Author/s:
Hui, BB;Padeniya, TN;Rebuli, N;Gray, RT;Wood, JG;Donovan, B;Duan, Q;Guy, R;Hocking, JS;Lahra, MM;Lewis, DA;Whiley, DM;Regan, DG;Seib, KL

Title:
A Gonococcal Vaccine Has the Potential to Rapidly Reduce the Incidence of Neisseria gonorrhoeae Infection among Urban Men Who Have Sex with Men

Date:
2022-03-15

Citation:
Hui, B. B., Padeniya, T. N., Rebuli, N., Gray, R. T., Wood, J. G., Donovan, B., Duan, Q., Guy, R., Hocking, J. S., Lahra, M. M., Lewis, D. A., Whiley, D. M., Regan, D. G. & Seib, K. L. (2022). A Gonococcal Vaccine Has the Potential to Rapidly Reduce the Incidence of Neisseria gonorrhoeae Infection among Urban Men Who Have Sex with Men. Journal of Infectious Diseases, 225 (6), pp.983-993. https://doi.org/10.1093/infdis/jiab581.

Persistent Link:
https://hdl.handle.net/11343/307488

The Journal of Infectious Diseases

MAJOR ARTICLE

A Gonococcal Vaccine Has the Potential to Rapidly Reduce the Incidence of *Neisseria gonorrhoeae* Infection Among Urban Men Who Have Sex With Men

Ben B. Hui,[1] Thilini N. Padeniya,[1] Nic Rebuli,[1] Richard T. Gray,[1] James G. Wood,[2] Basil Donovan,[1] Qibin Duan,[1,3] Rebecca Guy,[1] Jane S. Hocking,[4] Monica M. Lahra,[5,6] David A. Lewis,[7,8,9] David M. Whiley,[10] David G. Regan,[1,a] and Kate L. Seib[11,a]

[1]The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia, [2]School of Population Health, University of New South Wales, Sydney, New South Wales, Australia, [3]School of Mathematical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia, [4]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia, [5]Microbiology Department, New South Wales Health Pathology, The Prince of Wales Hospital, Randwick, New South Wales, Australia, [6]School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia, [7]Western Sydney Sexual Health Centre, Western Sydney Local Health District, Parramatta, New South Wales, Australia, [8]Westmead Clinical School, Faculty of Health and Medicine & Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia, [9]Division of Medical Virology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa, [10]Centre for Clinical Research, University of Queensland, Brisbane, Queensland, Australia, and [11]Institute for Glycomics, Griffith University, Gold Coast, Queensland, Australia

(See the Editorial Commentary by Christensen and Vickerman, on pages 931–3.)

Background. A gonococcal vaccine is urgently needed due to increasing gonorrhea incidence and emerging multidrug-resistant gonococcal strains worldwide. Men who have sex with men (MSM) have among the highest incidences of gonorrhea and may be a key target population for vaccination when available.

Methods. An individual-based, anatomical site-specific mathematical model was used to simulate *Neisseria gonorrhoeae* transmission in a population of 10 000 MSM. The impact of vaccination on gonorrhea prevalence was assessed.

Results. With a gonococcal vaccine of 100% or 50% protective efficacy, gonorrhea prevalence could be reduced by 94% or 62%, respectively, within 2 years if 30% of MSM are vaccinated on presentation for sexually transmitted infection (STI) testing. Elimination of gonorrhea is possible within 8 years with vaccines of ≥ 50% efficacy lasting 2 years, providing a booster vaccination is available every 3 years on average. A vaccine's impact may be reduced if it is not effective at all anatomical sites.

Conclusions. Our study indicates that with a vaccine of modest efficacy and an immunization strategy that targets MSM presenting for STI screening, the prevalence of gonorrhea in this population could be rapidly and substantially reduced.

Keywords. *Neisseria gonorrhoeae*; gonorrhea; sexually transmitted infection; gonococcal vaccine; mathematical model; individual-based model; men who have sex with men (MSM).

Neisseria gonorrhoeae, the causative agent of gonorrhea, is an urgent public health threat [1] due to rising incidence, the severe reproductive tract morbidities that it causes, and the difficulties of treating multidrug-resistant strains [2]. Although there is currently no vaccine of proven efficacy available, interest in developing gonococcal vaccines has greatly intensified [3], and mathematical modelling of vaccine impact is key to informing vaccine development and implementation [4].

An estimated 87 million gonorrhea infections are reported each year [5]. In many settings, the highest incidence of gonorrhea is reported in men who have sex with men (MSM) [6–9]. Incidence among MSM in Australia is reported to be 39 per 100 person-years [10] even though approximately 80% of MSM in urban Australia are tested annually [11].

N. gonorrhoeae can be transmitted through penile-vaginal, penile-anal, and penile-oral sex [12], and via other pathways such as oropharynx to oropharynx [13, 14]. Infection of the male urethra usually results in noticeable symptoms and infected men tend to promptly seek treatment [12]. However, anorectal and oropharyngeal infections are usually asymptomatic and may remain untreated allowing for ongoing transmission [15]. Complications of untreated gonococcal infection in men include urethral stricture, urogenital tract abscesses, epididymo-orchitis, infertility, and increased risk of human immunodeficiency virus (HIV) [16].

The World Health Organization (WHO) Global Health Sector Strategy on sexually transmitted infections (STIs) has set targets for reducing global gonorrhea incidence by 90% by 2030 [17]. *N. gonorrhoeae* has developed resistance to almost all classes of antibiotics used to treat it and extensively drug-resistant strains have been reported [18–20]. Therefore, vaccine development and implementation are considered priorities

Received 6 August 2021; editorial decision 14 October 2021; accepted 24 November 2021; published online 11 December 2021.

[a]D. G. R and K. L. S. are joint senior authors.

Correspondence: Ben Hui, PhD, The Kirby Institute, UNSW Sydney, Wallace Wurth Building, Sydney, NSW 2052, Australia (bhui@kirby.unsw.edu.au).

The Journal of Infectious Diseases® 2022;225:983–93

https://doi.org/10.1093/infdis/jiab581

to providing a long-term solution to gonorrhea [4]. Although challenging, the feasibility of developing a gonococcal vaccine is supported by a retrospective case-control study that estimated approximately 30% protective efficacy against gonorrhea by the MeNZB vaccine licensed for the closely related bacteria *Neisseria meningitidis* [21]. Mathematical modelling predicted that a vaccine with 30% efficacy could reduce gonorrhea prevalence by 50% within 20 years in a heterosexual population [22]. Vaccinating key, at-risk populations (eg, MSM) may be an effective strategy to reduce gonorrhea prevalence [4].

Here we model the potential impact on gonorrhea prevalence of vaccinating 15%, 30%, and 60% of MSM participating in routine STI testing each year, with and without booster vaccination. We investigate gonococcal vaccines that differ in their ability to prevent infection at all sites or at specific anatomical sites (protective efficacy), reduce transmission (transmission suppression efficacy), and/or reduce symptoms of infection (symptom suppression efficacy).

METHODS

Modelling *N. gonorrhoeae* Transmission Across Multiple Anatomical Sites in MSM

We developed an individual-based mathematical model to simulate *N. gonorrhoeae* transmission in an urban population of 10 000 MSM in Australia based on our previously described models [13, 14, 23]. Each member of the modelled population has 3 potential anatomical sites of infection (urethra, anorectum, and oropharynx) and *N. gonorrhoeae* can be transmitted bidirectionally between urethra-anorectum, urethra-oropharynx, anorectum-oropharynx, and oropharynx-oropharynx. We assume all infections are localized such that the course of infection at 1 infected anatomical site is independent of infection at any other site. Treatment is assumed to result in clearance of infection at all sites simultaneously.

The modelled population consists of 10 000 MSM aged 16–80 years who engage in regular and/or casual partnerships, with sexual behavior parameters and STI testing rates derived from published studies [11, 13, 24–28]. Sexual partnerships are represented as dynamic networks, with partnerships formation and dissolution governed by partnership type, partnership duration, and acquisition rate (Supplementary Table 2). Stochasticity in outputs arises through the probabilistic nature of transmission, variability in duration of the infectious period, and formation/dissolution of partnerships. Simulations were run for approximately 30 years, with vaccination introduced at 20 years after the introduction of gonorrhea into the population (referred to as year 0). The model was calibrated against the reported anatomical site-specific prevalence of urethral, anorectal, and oropharyngeal gonorrhea [13, 24, 26, 27, 29–32]. Calibration against gonorrhea prevalence at all anatomical sites was performed through adjustments of transmission probability for each type of sexual contact. Gonorrhea prevalence was tracked for 10 years, with an overall prevalence at any anatomical site of 12.0% (interquartile range [IQR], 11.0%–14.0%), and the anatomical site-specific prevalence at the urethra, anorectum, and oropharynx of 1.7% (IQR, 1.6%–1.9%), 6.7% (IQR, 6.3%–7.3%), and 8.8% (IQR, 7.9%–10.6%), respectively, at year 2 in the absence of vaccination. This is consistent with observed estimates of prevalence (urethra 2.0%, anorectum 8.0%, and oropharynx 8.3%) [33]. A detailed description of the model and calibration is in the Supplementary Material.

Vaccine Mode of Action

The properties of gonococcal vaccines investigated in our model are hypothetical and their mode of action is captured through 3 types of vaccine efficacy:

1. Efficacy in protecting a vaccinated individual against acquiring gonorrhea (protective efficacy): this measures the extent to which a vaccinated individual will be protected against acquiring gonorrhea from an infectious contact (eg, assuming the per sexual act probability of transmission from urethra to anorectum is 0.8 between unvaccinated individuals, then a vaccine with 50% protective efficacy will reduce the probability of transmission to 0.4 for the vaccinated individual.
2. Efficacy in reducing *N. gonorrhoeae* transmissibility from a vaccinated individual (transmission suppression efficacy): this measures the extent to which an unvaccinated individual will be protected from acquiring gonorrhea from a vaccinated but infectious contact (ie, a vaccinated individual with breakthrough infection). Again, assuming the per sexual act probability of transmission is 0.8, a vaccine with 50% transmission suppressive efficacy will reduce the probability of transmission to 0.4 if the infectious contact is vaccinated. We assume protective and transmission suppression efficacy are multiplicative, so the probability of transmission between 2 vaccinated contacts will be reduced to 0.2 if the vaccine has both 50% protective and 50% transmission suppression efficacy.
3. Efficacy in reducing gonorrhea symptoms in a vaccinated infected individual (symptom suppression efficacy): this measures the extent to which the vaccine reduces the likelihood of symptoms developing in vaccinated individuals with breakthrough infection. This is particularly relevant for urethral infections that are more likely to be symptomatic in males. We assume that the presence/absence of symptoms has no direct impact on transmission rates, but asymptomatic individuals will not seek treatment, leading to increased transmission.

Vaccination Scenarios

Gonorrhea prevalence was tracked for 10 years following the introduction of a vaccine having protective and/or transmission suppression efficacy of 0%, 25%, 50%, 75%, or 100%. We compared this with scenarios where the vaccine is ineffective for

infection at the oropharynx, and where the vaccine only suppresses symptoms. We also considered scenarios with different vaccine uptake rates, durations of vaccine-conferred protection, and booster vaccination.

Vaccination is implemented such that a proportion of MSM presenting for routine STI testing (assuming 80% of MSM are tested annually [11, 27]) are vaccinated each year. The vaccination uptake rate by MSM through STI clinic visits following a 2018 hepatitis A outbreak was approximately 60% [34]. We therefore made our baseline assumption for per-visit vaccination uptake at a more conservative rate of 30%. Individuals are only vaccinated once in their lifetime, and vaccine-conferred protection wanes after 2 years on average. Under this strategy, close to 40% of the population will be effectively vaccinated 2 years after the introduction of vaccination, with the proportion of the population protected by the vaccine declining to 20% and 6% after 5 and 10 years, respectively (Supplementary Figure 3). We compared the baseline scenario with scenarios whereby vaccinated individuals receive booster vaccinations every 3 years on average, per-visit vaccine uptake is halved to 15% and doubled to 60%, the vaccine is ineffective against infection at the oropharynx, and the vaccine suppresses the development of symptoms. Scenarios with longer vaccine-conferred protection (5 and 10 years) are presented in the Supplementary Material.

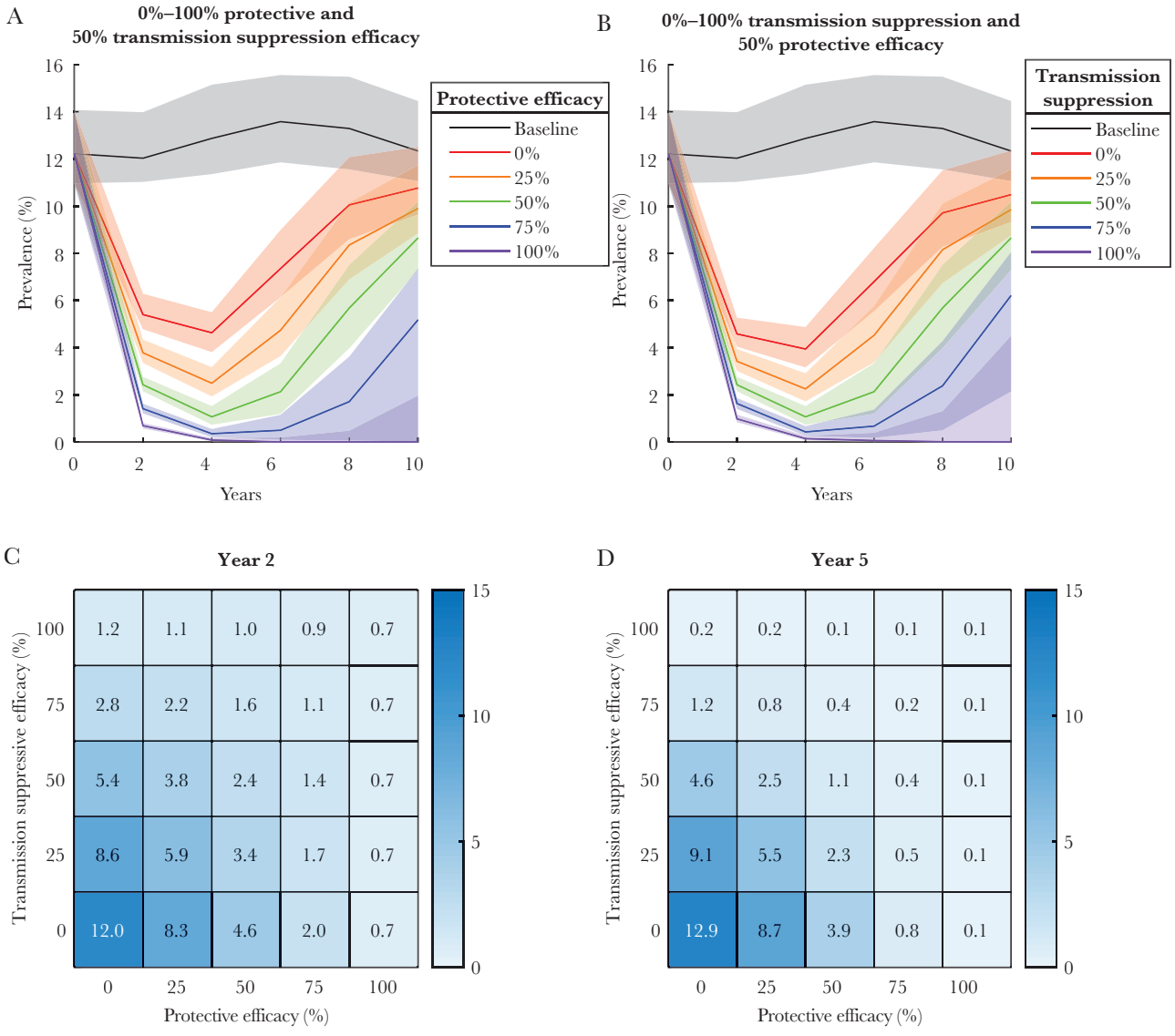

Figure 1. The impact on population gonorrhea prevalence of vaccines having a range of protective and transmission suppression efficacies, and 30% vaccine uptake. *A* and *B*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of vaccination with vaccines having either (*A*) different levels of protective efficacy (0%–100%) with transmission suppression efficacy fixed at 50% or (*B*) different levels of transmission suppression efficacy (0%–100%) with protective efficacy fixed at 50%. In all scenarios, it is assumed that vaccine-conferred protection wanes after 2 years on average and that 30% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated annually. The solid lines and shading are the median and interquartile range from 1000 model runs, respectively. *C* and *D*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A3 and A4) gonorrhea prevalence at any anatomical site at year 2 (*C*) and at year 5 (*D*) after the introduction of vaccination with vaccines having different combinations of protective and transmission suppression efficacy.

RESULTS

If a gonococcal vaccine becomes available that confers 100% protective efficacy, our modelling predicted a 94% relative reduction in gonorrhea prevalence at 2 years following the commencement of vaccination (12% to 0.7% prevalence; Figure 1A and 1C) and elimination within 5 years (Figure 1A and 1D), when 30% of MSM presenting for STI screening are vaccinated per visit and vaccine-conferred protection wanes after 2 years. Similarly, a vaccine with 100% transmission suppression efficacy would result in a 90% decrease in prevalence at 2 years (12% to 1.2% prevalence), even if the vaccine confers no protective efficacy. However, vaccines with lower levels of protective and/or transmission suppression efficacy would also have a substantial impact (Figure 1). For example, a vaccine with only 25% protective or 25% transmission suppression efficacy would reduce prevalence by approximately 30% at 2 years (12% to 8.3% or 8.6% prevalence, respectively), while a vaccine with both 25% protective and 25% transmission suppression efficacy would reduce prevalence by approximately 50% at 2 years (12% to 5.9% prevalence; Figure 1C).

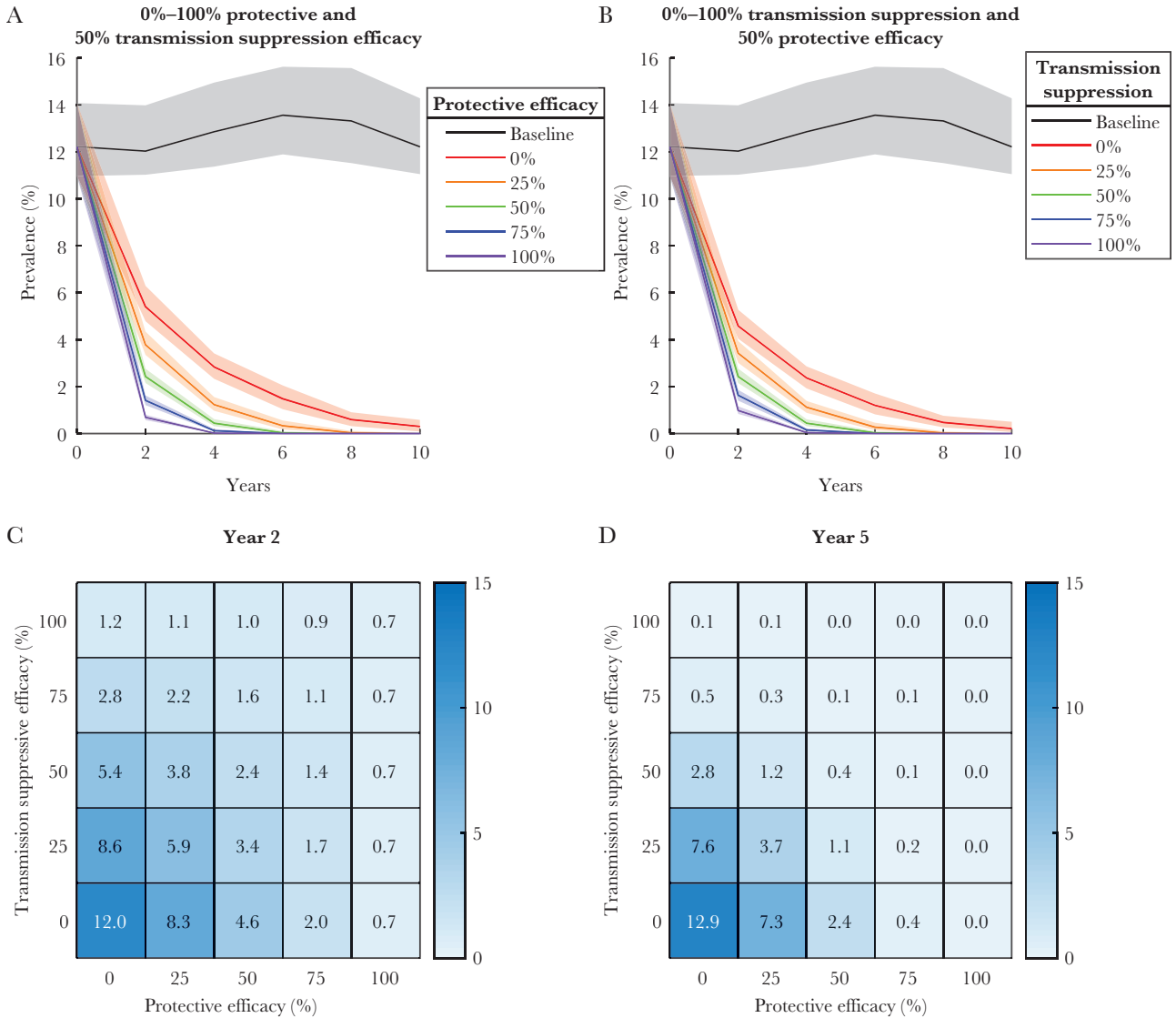

Figure 2. The impact on population gonorrhea prevalence of vaccines having a range of protective and transmission suppression efficacies, and 30% vaccine uptake. *A* and *B*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of vaccination with vaccines having either (*A*) different levels of protective efficacy (0%–100%) with transmission suppression efficacy fixed at 50% or (*B*) different levels of transmission suppression efficacy (0%–100%) with protective efficacy fixed at 50%. In all scenarios, it is assumed that vaccine-conferred protection wanes after 2 years on average and that 30% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated annually and that a vaccine booster is given every 3 years on average. The solid lines and shading are the median and interquartile range from 1000 selected model runs, respectively. *C* and *D*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A5 and A6) gonorrhea prevalence at any anatomical site at year 2 (*C*) and at year 5 (*D*) after the introduction of vaccination with vaccines having different combinations of protective and transmission suppression efficacy.

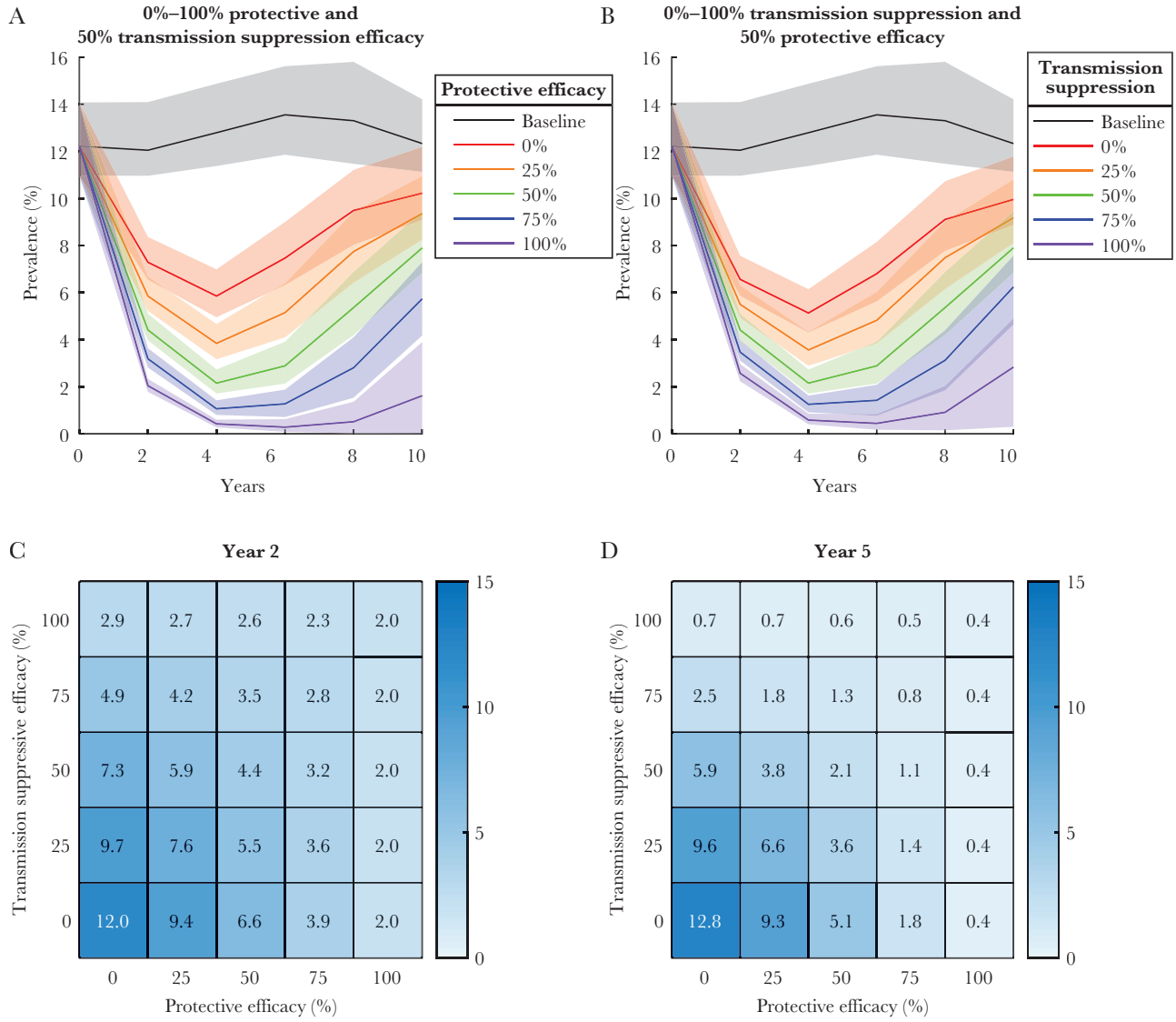

Figure 3. The impact on population gonorrhea prevalence with vaccines having a range of protective and suppressive efficacies, and 15% vaccine uptake. *A* and *B*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of vaccination with vaccines having either (*A*) different levels of protective efficacy (0%–100%) with transmission suppression efficacy fixed at 50% or (*B*) different levels of transmission suppression efficacy (0%–100%) with protective efficacy fixed at 50%. In all scenarios, it is assumed that 15% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated annually, and that vaccine-conferred protection wanes after 2 years on average. The solid lines and shading are the median and interquartile range from 1000 model runs, respectively. *C* and *D*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A7 and A8) gonorrhea prevalence at any anatomical site at year 2 (*C*) and at year 5 (*D*) after the introduction of vaccination with vaccines having different combinations of protective and transmission suppression efficacy.

In most vaccine scenarios investigated in this study with 30% vaccine uptake, the reduction in gonorrhea prevalence was not sustained for more than 4 years (Figure 1A and 1B) because the proportion of the population vaccinated dropped below approximately 20% after 5 years due to the vaccine waning at 2 years (Supplementary Figure 3). However, if all vaccinated individuals receive a vaccine booster shot every 3 years on average, the reduction in gonorrhea prevalence was sustained over time with a 70% relative reduction in prevalence at 5 years following the commencement of vaccination (13% to 4% prevalence) with vaccine conferring 25% protective and transmission suppression efficacy (Figure 2D), and elimination could potentially be achieved within 8 years even with vaccines of < 50% protective and transmission suppression efficacy (Figure 2A and 2B). When per-visit vaccine uptake was decreased from 30% to 15% for MSM presenting for STI screening, prevalence was reduced to 0.4% at 5 years if the vaccine confers 100% protective efficacy (Figure 3D), but reductions were not sustained in the absence of a booster (Figure 3B). When vaccine uptake was increased from 30% to 60% per visit, prevalence was slightly reduced at 2–4 years for all scenarios analyzed and elimination of gonorrhea was possible within 5 years if protective efficacy is 100% (Figure 4D). However, at lower protective efficacy, the reduction in prevalence was not sustained for more than 4 years in the absence of a booster (Figure 4B).

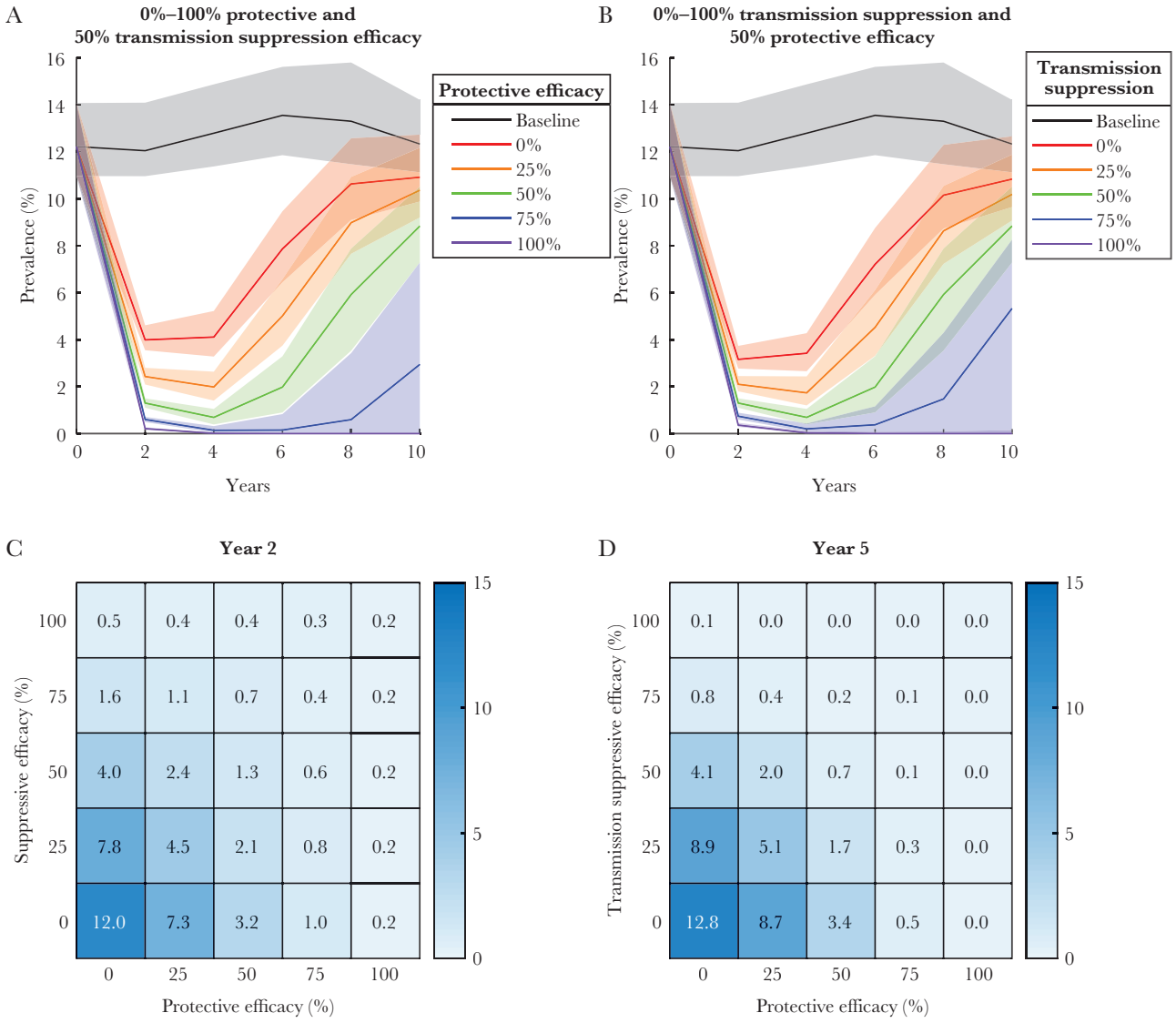

Figure 4. The impact on population gonorrhea prevalence with vaccines having a range of protective and suppressive efficacies, and 60% vaccine uptake. *A* and *B*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of vaccination with vaccines having either (*A*) different levels of protective efficacy (0%–100%) with transmission suppression efficacy fixed at 50% or (*B*) different levels of transmission suppression efficacy (0%–100%) with protective efficacy fixed at 50%. In all scenarios, it is assumed that 60% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated annually, and that vaccine-conferred protection wanes after 2 years on average. The solid lines and shading are the median and interquartile range from 1000 model runs, respectively. *C* and *D*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A9 and A10) gonorrhea prevalence at any anatomical site at year 2 (*C*) and at year 5 (*D*) after the introduction of vaccination with vaccines having different combinations of protective and transmission suppression efficacy.

The vaccine impacts described above were achieved under the assumption that the vaccine is equally effective at all anatomical sites (Figure 1 and Supplementary Figure 4). However, prevalence, transmissibility, and symptoms of gonorrhea differ between anatomical sites. In particular, infection at the oropharynx is more difficult to treat [15, 18, 35] and is believed to be a key driver of transmission in MSM [15, 36]. We found that a vaccine that completely protects against urethral and anorectal infection, but has no efficacy against acquisition or transmissibility of oropharyngeal infection, had a substantially reduced impact, with only a 33% reduction in gonorrhea prevalence at 5 years (12% to 8.1% prevalence; Figure 5C).

The impact of vaccines that prevent symptoms but do not offer complete protection against infection and transmission was also investigated, under the assumption that only symptomatic individuals will seek treatment. If a gonococcal vaccine suppresses symptoms at all anatomical sites, a reduction in gonorrhea prevalence was only observed if the vaccine's protective efficacy was ≥ 50% (if the vaccine does not suppress transmission), or the transmission suppression efficacy was ≥ 75% (if the vaccine does not protect against infection) (Figure 6B and 6C). If a vaccine has 50% preventive and 50% transmission suppression efficacy, gonorrhea prevalence will fall to 4.7% at 2 years if the vaccine suppresses symptoms, compared to 2.4%

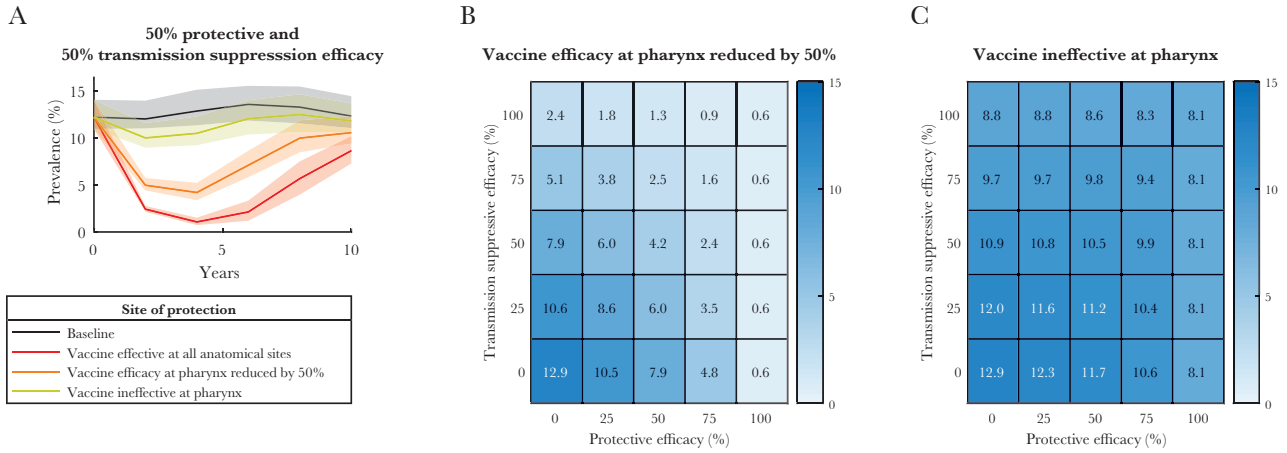

Figure 5. The impact on population gonorrhea prevalence of a vaccine that has reduced efficacy against oropharyngeal infection. *A*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of vaccines with 50% protective efficacy and 50% transmission suppression efficacy at all anatomical site (red), or with 50% protective and transmission suppression efficacy at nonpharyngeal sites, but with both efficacies 25% (orange) or 0% at pharynx (yellow). In all scenarios, it is assumed that 30% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated annually, and that vaccine-conferred protection wanes after 2 years on average. The solid lines and shading are the median and interquartile range from 1000 model runs, respectively. *B* and *C*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A11 and A12) gonorrhea prevalence at any anatomical site at year 5 after the introduction of vaccines that have different combinations of protective and transmission suppression efficacy at nonpharyngeal sites (ie, efficacy at urethra and rectum only), with efficacies at the oropharynx reduced further by 50% (*B*) or 100% (*C*).

for a vaccine that has no impact on symptoms (Figure 6A). However, if a vaccine suppresses symptoms but has 0% protective or transmission suppression efficacy, then gonorrhea prevalence may actually increase from the baseline prevalence of 12% to 25.9% at 2 years (Figure 6A).

DISCUSSION

There is currently great interest in developing gonococcal vaccines due to increasing disease rates and increasing AMR. Here we used an individual-based mathematical model that simulates anatomical site-specific *N. gonorrhoeae* transmission in MSM to assess the impact of a range of vaccine types and immunization strategies that target MSM participating in STI screening. Overall, our findings suggest that a gonococcal vaccine of moderate efficacy has the potential to substantially and rapidly reduce gonorrhea prevalence in this population.

To identify key characteristics required for a gonococcal vaccine to have optimal public health value, we considered

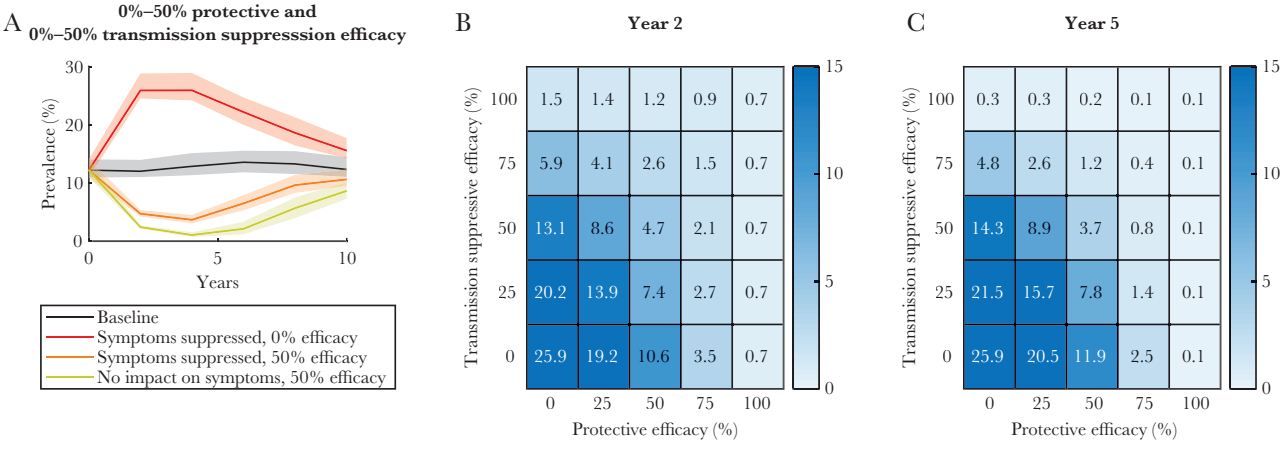

Figure 6. The impact on population gonorrhea prevalence of a vaccine that suppresses symptoms. *A*, Gonorrhea prevalence during 10 years in the absence of a vaccine (baseline) or after the introduction of a vaccine with 50% protective efficacy and 50% transmission suppression efficacy that has no impact on symptoms (red) or that suppresses symptoms (orange), or a vaccine with 0% protective and transmission suppression efficacy but that suppresses symptoms (yellow). In all scenarios, it is assumed that 30% per visit of unvaccinated individuals tested for sexually transmitted infections are vaccinated, and that vaccine-conferred protection wanes after 2 years on average. The solid lines and shading are the median and interquartile range from 1000 model runs, respectively. *B* and *C*, Heatmaps showing the median (of 1000 model runs, with interquartile range listed in Supplementary Tables A13 and A14) gonorrhea prevalence at any anatomical site at year 2 (*B*) and at year 5 (*C*) after the introduction of vaccines that have different combinations of protective and transmission suppression efficacies, and that also suppress gonorrhea symptoms.

3 main modes of potential vaccine-mediated efficacy: protection from infection, suppression of transmission, and suppression of symptoms. A vaccine with complete or high protective efficacy that ensures a vaccinated individual is protected against acquiring gonorrhea is the primary aim for vaccine development, and it is important to note that a vaccine with 100% protective efficacy will, by definition, also have 100% transmission and 100% symptom suppression efficacy. Our results show that an optimal vaccine with 100% protective efficacy at all anatomical sites could result in elimination of gonorrhea in the MSM population within 5 years if 30% of those presenting for STI screening per visit are vaccinated. However, elimination might not be achieved if the protective effect of the vaccine is reduced and/or wanes within 2 years on average. This is consistent with observations for MeNZB, where cases of gonorrhea increased as time after vaccination increased [21]. Our results show that gonorrhea elimination is more likely to be achieved if vaccine-conferred protection lasts for 5 years or more, either due to slower waning or booster vaccination.

Given that development of a gonorrhea-specific vaccine has been unsuccessful to date, and that the MeNZB vaccine was estimated to have 30% effectiveness against acquisition of gonorrhea [21], it was important to model the potential impact of vaccines with suboptimal characteristics. Our results suggest that a vaccine with low protective efficacy could still be beneficial if it can suppress transmission, such that an unvaccinated individual will be protected to a certain extent from acquisition of gonorrhea from a vaccinated infectious contact. This reduced transmission may be the result of a reduced bacterial load due to vaccination, and associations between infectious load and transmissibility have been found for STIs, including HIV [37] and human papillomavirus [38]. Associations between bacterial load and transmissibility have also been observed for *N. gonorrhoeae* although additional studies are needed to confirm this [39]. Nonetheless, our model predicts that a gonococcal vaccine with both 25% protective and 25% transmission suppression efficacy will reduce gonorrhea prevalence by 50% within 2 years, while a vaccine that has either 25% protective efficacy alone or 25% transmission suppression efficacy alone would still reduce prevalence by approximately 30% within 2 years (30% and 28% reduction, respectively).

A unique feature of this study is the consideration of the impact of a vaccine having differential efficacy by anatomical site. Our results indicate that gonococcal vaccines need to be effective against oropharyngeal infection for gonorrhea prevalence to be substantially reduced in the MSM population modelled in this study, with elimination unlikely even if vaccine efficacy at the urethra and anorectum is close to 100%. Although the role of oropharyngeal infection in sustaining gonorrhea prevalence has not yet been firmly established, several studies have suggested that oropharyngeal infection could be a key factor in sustaining high prevalence in MSM [40]. This highlights a need to ensure that a gonococcal vaccine designated for an MSM population is effective at all anatomical sites. It remains difficult to predict vaccine impact at different anatomical sites as this may vary between vaccines. For example, meningococcal C [41] but not meningococcal B reduce nasopharyngeal carriage of *N. meningitidis* [42].

Concern has been expressed that a partially protective vaccine that suppresses symptoms but does not prevent infection could result in a higher proportion of asymptomatic cases. For example, coronavirus disease 2019 (COVID-19) [43], pertussis [44], and hepatitis B [45] vaccines suppress symptoms but do not completely prevent infection. Under the assumption that asymptomatic and symptomatic infection are equally transmissible, our model suggests that the potential reduction in gonorrhea prevalence achievable with a vaccine of less than 100% protective efficacy could be offset if the vaccine also suppresses symptoms, as the proportion of infected individuals seeking treatment is reduced. Furthermore, our results suggest that a vaccine would need to have protective and transmission suppression efficacy of more than 25% for a symptom suppressing vaccine to reduce gonorrhea prevalence. This finding differs from predictions of previous vaccine impact modelling focused on a heterosexual population, which suggested that a vaccine that suppresses symptoms will not lead to an increase prevalence [22]. However, both outcomes to be feasible as our study focused on an MSM population rather than a lower prevalence heterosexual population in which a higher portion of infections are urethral and symptomatic and therefore likely to lead to earlier treatment. Our predictions of impact on prevalence are likely to be conservative as we have not considered other interventions such as contact tracing and engagement with sexual health services for the purposes of receiving HIV preexposure prophylaxis (PrEP) or HIV clinical care that could lead to early treatment of asymptomatic infection. Asymptomatic infection may also be less transmissible than symptomatic infection due to a reduced bacterial load. Nevertheless, our findings suggests that if a vaccine does have low efficacy and suppresses symptoms, it may not be beneficial for a population where most infections are managed through symptom-based control strategies.

The ideal target group(s) for vaccination in terms of public health impact and cost-effectiveness will likely depend on the setting as there is wide variability in gonorrhea epidemiology. For example, broad-based vaccination during early adolescence aimed at before sexual debut may be preferred in countries with relatively high gonorrhea prevalence in young sexually active populations, while strategies targeting key populations may be preferred in countries with relatively low prevalence in the general population but high prevalence among specific populations such as MSM [4]. We considered scenarios where either 30% or 60% per visit of unvaccinated MSM presenting for STI

screening are vaccinated and compared these with the scenario where vaccine uptake remains at 30% but booster vaccination is provided every 3 years. While higher vaccine uptake did lead to reduced prevalence in scenarios where vaccine efficacy waned at 2 years, the scenario with 30% vaccine uptake with booster vaccination resulted in the most favorable outcomes in terms of potential gonorrhea elimination. On the other hand, a vaccination program requiring the administration of booster vaccination is more costly and logistically challenging for implementation. Other gonococcal vaccine impact modelling studies have also showed that vaccinating core-group individuals (those with high numbers of sexual partners, assumed to be just 4%–5% of the population) resulted in comparable population-level reductions in prevalence as achieved when vaccinating all men and women [22, 46]. A key barrier for targeting high-risk groups is the potential difficulty in identifying and accessing the target group to provide vaccination. Given that a past diagnosis of an STI is a key factor associated with the risk of acquiring subsequent STIs [10], vaccinating MSM presenting for STI screening is a pragmatic strategy. Because bridging between MSM and heterosexuals is likely to occur (through men who have sex with men and women) [47], the reduction of gonorrhea prevalence in core groups such as MSM will likely also impact prevalence in the wider population.

A limitation of our study is the uncertainty of transmission probabilities for different transmission pathways (eg, anal sex, oral sex, kissing), as highlighted in other modelling studies [48]. Furthermore, due to a lack of robust data to the contrary, we assumed that transmission probabilities are the same for asymptomatic and symptomatic infection, and that vaccine efficacy will be similar for all gonococcal strains. These issues will likely remain unresolved until data informing per-act transmissibility is available for all transmission pathways in the presence and absence of symptoms. Our study also did not consider changes in sexual behavior that may emerge with the introduction of a gonococcal vaccine, such as decreased risk-reduction behaviors (eg, condom use) that have been observed following the introduction of PrEP [49]. Our main analysis assumed a relatively high per-visit vaccine uptake rate (30%), on top of high annual STI testing coverage (80%) [11, 27]. These assumptions result in an effective vaccination coverage peaking close to 40% within 2 years. As vaccination uptake is tied to STI testing visits, vaccination coverage will increase more slowly in settings, such as in the United States [50], where STI testing coverage is lower. The effect on *N. gonorrhoeae* prevalence under lower STI testing coverage is predicted to be comparable to scenarios with lower vaccine uptake, on top of other effects caused by lower baseline STI testing. In this regard, we also considered a lower 15% per-visit vaccination uptake. Finally, we only considered sexual contacts between men in the model and have not considered the role of men who have sex with both men and women and the possible bridging with heterosexual populations.

In conclusion, this modelling study indicates that a vaccine of modest efficacy and an immunization strategy that targets MSM presenting for STI screening could significantly, and rapidly, reduce the incidence of gonorrhea in this population. These findings will inform the potential implementation of gonococcal vaccination programs and, given the high rates of gonorrhea in MSM, a targeted immunization strategy could significantly contribute to the WHO targets for reducing gonorrhea incidence by 90% by 2030.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. B. B. H., R. T. G., J. G. W., D. G. R., and K. L. S. contributed conceptualization of the study. B. B. H. developed the model. B. B. H., T. N. P., N. R., R. T. G., J. G. W., D. G. R., and K. L. S. discussed the main model findings. B. B. H., D. G. R., and K. L. S. wrote the original manuscript. D. G. R. and K. L. S. supervised the work and contributed resources. All authors contributed and edited the manuscript.

Financial support. This study was supported by the National Institutes of Health (grant number U19 AI144182); and the National Health and Medical Research Council (grant number 1145642). The Kirby Institute is funded by the Australian Government Department of Health, and is affiliated with the Faculty of Medicine, University of New South Wales, Sydney, Australia.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed

References

1. Department of Health. Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015–2019. Canberra, Australia: Department of Health, Australian Government, **2015**. https://www.amr.gov.au/resources/national-amr-strategy.
2. Edwards JL, Jennings MP, Apicella MA, Seib KL. Is gonococcal disease preventable? The importance of understanding immunity and pathogenesis in vaccine development. Crit Rev Microbiol **2016**; 42:928–41.
3. Gottlieb SL, Deal CD, Giersing B, et al. The global roadmap for advancing development of vaccines against sexually

transmitted infections: update and next steps. Vaccine **2016**; 34:2939–47.
4. Gottlieb SL, Ndowa F, Hook EW, 3rd, et al. Gonococcal vaccines: public health value and preferred product characteristics; report of a WHO global stakeholder consultation, January 2019. Vaccine **2020**; 38:4362–73.
5. Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ **2019**; 97:548–62P.
6. Callander D, Guy R, Fairley CK, et al. Gonorrhoea gone wild: rising incidence of gonorrhoea and associated risk factors among gay and bisexual men attending Australian sexual health clinics. Sex Health **2018**.
7. Kent CK, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis **2005**; 41:67–74.
8. Dudareva-Vizule S, Haar K, Sailer A, et al. Prevalence of pharyngeal and rectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections among men who have sex with men in Germany. Sex Transm Infect **2014**; 90:46–51.
9. Rebe K, Lewis D, Myer L, et al. A cross sectional analysis of gonococcal and chlamydial infections among men-who-have-sex-with-men in Cape Town, South Africa. PLoS One **2015**; 10:e0138315.
10. Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. JAMA **2019**; 321:1380–90.
11. Lee E, Mao L, Broady T, et al. Gay community periodic survey: Melbourne 2018. Sydney, Australia: Centre for Social Research in Health, University of New South Wales, **2018**.
12. Holmes KK. In: Holmes KK, Sparling PF, Stamm WE, et al, eds. Sexually transmitted diseases. 4th ed. New York: McGraw-Hill, **2007**.
13. Zhang L, Regan DG, Chow EPF, et al. *Neisseria gonorrhoeae* transmission among men who have sex with men: an anatomical site-specific mathematical model evaluating the potential preventive impact of mouthwash. Sex Transm Dis **2017**; 44:586–92.
14. Fairley CK, Hocking JS, Zhang L, Chow EP. Frequent transmission of gonorrhea in men who have sex with men. Emerg Infect Dis **2017**; 23:102–4.
15. Janier M, Lassau F, Casin I, Morel P. Pharyngeal gonorrhoea: the forgotten reservoir. Sex Transm Infect **2003**; 79:345.
16. Workowski KA, Berman SM, Douglas JM. Emerging antimicrobial resistance in *Neisseria gonorrhoeae*: urgent need to strengthen prevention strategies. Ann Intern Med **2008**; 148:606–13.
17. World Health Organization. Global health sector strategy on sexually transmitted infections, 2016–2021. https://www.who.int/reproductivehealth/publications/rtis/ghss-stis/en/.
18. Eyre DW, Sanderson ND, Lord E, et al. Gonorrhoea treatment failure caused by a *Neisseria gonorrhoeae* strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. Euro Surveill **2018**; 23.
19. European Centre for Disease Prevention and Control (ECDC). Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* in the United Kingdom and Australia. Stockholm, Sweden: ECDC, **2018**.
20. Whiley DM, Jennison A, Pearson J, Lahra MM. Genetic characterisation of *Neisseria gonorrhoeae* resistant to both ceftriaxone and azithromycin. Lancet Infect Dis **2018**; 18:717–8.
21. Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet **2017**; 390:1603–10.
22. Craig AP, Gray RT, Edwards JL, et al. The potential impact of vaccination on the prevalence of gonorrhea. Vaccine **2015**; 33:4520–5.
23. Hui B, Fairley CK, Chen M, et al. Oral and anal sex are key to sustaining gonorrhoea at endemic levels in MSM populations: a mathematical model. Sex Transm Infect **2015**.
24. National Centre in HIV Epidemiology and Clinical Research. Phase A of the National Gay Men's Syphilis Action Plan: Modelling evidence and research on acceptability of interventions for controlling syphilis in Australia. Sydney, Australia: National Centre in HIV Epidemiology and Clinical Research, **2009**.
25. Fogarty A, Mao L, Zablotska Manos I, et al. The Health in Men and Positive Health cohorts: a comparison of trends in the health and sexual behaviour of HIV-negative and HIV-positive gay men, 2002–2005. Sydney, Australia: National Centre in HIV Social Research, **2006**.
26. Prestage GP, Hudson J, Bradley J, et al. TOMS—three or more study. Sydney, Australia: National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, **2008**.
27. National Centre in HIV Social Research. Gay community periodic survey Melbourne. **2013**.
28. Challander D, Donovan B, Guy R. The Australian collaboration for coordinated enhanced sentinel surveillance of sexually transmissible infections and blood borne viruses: NSW STI Report 2007-2014. Sydney, Australia: University of New South Wales, Australia, **2015**.
29. Crawford JM, Kippax SC, Mao L, et al. Number of risk acts by relationship status and partner serostatus: findings from the HIM cohort of homosexually active men in Sydney, Australia. AIDS Behav **2006**; 10:325–31.

30. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2013. Sydney, Australia: The Kirby Institute, the University of New South Wales, **2013**.
31. Phang CW, Hocking J, Fairley CK, Bradshaw C, Hayes P, Chen MY. More than just anal sex: the potential for sexually transmitted infection transmission among men visiting sex-on-premises venues. Sex Transm Infect **2008**; 84:217–9.
32. STIs in Gay Men Action Group. Australian STI and HIV testing guidelines for asymptomatic MSM 2014. http://stipu.nsw.gov.au/stigma/sti-testing-guidelines-for-msm/.
33. Cornelisse VJ, Chow EP, Huffam S, et al. Increased detection of pharyngeal and rectal gonorrhea in men who have sex with men after transition from culture to nucleic acid amplification testing. Sex Transm Dis **2017**; 44:114–7.
34. Burrell S, Vodstrcil LA, Fairley CK, et al. Hepatitis A vaccine uptake among men who have sex with men from a time-limited vaccination programme in Melbourne in 2018. Sex Transm Infect **2020**; 96:110–4.
35. Read PJ, Limnios EA, McNulty A, Whiley D, Lahra MM. One confirmed and one suspected case of pharyngeal gonorrhoea treatment failure following 500 mg ceftriaxone in Sydney, Australia. Sex Health **2013**; 10:460–2.
36. Bernstein KT, Stephens SC, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the oropharynx to the urethra among men who have sex with men. Clin Infect Dis **2009**; 49:1793–7.
37. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med **2000**; 342:921–9.
38. Bleeker MC, Hogewoning CJ, Berkhof J, et al. Concordance of specific human papillomavirus types in sex partners is more prevalent than would be expected by chance and is associated with increased viral loads. Clin Infect Dis **2005**; 41:612–20.
39. Bissessor M, Tabrizi SN, Fairley CK, et al. Differing *Neisseria gonorrhoeae* bacterial loads in the pharynx and rectum in men who have sex with men: implications for gonococcal detection, transmission, and control. J Clin Microbiol **2011**; 49:4304–6.
40. Chow EP, Lee D, Tabrizi SN, et al. Detection of *Neisseria gonorrhoeae* in the pharynx and saliva: implications for gonorrhoea transmission. Sex Transm Infect **2016**; 92:347–9.
41. Maiden MC, Stuart JM, Group UKMC. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. Lancet **2002**; 359:1829–31.
42. McMillan M, Walters L, Sullivan T, et al. Impact of meningococcal B (4CMenB) vaccine on pharyngeal *Neisseria meningitidis* carriage density and persistence in adolescents. Clin Infect Dis **2021**; 73:e99–106.
43. Swan DA, Bracis C, Janes H, et al. COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact. Sci Rep **2021**; 11:15531.
44. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci USA **2014**; 111:787–92.
45. Werner JM, Abdalla A, Gara N, Ghany MG, Rehermann B. The hepatitis B vaccine protects re-exposed health care workers, but does not provide sterilizing immunity. Gastroenterology **2013**; 145:1026–34.
46. Garnett GP. The theoretical impact and cost-effectiveness of vaccines that protect against sexually transmitted infections and disease. Vaccine **2014**; 32:1536–42.
47. Trembizki E, Wand H, Donovan B, et al. The molecular epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in Australia: a nationwide cross-sectional study, 2012. Clin Infect Dis **2016**; 63:1591–8.
48. Spicknall IH, Mayer KH, Aral SO, Romero-Severson EO. Assessing uncertainty in an anatomical site-specific gonococcal infection transmission model of men who have sex with men. Sex Transm Dis **2018**.
49. Gafos M, Horne R, Nutland W, et al. The context of sexual risk behaviour among men who have sex with men seeking PrEP, and the impact of PrEP on sexual behaviour. AIDS Behav **2019**; 23:1708–20.
50. Jenness SM, Weiss KM, Prasad P, Zlotorzynska M, Sanchez T. Bacterial sexually transmitted infection screening rates by symptomatic status among men who have sex with men in the United States: a hierarchical Bayesian analysis. Sex Transm Dis **2019**; 46:25–30.