.3	-61.1	-73.0	-31.1
4	10%	10%	-38.1	-55.8	-6.2	-37.3	-55.2	-4.6	-38.7	-56.4	-7.2	-40.3	-57.5	-8.3
4	10%	15%	-13.5	-36.2	24.2	-12.1	-35.1	26.5	-14.6	-37.5	22.6	-16.8	-38.9	21.1
4	10%	20%	12.0	-16.4	58.9	14.0	-14.8	62.0	10.1	-18.5	53.5	7.5	-20.1	52.2
4	10%	25%	37.4	4.1	85.4	40.0	6.3	88.0	34.8	1.0	78.9	31.8	-0.7	76.8
3	15%	0%	-94.0	-97.5	-89.6	-93.9	-97.5	-89.4	-94.1	-97.6	-89.7	-94.2	-97.6	-89.9
4	15%	5%	-86.9	-93.7	-67.6	-86.7	-93.6	-67.1	-87.0	-93.8	-68.3	-87.4	-93.9	-69.2
4	15%	10%	-74.4	-87.3	-45.3	-73.9	-87.1	-44.3	-74.6	-87.5	-46.5	-75.6	-87.9	-48.2
4	15%	15%	-58.1	-77.8	-18.3	-57.2	-77.4	-16.7	-58.5	-78.4	-20.5	-60.2	-79.0	-23.0
4	15%	20%	-37.3	-64.7	10.6	-35.9	-63.9	13.0	-38.3	-65.7	7.2	-40.8	-66.9	4.1
4	15%	25%	-14.5	-48.5	33.7	-12.3	-47.1	37.5	-16.3	-50.2	30.5	-19.4	-51.9	26.0
3	20%	0%	-98.7	-99.7	-97.0	-98.7	-99.7	-96.9	-98.8	-99.7	-97.0	-98.8	-99.7	-97.1
4	20%	5%	-96.9	-99.0	-89.4	-96.9	-99.0	-89.2	-97.0	-99.1	-89.7	-97.1	-99.1	-90.0
4	20%	10%	-93.1	-97.9	-78.1	-93.0	-97.8	-77.6	-93.3	-97.9	-78.7	-93.5	-98.0	-79.5
4	20%	15%	-86.3	-95.9	-59.9	-85.9	-95.8	-59.0	-86.6	-96.0	-61.1	-87.2	-96.1	-62.7
4	20%	20%	-75.8	-92.2	-36.3	-75.1	-92.0	-34.5	-76.2	-92.5	-38.7	-77.4	-92.8	-41.4

4	20%	25%	-61.3	-85.6	-14.5	-60.2	-85.1	-11.9	-62.0	-86.1	-17.4	-64.0	-86.7	-20.0
3	25%	0%	-99.8	-100.0	-99.2	-99.8	-100.0	-99.2	-99.8	-100.0	-99.3	-99.8	-100.0	-99.3
4	25%	5%	-99.4	-99.9	-97.1	-99.4	-99.9	-97.0	-99.4	-99.9	-97.2	-99.5	-99.9	-97.2
4	25%	10%	-98.7	-99.8	-93.4	-98.6	-99.8	-93.3	-98.7	-99.8	-93.6	-98.7	-99.8	-93.8
4	25%	15%	-97.1	-99.5	-86.0	-97.0	-99.5	-85.6	-97.1	-99.6	-86.5	-97.3	-99.6	-87.0
4	25%	20%	-93.8	-99.0	-74.4	-93.6	-99.0	-73.5	-94.0	-99.1	-75.5	-94.2	-99.1	-76.8
4	25%	25%	-88.2	-97.9	-57.2	-87.8	-97.8	-55.7	-88.6	-98.0	-59.1	-89.2	-98.1	-61.4

2) Results based on 3,049 MSM attending a health center in the USA[7]

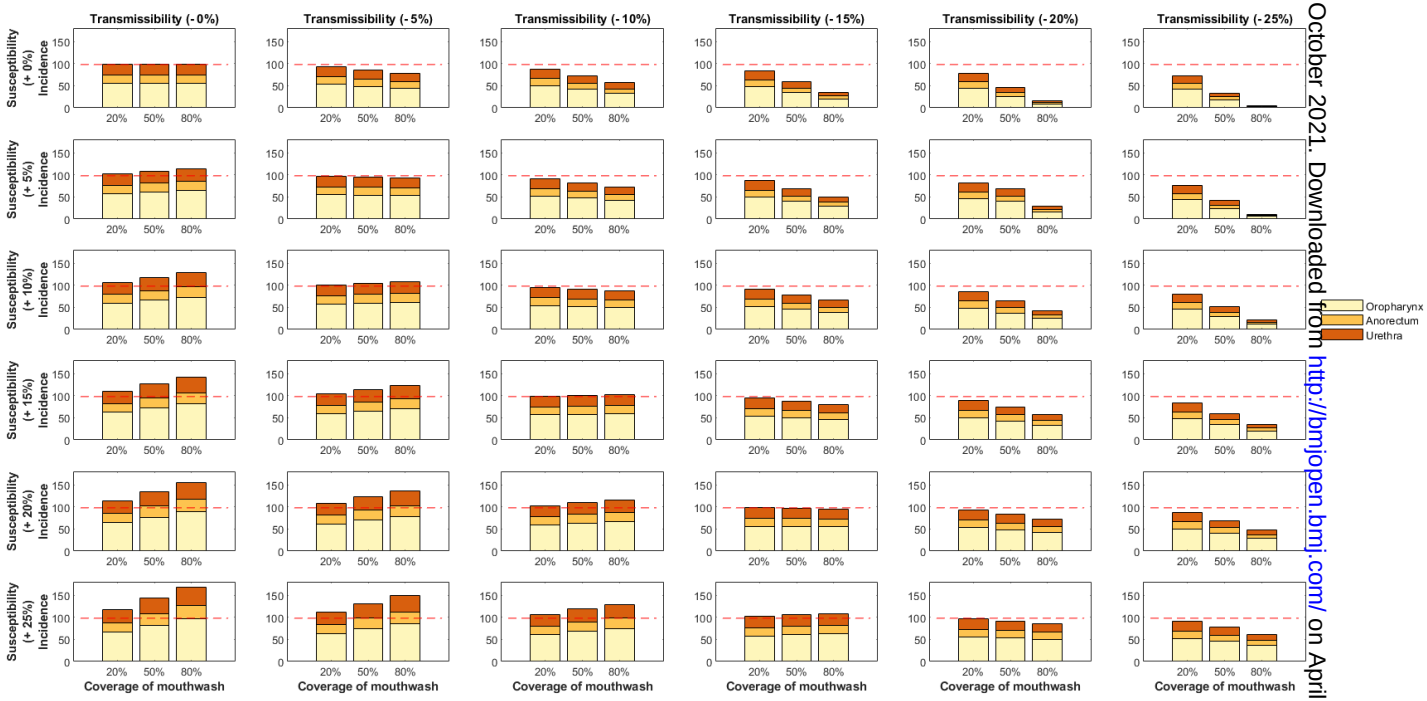


Figure 2a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

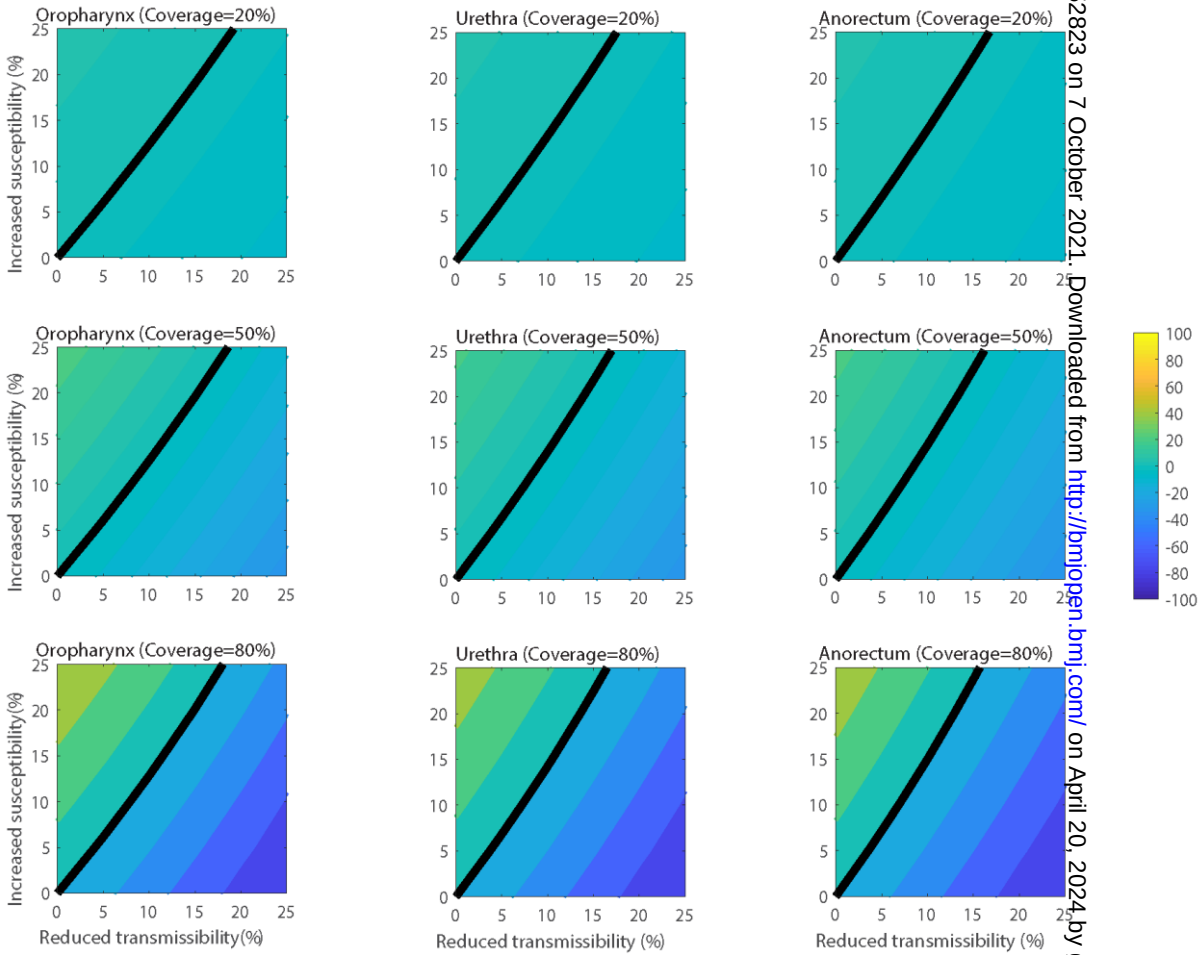


Figure 2b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

3）Results based on 393 MSM attending STD & HIV care clinics in the USA[8]

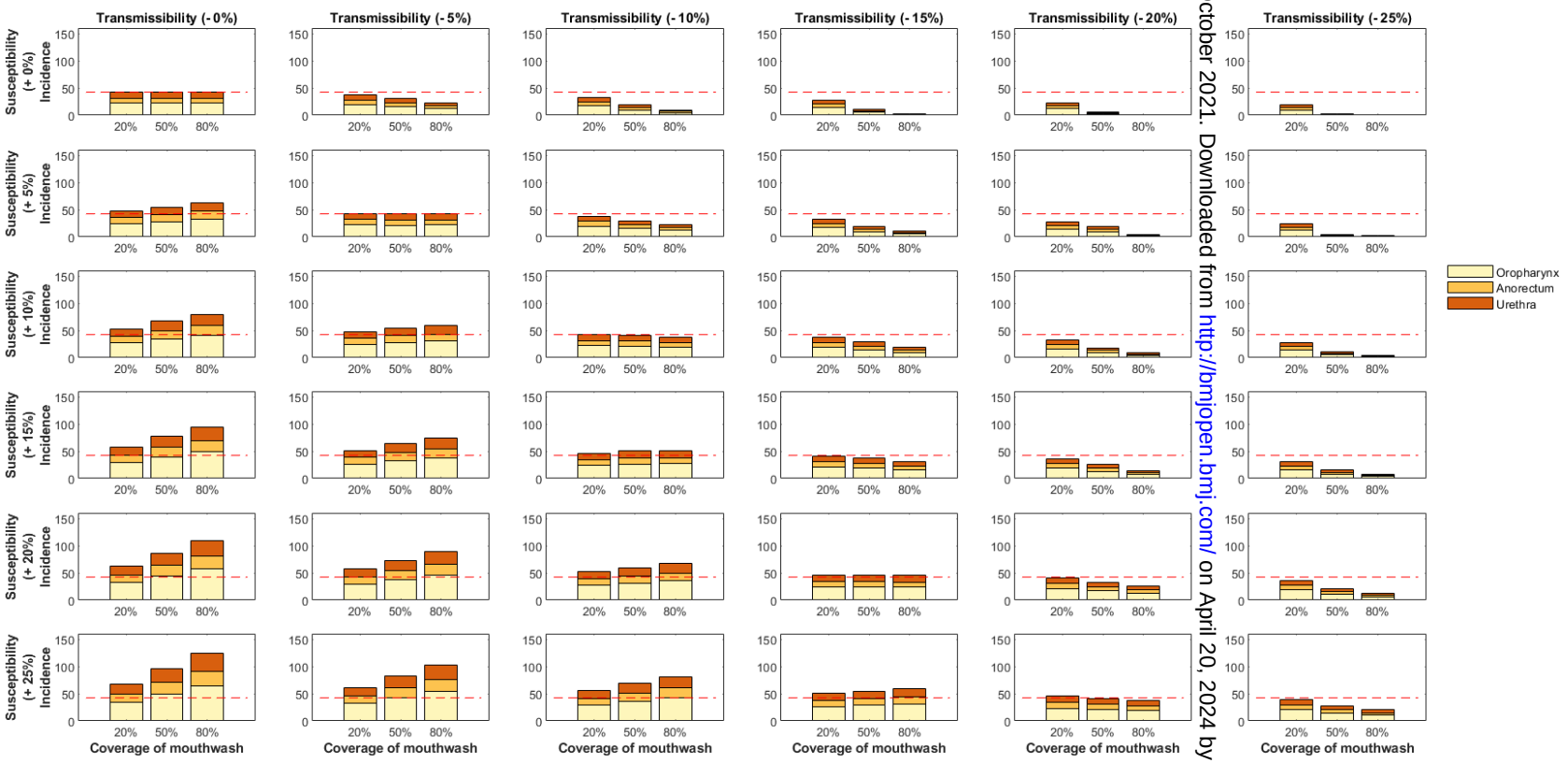


Figure 3a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

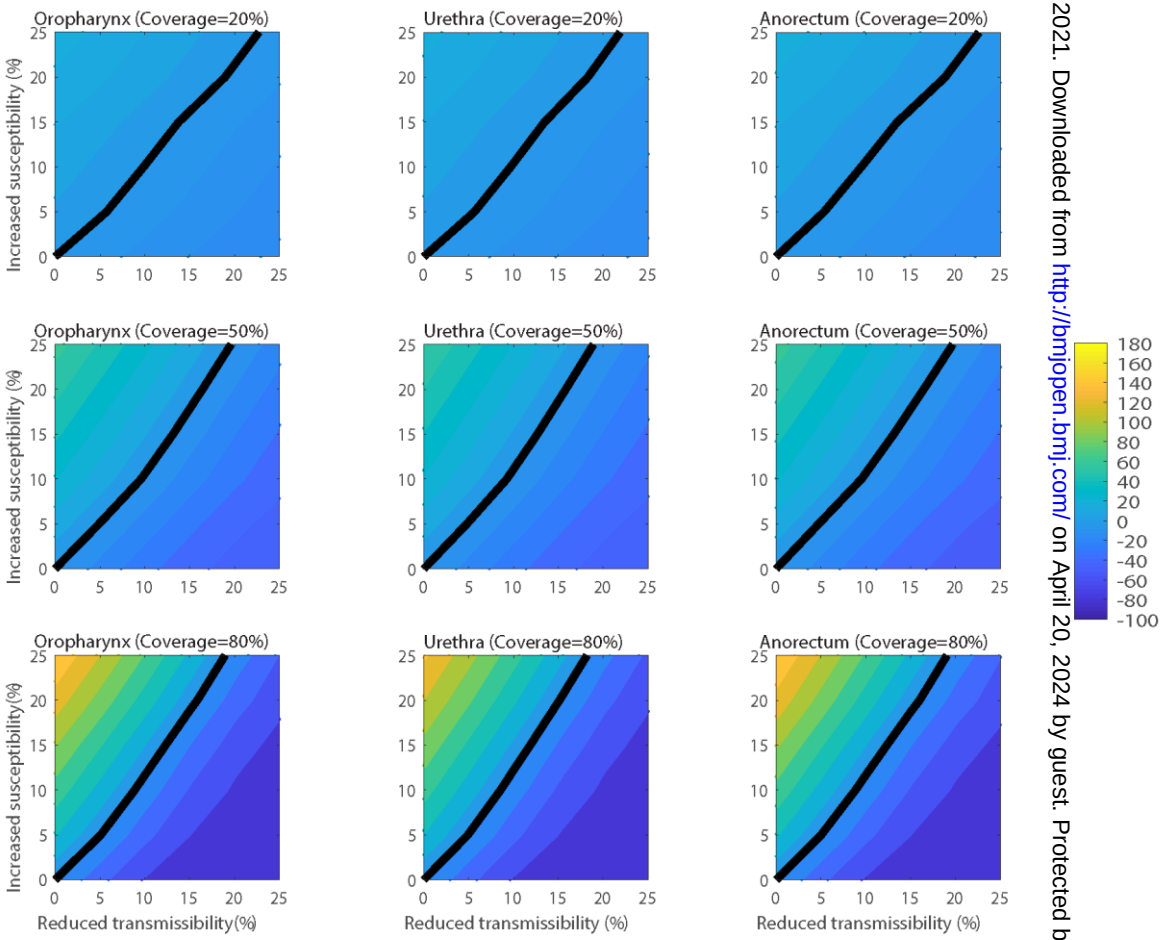


Figure 3b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

4) Results based on 179 MSM with HIV in the USA[9]

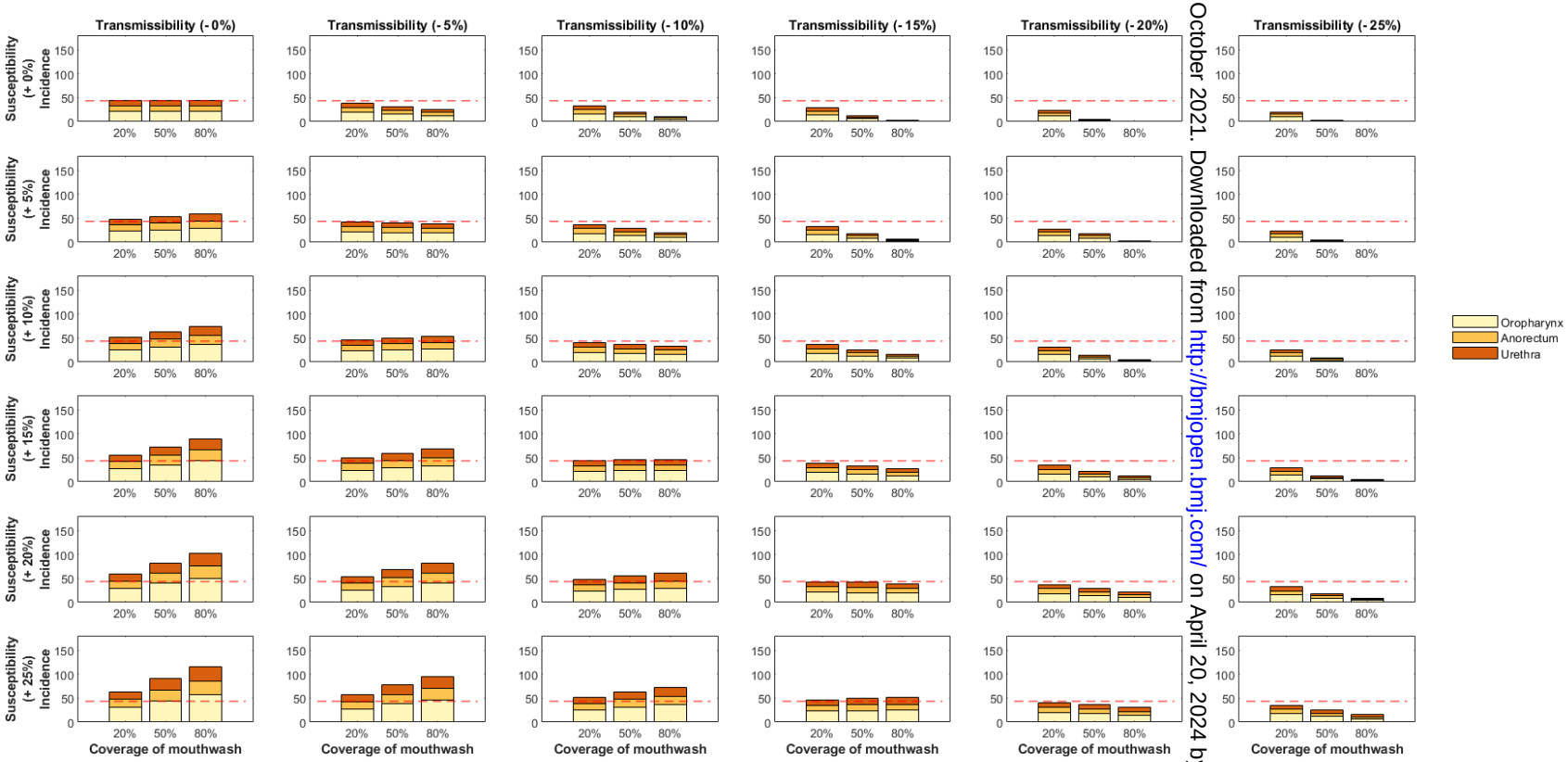


Figure 4a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

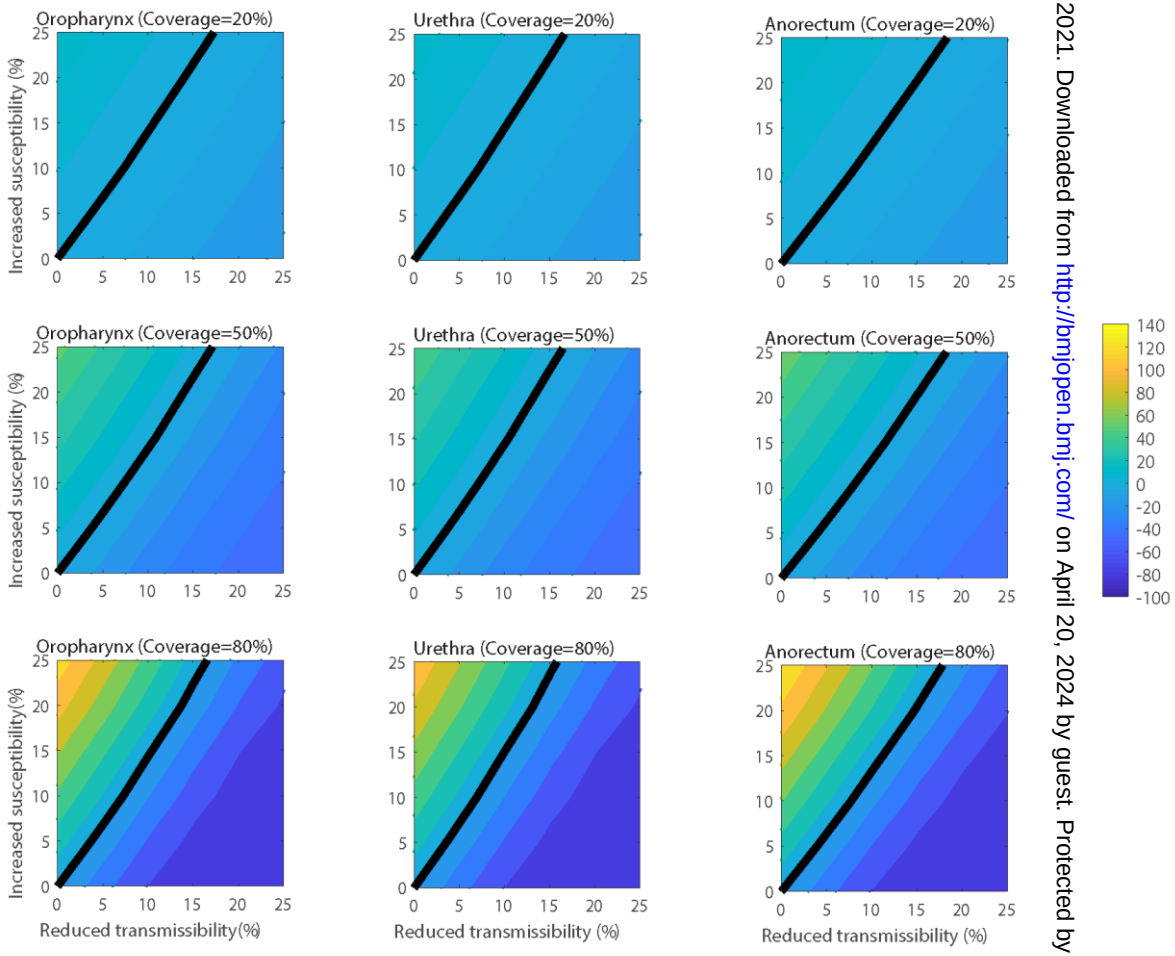


Figure 4b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

5) Results based on MSM surveillance data (271, 242 consultations) from all Dutch STI clinics[10]

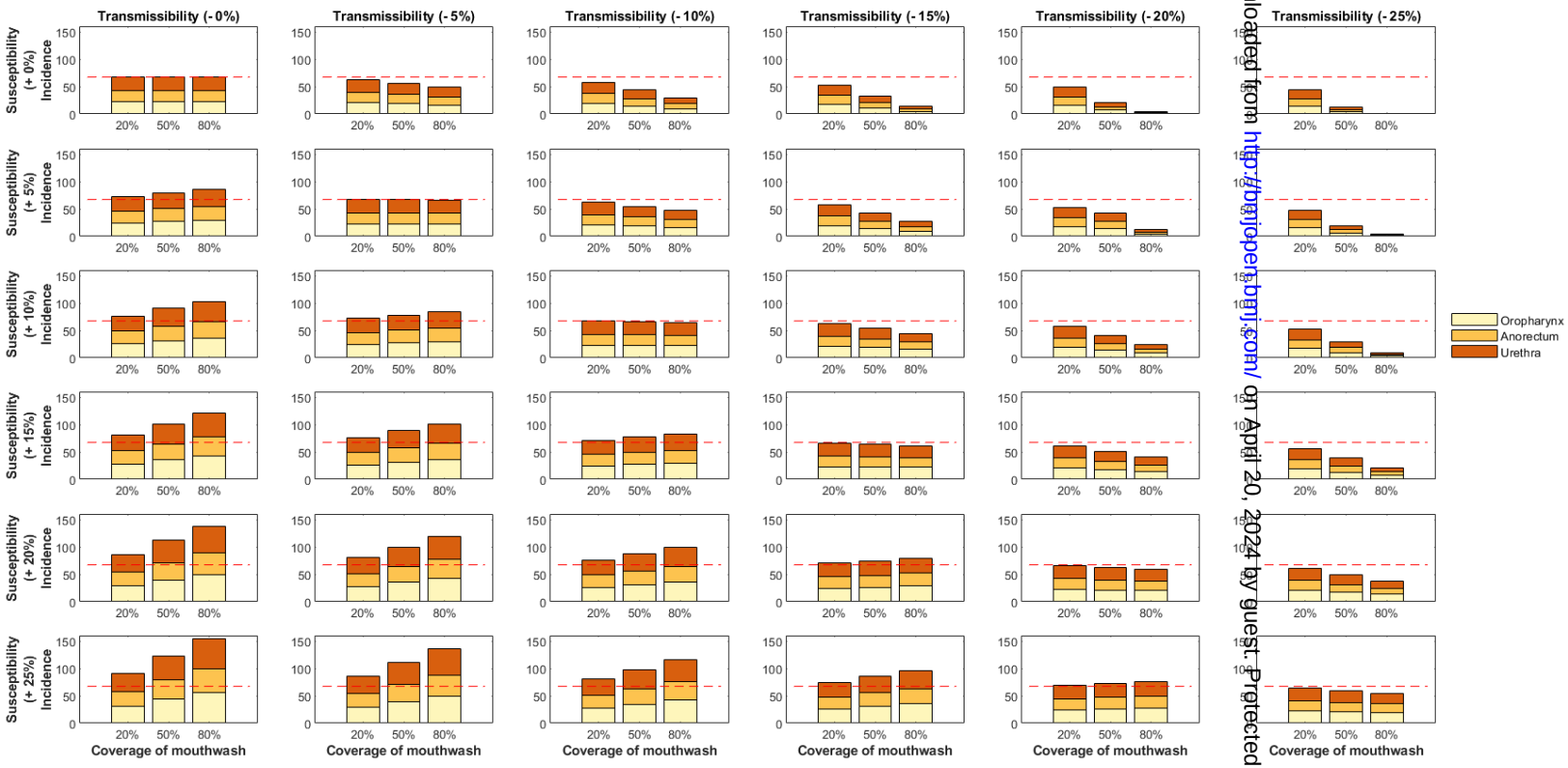


Figure 5a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

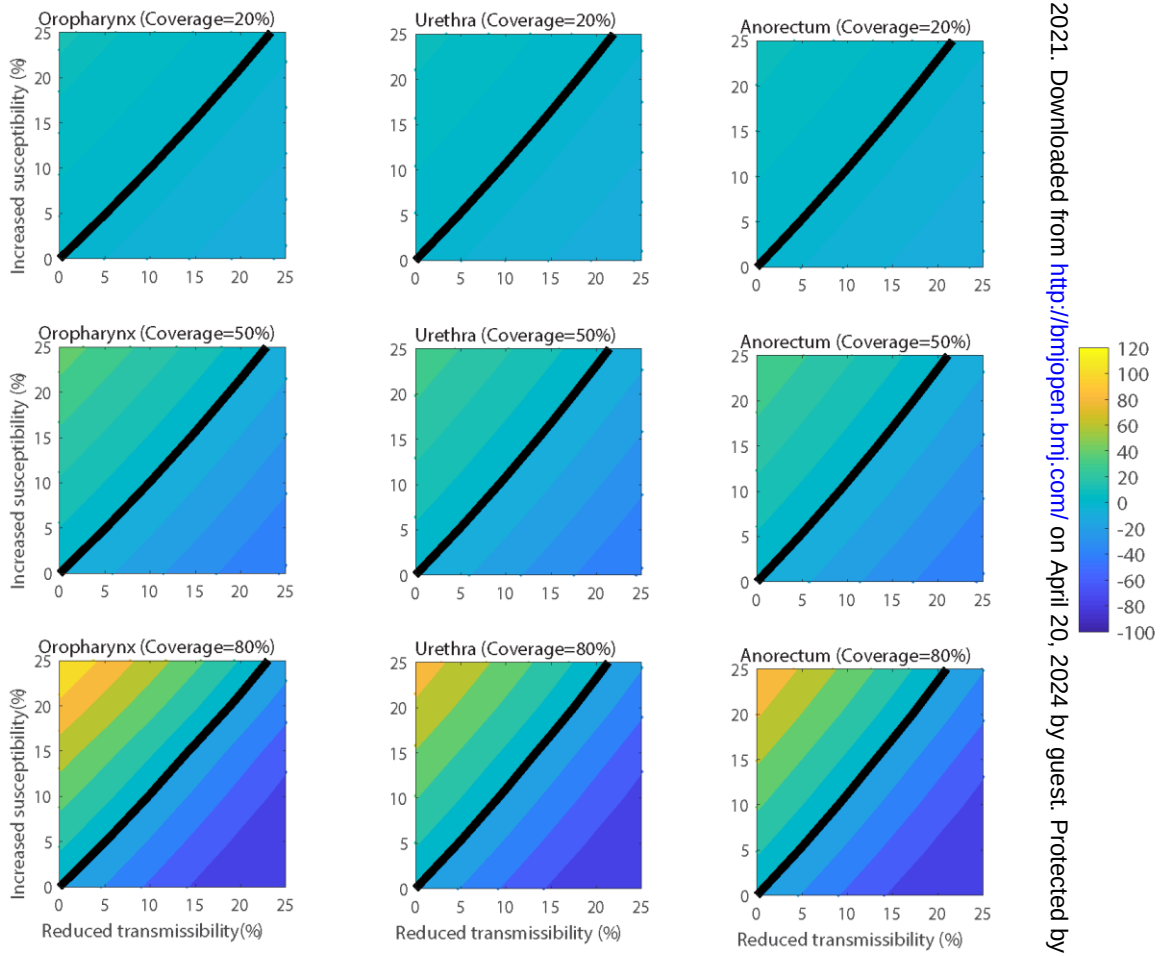


Figure 5b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

6) Results based on 1,610 community samples of MSM in Thailand[11]

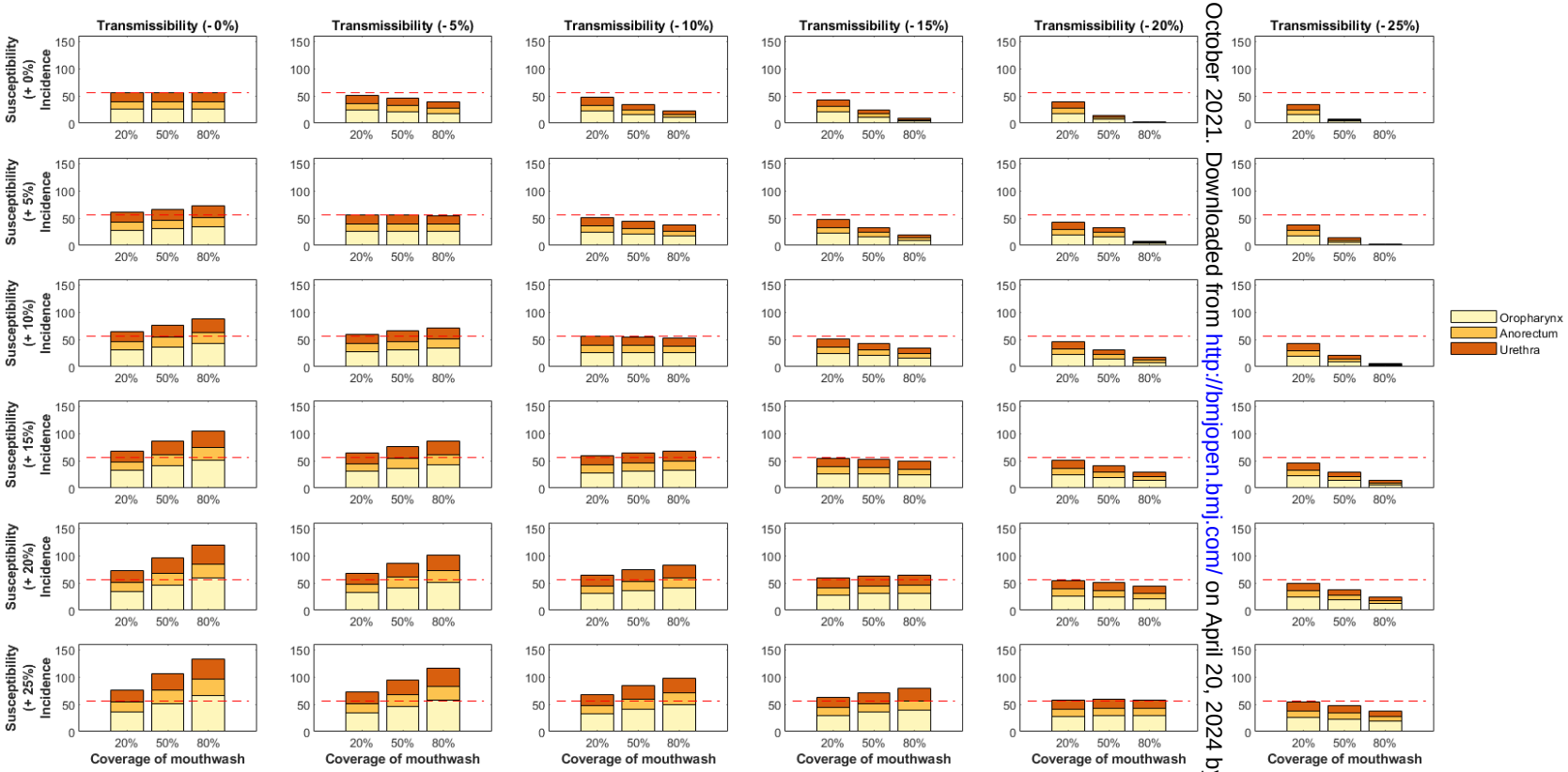


Figure 6a. *Estimated the effect of antibacterial mouthwash on incident Neisseria gonorrhoeae cases that occur at the oropharynx, anorectum or urethra in MSM.*

1) Baseline (scenario 1); 2) Increasing susceptibility of oropharyngeal gonorrhoea only (scenario 2); 3) Reducing transmissibility of gonorrhoea only (scenario 3); 4) Reducing transmissibility from the oropharynx and increasing susceptibility to the oropharynx (scenario 4)

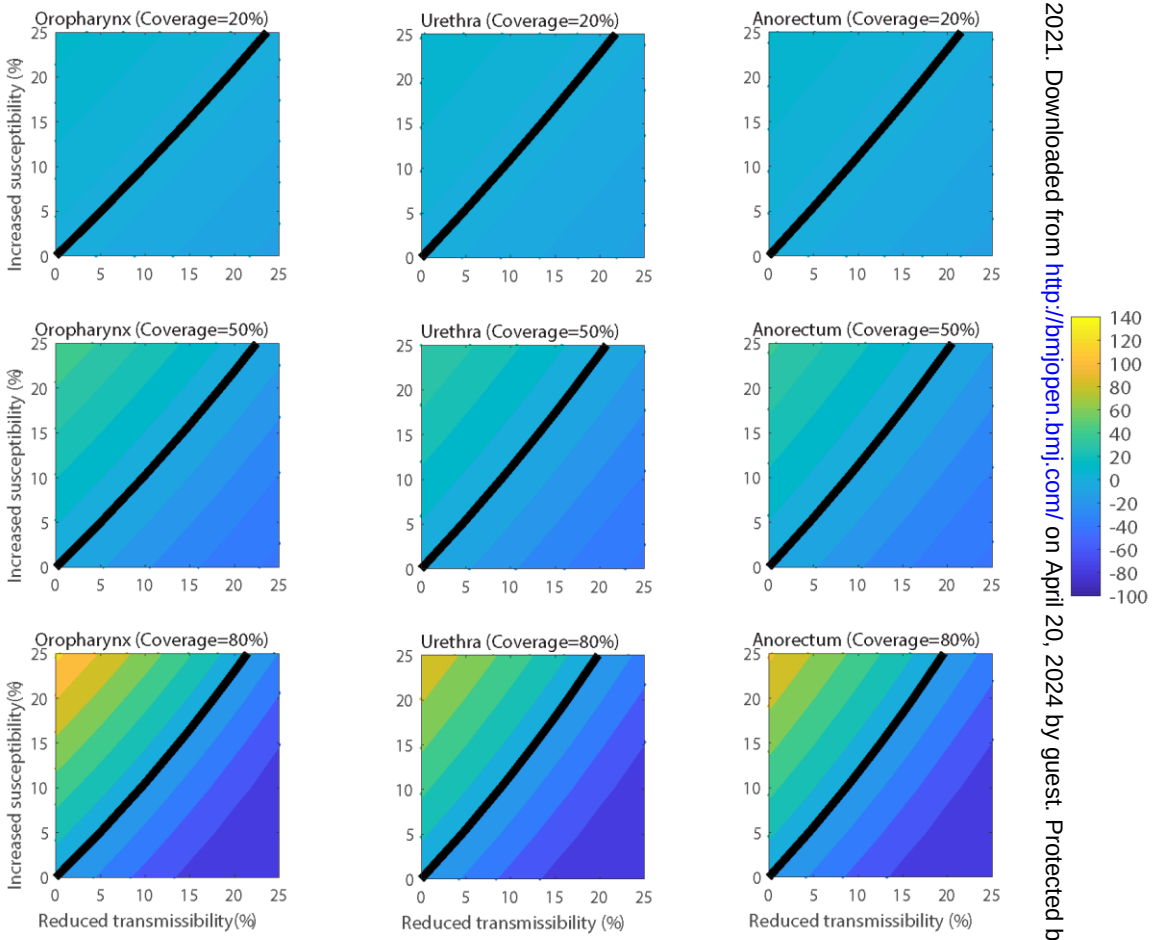


Figure 6b. *Contour plots for the effect of antibacterial mouthwash on the percentage change of incidence at the oropharynx, anorectum or urethra by increasing susceptibility of oropharyngeal gonorrhoea and reducing transmissibility of gonorrhoea from the oropharynx.*

The black solid isoclines indicate the threshold that the percentage change of incidence is zero.

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