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Rationale and Ethical Assessment of an Oropharyngeal Gonorrhea Controlled Human Infection Model

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Infection with *Neisseria gonorrhoeae*, the causative agent of gonorrhea, causes significant morbidity worldwide and can have long-term impacts on reproductive health. The greatest global burden of gonorrhea occurs in low- and middle-income settings. Global public health significance is increasing due to rising antimicrobial resistance, which threatens future gonorrhea management. The oropharynx is an important asymptomatic reservoir for gonorrhea transmission and a high-risk site for development of antimicrobial resistance and treatment failure. Controlled human infection model (CHIM) studies using *N gonorrhoeae* may provide a means to accelerate the development of urgently needed therapeutics, vaccines, and other biomedical prevention strategies. A gonorrhea urethritis CHIM has been used since the 1980s with no reported serious adverse events. Here, we describe the rationale for an oropharyngeal gonorrhea CHIM, including analysis of potential ethical issues that should inform the development of this novel study design.

Keywords. controlled human infection model; ethics; gonorrhea; sexually transmitted infection; antimicrobial resistance.

Infection with *Neisseria gonorrhoeae*, the causative agent of gonorrhea, causes a wide spectrum of conditions, including asymptomatic infection at mucosal surfaces and symptomatic urogenital gonorrhea, as well as, in rare cases, disseminated gonococcal infection (DGI) manifesting as purulent arthritis, tenosynovitis-dermatitis-polyarthritis syndrome, or serious complications such as meningitis and endocarditis [1, 2]. Untreated urogenital tract infection can result in long-term sequelae, such as ectopic pregnancy, infertility, and adverse pregnancy outcomes in females [1, 3], as well as neonatal blindness [3], infertility in males [4], and increased risk of HIV acquisition [5]. Worldwide, an estimated 82.4 million people had gonorrhea in 2020 [6]. Antimicrobial resistance (AMR) in *N gonorrhoeae* is a key concern, identified as 1 of the top 5 AMR pathogens by the US Centers for Disease Control and Prevention [7]. In the setting of increasing AMR [8] and rates of infection worldwide [9], gonorrhea represents an increasingly urgent public health threat.

Innovative prevention and therapeutic strategies against *N gonorrhoeae* infection will be key to combatting the threat of untreatable gonorrhea and reversing the upward trend in disease burden. The WHO Global Health Sector Strategy on Sexually Transmitted Infections has set an ambitious aim of reducing global *N gonorrhoeae* incidence by 90% by 2030 [10]. Gonorrhea vaccines are a key priority, and there is increasing momentum in gonorrhea vaccine development, with observational studies suggesting that serogroup B *Neisseria meningitidis* outer membrane vesicle vaccines may be moderately protective against gonorrhea [11]. At this critical juncture of increasing gonorrhea incidence, emerging AMR, and the potential feasibility of effective gonococcal vaccines, clinical trial platforms to evaluate the efficacy of new interventions are urgently needed. In this respect, controlled human infection models (CHIMs) may contribute to accelerating the development of novel diagnostic, treatment, and prevention strategies.

CHIMs have been used to accelerate licensure of new vaccines and treatments for diseases such as typhoid, malaria, respiratory syncytial virus, and influenza [12]. CHIMs have also played an important role in characterizing disease pathogenesis and performance of diagnostic tests. For example, the first

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SARS-CoV-2 CHIM improved understanding of the incubation period of SARS-CoV-2 infection, identifying the median incubation period as 2 days, as compared with contemporary observational study estimates of 5 days [13]. In addition, the first SARS-CoV-2 CHIM demonstrated a strong correlation between positive lateral flow antigen tests and detection of culturable virus, supporting their utility as a surrogate of virus transmissibility [13]. CHIMs are particularly important platforms for the study of obligate human pathogens such as *N gonorrhoeae*. Although a 17β-estradiol–treated mouse model is available [14–18] and used in preclinical studies, mouse models can never fully represent the complex host-pathogen responses of human *N gonorrhoeae* infection. Although other models, such as a hollow fiber infection model [19, 20] and an invertebrate *Galleria mellonella* greater wax moth model [21], have been used for preclinical antimicrobial assessment, these are not appropriate for vaccine studies. Human organoids are an emerging technique for assessment of pathogenesis [22], immunity [23], and treatment [24] but have yet to be well established as a model for oropharyngeal gonorrhea treatment and prevention. In addition, as no robust immune correlate of protection has been established for gonorrhea, preclinical models have limited capacity to predict vaccine efficacy.

A male gonorrhea urethritis CHIM developed in the 1980s in the United States has been used for a range of purposes [25]. Over 200 participants have participated in pathogenesis and vaccine efficacy studies without any reported serious adverse events [25, 26]. Here we describe the rationale for a novel *N gonorrhoeae* CHIM using an alternative challenge strain and anatomic site of infection. In brief, this proposed model entails oropharyngeal inoculation of healthy male volunteers with *N gonorrhoeae* and outpatient monitoring through attendance at daily reviews for 5 to 7 days. Upon completion of the study or development of symptomatic pharyngitis, participants would be treated with curative antimicrobial therapy.

RATIONALE FOR AN OROPHARYNGEAL GONORRHEA CHIM

An oropharyngeal gonorrhea CHIM could significantly advance scientific understanding for several reasons. First, because oropharyngeal gonorrhea is largely asymptomatic, the pathogenesis, transmission, and host responses to infection of this site remain poorly understood. However, it is hypothesized that the oropharynx plays a major role in gonorrhea transmission [27]. An oropharyngeal gonorrhea CHIM could provide critical data that are otherwise difficult to obtain, such as the incubation period from exposure to infection and the nature of immune responses to infection at oropharyngeal mucosal and systemic sites. It would also provide an opportunity for studies of infectiousness and/or transmission that reflect these hypothesized modes of transmission. This information would be invaluable for understanding the individual-level impact and public health implications of oropharyngeal *N gonorrhoeae* infection.

Second, a detailed microbiological assessment of *N gonorrhoeae* evolution over the course of oropharyngeal infection will be possible with this model, including genomics, transcriptomics, and changes in the microbiome. Because oropharyngeal gonorrhea is largely asymptomatic, nonchallenge research among individuals diagnosed with oropharyngeal gonorrhea is unlikely to capture the natural history of early infection. Cohort studies of high-risk cases require intensive longitudinal sampling over a prolonged period to study the natural history of early infection and so face other feasibility and ethical constraints [28, 29]. Improving understanding of *N gonorrhoeae* infection of the oropharynx is important, as the oropharynx is a high-risk site for AMR, due to prolonged colonization [28] and the potential for horizontal transfer from commensal microorganisms of genetic elements conferring AMR [30]. Importantly, data regarding *N gonorrhoeae* infection dynamics at the oropharynx have mainly been derived from nucleic acid amplification tests that detect viable and nonviable DNA [31]. The detailed microbiological data facilitated by an oropharyngeal gonorrhea CHIM may be used to characterize the natural history of viable *N gonorrhoeae* infection at this site. This work may ultimately contribute to the development of next-generation diagnostic tests that encompass assessment of viability, thereby reducing overtreatment due to false-positive results from nucleic acid amplification tests [31]. Increased understanding of the natural history of *N gonorrhoeae* infection and genomic/transcriptomic evolution over time may facilitate risk assessment strategies that inform the optimal frequency of screening for oropharyngeal *N gonorrhoeae* infection.

Third, as the oropharynx is a high-risk site for AMR [30] and gonorrhea treatment failure [32], a CHIM may provide a platform for testing novel antimicrobials and inform optimal dose and duration of therapy needed to treat and/or clear carriage at this challenging site. The majority of reported ceftriaxone treatment failures have had oropharyngeal infection, with ceftriaxone minimum inhibitory concentrations ranging between 0.25 and 1 mg/L [33]. By contrast, there are multiple reports of successful treatment of ceftriaxone-resistant urogenital infections within this minimum inhibitory concentration range [34]. The pharmacokinetic effect of antimicrobials at the oropharynx is complex, with salivary antimicrobial levels significantly lower than serum levels and with reduced bioavailability of some antimicrobials [32]. The inferior performance of new antimicrobials in the oropharynx (eg, zoliflodacin [35]) indicates that assessment of novel antimicrobials for gonorrhea should include detailed pharmacometric evaluation at the oropharynx [32]. An oropharyngeal gonorrhea CHIM offers a platform to undertake such clinical studies. Furthermore, the oropharynx

represents an opportune site for development of novel biomedical preventative strategies. Although randomized controlled trials of antibacterial mouthwash did not demonstrate efficacy against *N gonorrhoeae* infection [36, 37], there is evidence that multiple compounds can inhibit *N gonorrhoeae* growth in vitro [38]. This suggests an ongoing opportunity to develop alternative biomedical prevention compounds against oropharyngeal *N gonorrhoeae* infection.

Fourth, an oropharyngeal CHIM can provide a powerful model to accelerate vaccine development for gonorrhea. Although the urethritis model is already being used for this purpose [26], there is currently a single site undertaking these studies, which is unlikely to be able to support the demand for such models for vaccine development. An oropharyngeal gonorrhea CHIM may further inform vaccine development, as it is estimated that the public health impact of gonorrhea vaccines will be significantly attenuated without efficacy at the oropharynx [39]. Indeed, data from the first randomized controlled trial of the 4CMenB meningococcal B vaccine for prevention of gonorrhea in men who have sex with men suggest that there may be differences in vaccine efficacy at different anatomic sites [40].

Several recent large clinical trials of treatment and prevention strategies for gonorrhea have been unsuccessful [36, 37, 41]. An oropharyngeal CHIM may help to redirect future investment into more promising preventative and therapeutic strategies. As gonorrhea vaccine development progresses, the availability of relevant CHIMs may accelerate vaccine evaluation and enable selection of the most promising candidates.

POTENTIAL ETHICAL ISSUES RELATED TO AN OROPHARYNGEAL GONORRHEA CHIM

Despite the potential benefits of CHIMs, robust ethical assessment is necessary to ensure that the risks of exposing a healthy participant to *N gonorrhoeae* are acceptable after appropriate mitigation measures. While the ethical considerations for CHIMs are similar to those for research in general, exposure of healthy volunteers to risks is one reason why fulfilling appropriate ethical criteria is particularly important. Such criteria include the need for scientific justification, risk-benefit assessment, consultation and engagement with the public, coordination between key stakeholders, and appropriate site and participant selection to minimize risk [42]. Independent ethical review and robust informed consent with a test of understanding represent important components [42]. Here we outline the features of an oropharyngeal gonorrhea CHIM that we consider the most challenging issues to address.

Scientific Justification

One key question to consider in assessing the scientific justification of an oropharyngeal gonorrhea CHIM is whether equivalent data could be obtained via alternative methods. Phase 3 field trials are typically the gold standard for assessing efficacy of novel treatment and prevention strategies. One large gonorrhea trial was conducted with the primary outcome being the prevention of oropharyngeal gonorrhea with antibacterial mouthwash [36]. Additionally, prospective longitudinal cohort studies have been performed to determine the incidence and duration of oropharyngeal gonorrhea [28, 29]. These studies have shown that field trials with oropharyngeal gonorrhea as the primary outcome are feasible. However, these studies require an extended duration of follow-up and sampling, may be difficult to control for factors influencing trial outcomes, and can face challenges related to recruitment and participant retention. For example, one-third of the 786 potential participants screened for the OMEGA antibacterial mouthwash study were ineligible, and approximately 15% of the enrolled participants were lost to follow-up [28]. The ExGen prospective longitudinal cohort study enrolled 140 men who have sex with men to perform self-collected oropharyngeal swabs weekly for 48 weeks. Yet, 28 participants (20%) did not complete any at-home testing, and only 56 (40%) completed at least 40 weeks of testing [28].

Although a small number of participants with oropharyngeal gonorrhea have been included in trials of investigational antimicrobials for treatment of gonorrhea, most studies have been designed to study efficacy against uncomplicated urogenital infection [35, 41, 43]. However, when we consider that the oropharynx is the predominant site for acquisition of AMR and treatment failure [32] and is likely a significant driver of transmission, there is a clear imperative for novel antimicrobials to have robust efficacy at the oropharynx. An oropharyngeal gonorrhea CHIM would enable preliminary efficacy assessment of novel antimicrobials at this site prior to larger licensing studies.

Risk Assessment and Mitigation

For the risk assessment of an oropharyngeal gonorrhea CHIM, it is essential to consider the risks to individuals and the community (Table 1).

Although rare, the development of DGI is the most severe immediate complication that requires mitigation for the safety of the CHIM participant. In recent studies that utilized public health notification data, DGI represented 0.06% to 1.3% of all gonorrhea cases [44, 45]. However, the proportion of gonorrhea infections that present with DGI as reported in these studies is likely an overestimate due to underascertainment of asymptomatic oropharyngeal gonorrhea [29]. A single-center study from the 1970s suggested that oropharyngeal gonorrhea may be associated with DGI, due to the observation that *N gonorrhoeae* was isolated in 10 of 60 individuals with DGI over a 2-year period [46]. Yet, no clear association between oropharyngeal infection and DGI has been demonstrated in contemporary studies comprising systematically collected mandatory

Table 1. Risk Assessment and Mitigation Procedures of an Oropharyngeal Gonorrhea Controlled Human Infection Model for Participants and the Community

Risk Assessment: Risk	Mitigation Procedures
Individual participant risks: short term	
Severe or disseminated disease (eg, DGI)	Clearance of oropharyngeal gonococcal infection with effective antimicrobials after several days of infection. Exclusion of potential participants with risk factors for DGI (eg, complement deficiency and eculizumab use; immunocompromise including HIV, diabetes, and drug/alcohol misuse). Utilization of a *Neisseria gonorrhoeae* challenge strain selected to minimize risk of DGI (eg, absence of PorB1A allele and serum resistance).
Treatment failure	Utilization of a *N gonorrhoeae* challenge strain that is susceptible to multiple classes of antimicrobials to ensure that there are multiple antimicrobial options available in case of treatment failure due to in vivo development of resistance. Exclusion of potential participants with a history of antimicrobial use in the past 6 months to reduce the risk of selection of antimicrobial-resistant commensals with a propensity for genetic exchange of AMR determinants to *N gonorrhoeae* challenge strain. Inclusion of multiple post-treatment clinical assessments, sampling methods (gonococcal culture and NAAT), and time points at all relevant anatomic sites to maximize ascertainment of persistent infection.
Individual participant risks: medium to long term	
Adverse reproductive health impacts	Exclusion of people assigned female at birth from undetermined risk of self-inoculation and ascending genital infection, which may result in unacceptable long-term damage to the female reproductive system. Exclusion of people who have sex with those assigned female at birth due to risk of gonorrhea transmission, ascending genital infection, and adverse reproductive health outcomes in sexual partners.
Psychosocial risks (eg, stigma)	Qualitative research exploring attitudes of key stakeholders (including potential CHIM participants) to an oropharyngeal gonorrhea CHIM study. Community consultation and stakeholder engagement in clinical trial design, including methods to mitigate psychosocial risks (eg, recruitment procedures, informed consent, clinical trial support).
Community-level risks	
Risks to third parties	Education of participants and restrictions on sexual contact, including open-mouth kissing, using saliva in sexual activity, and sharing of objects that may be put in the mouth such as cutlery and toothbrushes. Exclusion of potential participants with household or occupational contact with children aged <18 y. Appropriate infection control procedures within challenge unit that reduce the risk of bacteria transmission via direct contact (eg, hand hygiene, disinfection of surfaces, standard precautions in handling and processing of clinical samples).
General risks to individuals and community	
Improper clinical trial conduct	Independent regulatory review of the *N gonorrhoeae* challenge strain and cell bank manufacturing procedure and CHIM study protocol. Independent human research ethics committee review and oversight of the CHIM study. Careful informed consent procedure with test to confirm that participants understand the key concepts and behavioral restrictions of the model. Efforts to confirm the relevant medical history of participants (eg, independent laboratory testing with validated procedures, consent from participant's doctor to provide medical history or access to digital health record). Conduct of CHIM study in dedicated clinical trial challenge unit with strong governance and quality management system. Use of validated clinical laboratory assays for CHIM study safety and efficacy end points. Independent review board to oversee conduct of the CHIM study.

Abbreviations: AMR, antimicrobial resistance; CHIM, controlled human infection model; DGI, disseminated gonococcal infection; NAAT, nucleic acid amplification test.

gonorrhea notification data [44, 45]. Interpretation of associations between oropharyngeal gonorrhea and DGI may be confounded by factors such as heterogeneous sample collection from asymptomatic mucosal sites in individuals with DGI. Given that the median duration of *N gonorrhoeae* carriage at the oropharynx is 16 weeks [28], it is plausible that extended carriage may increase the risk of systemic infection. This risk can be mitigated in an oropharyngeal gonorrhea CHIM by terminating infection with effective antimicrobials after several days of infection, selecting a strain without specific features associated with DGI [47], and excluding participants with reported risk factors for DGI (eg, complement deficiency, immunocompromise, and drug and/or alcohol misuse) [44, 45]. Although the oropharyngeal gonorrhea model can be designed to mitigate risk, the risk of DGI cannot be eliminated. Importantly, DGI and other invasive forms of *N gonorrhoeae* infection remain treatable and are rarely associated with long-term morbidity or mortality if treated early [2, 44, 45]. Many CHIM studies have been undertaken with treatable pathogens that cause potentially severe systemic disease, including malaria and typhoid. The rates of serious adverse events associated with CHIM studies is low, with 0.2% among 10 016 participants in a recent systematic review [48]. This demonstrates that careful CHIM study design can mitigate disease risks associated with human challenge.

The risk of treatment failure is another consideration. The oropharynx is typically colonized with numerous organisms, including commensal *Neisseria* species. There is a risk that

the *N gonorrhoeae* challenge strain may acquire AMR due to horizontal genetic exchange. Although such transformation can occur rapidly in vitro [49], the prospective development of resistance in the oropharynx has not been studied. These risks could be mitigated by excluding participants at higher risk of carrying oral flora with AMR determinants (eg, those with antimicrobial exposure in the past 6 months). Additionally, using challenge strains susceptible to multiple antimicrobial classes would ensure that multiple treatment options are available in case resistance develops in vivo.

Furthermore, there is a risk of genetic exchange of virulence determinants from *N gonorrhoeae* to *N meningitidis* isolates at the oropharyngeal site, which may increase the risk for this potential pathogen to cause disease. Recombination events between *N gonorrhoeae* and *N meningitidis* have been observed with the US *N meningitidis* urethritis clonal complex 11.2 clade (N*m*UC), which has caused outbreaks of meningococcal urethritis in men since 2015 [50]. Virulence factors acquired from *N gonorrhoeae* have been identified through genomic analysis of these isolates, including the *aniA-norB* denitrification apparatus [51] and *isp* [52], both of which may promote N*m*UC growth and survival in the microaerobic urethral environment. The risk of exchange of *N gonorrhoeae* virulence determinants to potentially pathogenic commensal *N meningitidis* isolates in the oropharynx during oropharyngeal gonorrhea CHIM could be mitigated by excluding participants with nasopharyngeal meningococcal carriage in the week prior to challenge.

The risk of long-term sequelae of *N gonorrhoeae* infection largely occurs in women and neonates. These risks can be mitigated by excluding women from gonorrhea CHIM studies. Although *N gonorrhoeae* would not be inoculated in the urogenital tract in an oropharyngeal model, there is an undetermined risk of self-inoculation and ascending genital infection, which may result in unacceptable long-term damage to the female reproductive system.

Challenge models involving a sexually transmitted infection could plausibly involve psychosocial risks, including potential stigma. A key aspect of the development and ethical assessment of any proposed CHIM is community consultation and engagement. This is particularly important for a CHIM involving a sexually transmitted infection. Formal community consultation and qualitative research exploring the attitudes of key stakeholders, including potentially eligible CHIM participants, are arguably essential for the ethical acceptability of a gonorrhea CHIM.

Managing the risk of gonorrhea transmission to sexual partners and the broader public health implications of an oropharyngeal gonorrhea CHIM relies in part on behavioral management strategies. In the CHIM setting, where participants are aware of their infection status, transmission risk can be mitigated by infection prevention measures, education, and advice to participants regarding potential risk behaviors—specifically, restrictions on sexual contact (eg, open-mouth kissing), the use of saliva in sexual activity, and the sharing of sex toys and objects that may be put in the mouth (eg, cutlery and toothbrushes). Although *N gonorrhoeae* is usually transmitted by sexual contact or vertical transmission, there are several case reports of transmission via fomites, usually in children. Individuals with household or occupational contact with people aged <18 years will therefore be excluded from participation. Despite behavioral modification advice, there may be persistent risks of transmission of *N gonorrhoeae* to participants' sexual partners. To manage this risk, regular sexual partners of potential participants may be corecruited for screening and treatment of gonorrhea infection as part of the trial.

COMPENSATION

Volunteers in CHIMs typically receive compensation for the time required to participate in such studies. A potential baseline for such compensation is the local minimum wage hourly rate. If the oropharyngeal gonorrhea CHIM is considered safe and approved by an ethics committee as an outpatient study, time commitments would likely be approximately 50 hours over a 6-month period—similar to many other CHIM designs. Where time commitments are significant (eg, for inpatient studies requiring several days of isolation), large total payments are widely considered to be ethically acceptable [53]. Potential concerns associated with large payments include that they might sometimes constitute an undue inducement to participate and/or conceal relevant medical history (eg, which might increase study risks or distort study findings). Enrollment should therefore include (1) a careful informed consent process to ensure that participants understand the study and its associated risks and (2) efforts to confirm the relevant medical history of participants, which may include requesting consent for their doctor to provide this information or grant access to their digital health record.

CONCLUSIONS

Here we describe the rationale for an oropharyngeal gonorrhea CHIM and the key ethical considerations that should be addressed prior to implementation. Accelerating the pipeline of interventions to halt gonorrhea transmission and manage emerging AMR is a key priority for global public health agencies. An oropharyngeal gonorrhea CHIM may help to improve initial testing of new interventions and provide a platform to accelerate the next generation of vaccines and therapeutics. Clinical studies in at-risk populations for gonorrhea infection at various anatomic sites will still be required, as CHIM studies cannot replicate the complexity involved in natural human infection, including variabilities in *N gonorrhoeae* strains, transmission risk behaviors, and host immune factors. However,

as field trials are complex and resource intensive, an oropharyngeal gonorrhea CHIM may provide a platform to test preliminary hypotheses and enhance overall resource utilization by identifying the most promising candidates for future clinical trials.

Notes

Author contributions. E. W., E. J., J. S. M., and D. A. W. were responsible for conceptualization. E. W. was responsible for the original draft. E. J. and J. S. M. provided supervision of the project. All authors contributed to the critical review of the manuscript.

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