Sexually Transmitted Diseases Among Pastoralists in Kaokoland, Namibia: Epidemiology, Ecology, and Behavior

by

Mary-Ashley Hazel

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Natural Resources and Environment)
in the University of Michigan
2012

Doctoral Committee:

Professor Bobbi S. Low, Co-Chair
Professor Betsy Foxman, Co-Chair
Professor Carl P. Simon
Associate Professor Johannes Foufopoulos
Associate Professor Rebecca Hardin

DEDICATION

This dissertation is dedicated to my favorite Namibians.

Kemuu Jakurama

A peerless translator, from whom I learned that, "*In life, you never know.…"*

Rhyn Tjituka

My otjiHerero translator: Etu over epanga randje komunyo

Beatrice Sandelowsky

The most remarkable woman I know. May our fireside chats continue for many years to come.

ACKNOWLEDGEMENTS

I have enormous amounts of gratitude to so many people for their support at every stage of this dissertation. First and foremost, I am indebted to my advisors and dissertation committee members. Bobbi Low and Betsy Foxman both gave me the freedom to build my own research program while simultaneously offering careful, critical guidance; they let me be creative, but they also taught me how to buckle down and see a project through to the end. Carl Simon, the most patient mathematician I know, gladly came on to my committee as a cognate in the last year of my dissertation work and taught me—from the ground up—how to understand and build differential equation models of disease transmission. Mathematical work presented me with one of the steepest learning curves I have ever faced, as well as some of the most satisfying problem solving I've ever done. Johannes Foufopoulos and Rebecca Hardin provided valuable insights—particularly at the bookends of the dissertation process—from different disciplinary perspectives. These perspectives gave me fresh ideas on how to approach some aspects of data collection and also helped me to hone my arguments in my final dissertation manuscripts. In science, there are always things that one would do differently if given a second chance. However, I know that if there is one thing I got exactly right the first time, it was the selection of my committee. I am forever indebted to them for their professional and personal guidance over these past several years.

My advisors were not only exceptional mentors to me; they have mentored countless other students over many decades and, consequently, have fostered strong support

communities in their labs. My peers in “Bobbi-lab” and the MAC-EPID group—past and present—have been both teachers and friends. I cannot measure how much my life has been enriched by these relationships. There are too many to list, but I am thinking of each and every one as I write this.

The year I conducted my fieldwork was one of the most memorable, challenging, and joyous times in my life. I am grateful to all the Namibians who helped make this happen. The research would never have gotten off the ground if hadn’t been lucky enough to meet the indefatigable Dr. Beatrice Sandelowsky, who helped me navigate the Namibian bureaucracy and get my research permits. Rhyn Tjituka spent many hours teaching me the complexities of Herero grammar until I could speak enough to show study participants that I was willing to work hard to earn their trust. Kemuu Jakurama was my field guide and translator. Working side by side for eight months straight wasn’t always easy but he never stopped making me laugh, helping me solve unexpected problems, or being a tireless diplomat for our study. Without him, I am sure I would not have obtained either the quantity or quality of data that I did.

I wouldn’t have made it out to Namibia—lab supplies and all—if it weren’t for Joan DeBusscher and Dawn Reed, who saw that all my equipment arrived safely and legally in Windhoek in time for me to collect it.

I also had a phenomenal amount of data management and analytical help upon my return from fieldwork. Sree Ponnulari, Gregg Davis and Laxmi Modali picked up where Joan left off in the lab and made me proficient in designing and troubleshooting for qPCR. Duane Newton offered project-saving advice when I couldn’t account for some strange results early in my lab work. I would *never* have finished this dissertation if Dawn Reed didn’t come on board to help me code and enter all my survey data.

Once I had all the data in shape, I needed to make sense of it. Thank you to Brady West and Jason Goldstick for taking the time to explain logistic models to me and help me find the right statistical tests for my questions. Darlene Bhavnani, in the final throes of her own dissertation work, gave up several hours of her time to help me build a GIS map of my villages sites and HSV-2 prevalence. This is only one example of the enormous generosity from which I benefit through my friendship with Darlene. After Darlene left Ann Arbor, I had to make some updates to the map and Amy Burnicki offered her amazing skills.

My friendship with Dana Jackman is another example of how I have been enriched intellectually and personally by my grad school relationships. Dana is one of the best teachers I've ever met and she has been instrumental in helping me understand much of the underlying math necessary to build the model in Chapter 4.

Thank you to the Sweetland Writing Center for accepting me into the 2010 Dissertation Writing Institute. I learned some valuable tips on how to get through early writer's block and how to edit and be edited.

Of course, none of this work would be possible without the funding that supported my education and my research. I am deeply grateful to my fellowships—Interdisciplinary Program in Infectious Diseases (NIH training grant T32 A1049816) and LIFE: International Max Planck Research School on the Human Life Course (Rackham, Max Planck Institute for Human Development). Bobbi Low supported my living costs in the 2012 winter semester and Margaret Evans hired me many times as a GSRA. My dissertation research was funded by the Robert Wood Johnson Health and Society Program, the Wenner-Gren Dissertation Fieldwork Grant, the American Philosophical Society's Lewis & Clark Fund for Exploration and Fieldwork, Rackham Graduate School,

School of Natural Resources and Environment (SNRE) and the Center for Social Epidemiology and Public Health. I travelled and will travel again to Namibia through the generosity of SNRE, Rackham and the International Institute's travel grant programs, as well as the Engaged Anthropology Grant from the Wenner-Gren Foundation.

Finally, thank you to my family for supporting me despite my questionable taste in research topics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

The pastoralist communities in Kaokoland, Namibia, have long been presumed to have high prevalence of sexually transmitted diseases (STDs) and associated morbidities. Though their geographic remoteness makes access to healthcare difficult, rapid ecological and sociological changes may decrease their remoteness while simultaneously bringing dramatic shifts in disease risk. This dissertation research uses an interdisciplinary approach—combining fieldwork, laboratory methods and theoretical mathematical models—to estimate and characterize endemic herpes and gonorrhea in rural Kaokoland. To our knowledge this is the first set of cross-sectional studies to report on STD burden in a population as remote and undertreated as the Kaokoland pastoralists.

Both diseases were found to be highly prevalent and some unique patterns emerged. Positive herpes status was significantly associated with female gender, increasing age (by category, not year) for both men and women, and, with increased wealth among men. We speculate that sex-based differences in risk are exacerbated, in part, by local hygiene practices and a preference for “dry” sex. There was also considerable variation in prevalence by region, which may be due to geographic barriers that limit access to partners.

Meanwhile, 64% of participants were positive for gonorrhea. Sixteen percent of participants had high-level infections ($\geq$ ID50 dose) that were temporally and spatially clustered; 48% had low-level infections (< ID50 dose) that were distributed

homogeneously. The vast majority of infections were asymptomatic, which is problematic because all disease is managed syndromically.

We further explored the role of low-level GC infections in a compartmental mathematical model. This model suggests that asymptomatic infections—both high and low level—have a longer duration than previously thought and that low level infections might reveal an important role for strain-specific immunity in populations where gonorrhea is highly endemic.

CHAPTER 1: INTRODUCTION

Background

Sexually transmitted diseases (STDs) remain a major source of morbidity in undertreated, resource poor populations. In the absence of reliable and comprehensive healthcare, treatable STDs may persist at high endemic levels, can lead to dangerous secondary morbidities, stigma and reproductive dysfunction, and can increase infant mortality through vertical transmission. The reasons why some populations are undertreated—remoteness, lack of infrastructure, cultural or social constraints to accessing treatment—are the same reasons that make studying disease in remote, underserved areas difficult. These difficulties, however, do not diminish the value of conducting STD research in these populations. Such research will generate much-needed information of public health importance for vulnerable populations; it can also provide insights into the natural history of sexually transmitted pathogens and reveal how people's environments—physical and social—influence their risk for disease.

These reasons motivated me to investigate epidemiological, behavioral and ecological aspects of common sexually transmitted diseases in a remote, vulnerable population. I had the opportunity to conduct this work among the multi-tribal population of subsistence-based, semi-nomadic pastoralists in the remote regions of Kaokoland, northwestern Namibia. Remoteness and minimal local infrastructure contribute to poor access to medical care; all STDs are managed syndromically, which means that only symptomatic people who present themselves to the clinic can receive treatment.

Coupled with my theoretical training, I used the knowledge I gained about the people and environment of Kaokoland during a 2007 pilot study to design a study built around several environmental and behavior based predictions about STD burden.

The Kaokoland pastoralists

Frequent sexual partner exchange and partner concurrency among the Kaokoland pastoralists are important risk factors for STDs. Local cultural traditions allow for many overlapping styles of sexual relationships that include polygyny, non-married sexual relationships and extra-marital sexual relationships. A small percentage of very wealthy men have more than one wife, but both men and women regularly engage in extra- or non-marital sexual relationships. Non-marital relationships can last decades or a single night—and regardless of the relationship duration, condoms are seldom used, although they may be increasing in popularity among the younger adults.

Anthropologists and local healthcare workers have long presumed that gonorrhea was endemic in remote Kaokoland, but its prevalence has never been measured. Herpes is also likely to be common among the pastoralists, because it has lifelong infectiousness and, as with gonorrhea, infectious people are often asymptomatic. In the absence of regular healthcare and disease prevention measures, I expect ecological and behavioral contributors to disease to be important: e.g. spatial dynamics (population densities and movement), ecological/resource stress, and local sexual practices.

***Neisseria gonorrhoeae* (GC) and herpes simplex virus type II (HSV-2)**

Gonorrhea—a bacterium—and herpes—a virus—have very different biology and natural histories and cause markedly different symptoms, yet they both can cause very serious morbidities. Both diseases are highly infectious (i.e. GC has high per-contact

transmission probability, while HSV-2 has high per-partnership transmission probability) and instigate an incomplete immune response. However, gonorrhea infectiousness is self-limiting while herpes remains infectious throughout the host's lifetime. Further, symptom presentation between the two is very different. Gonorrhea symptoms, when present, are acute and diminish as infection duration increases. They involve foul discharge, dysuria and abdomen pain—symptoms that are not hard to identify with the infecting sex act. Herpes, on other hand, results in clusters of small lesions around the genitals, which, after seroconversion, may not appear for up to 30 days after the infecting sex act. Herpes lesions resolve after a couple of weeks but can reappear throughout the host's life

If left untreated (GC) or unmanaged (HSV-2), these diseases can cause different but very serious health problems. Untreated gonorrhea can cause pelvic inflammatory disease and, eventually, sterility. Vertical transmission of gonorrhea can occur during labor and cause ocular infections in newborns; if left untreated, these infections can cause blindness. HSV-2 symptoms are usually not serious in adults but vertical transmission can cause fatal meningitis.

Though gonorrhea and herpes are serious diseases in their own right, much concern about them among STD researchers is about how the presence of these diseases in HIV-prevalent regions might increase risk for HIV. This is a growing concern in Kaokoland. Though northwestern Namibia has the lowest HIV rates in the country (~7.9%), HIV is still a severe epidemic in adjacent regions of Namibia where prevalence is above the national average of ~15%. Economic development, resource speculation and tourism in Kaokoland are bringing new forms of travel, currency, and cultures into the area. Much of this inflow is by people from these high HIV, high population density regions.

I take an interdisciplinary approach to designing this study, which drew upon questions, methods, and analytic techniques from epidemiology, anthropology, and ecology. I developed skills in laboratory methods and complex systems analysis in addition to my theoretical training in epidemiology and behavioral ecology. I went to Namibia in 2009 to collect data to test the following predictions:

Prediction 1: Prevalence of gonorrhea should increase with distance from standing medical clinics because of decreased access to antibiotic treatment.

Prediction 2: Prevalence of herpes, which is incurable, should decrease with distance from standing medical clinics, because living closer to clinics corresponds to living closer to urban centers and greater opportunities for sexual partner exchange.

Prediction 3: Difference in resource access should predict sex behavior and, thereby, likelihood of having gonorrhea. (This prediction does not apply to herpes, which is a lifelong infection, and will persist in an individual regardless of changes in sexual behavior.) Young men who do not own livestock will have, I predict, the most geographically diverse sexual partners because they need to travel for economic opportunities. These men might appear as important spreaders among the population, and geographical distribution of gonorrheal genetic markers will reflect important travel routes of these most mobile members of the population. I expect resource-stressed women (especially mothers without livestock) to have higher gonorrhea burden than women with greater resource stability because they will be more likely to engage in sexual relationships in exchange for resources.

Reframing the dissertation

My results, in the end, did not fit within the framework of these predictions. Before my field season, my biggest fear was that I would not detect enough disease—either due to a failure of the sample processing protocol or difficulty recruiting participants—from which to draw meaningful conclusions. In fact, I found higher prevalence for both herpes and gonorrhea than I expected. Not only did this change my analytical approach, it also lead to a restructuring of the dissertation and a reframing of the key questions about STDs in Kaokoland. Most importantly, it revealed how problematic sexually transmitted diseases really are in rural Kaokoland.

This dissertation includes three chapters that were written as stand-alone manuscripts, each focusing on a different component. Chapter 2 provides the results of the HSV-2 prevalence study in a narrative format that allowed me to contextualize the epidemiologic findings with cultural and environmental qualitative data. Chapter 3 outlines the major findings about gonorrhea prevalence in a straightforward epidemiologic context. Chapter 4 introduces a theoretical mathematical model of GC transmission in Kaokoland, which allows me to explore characteristics of gonorrhea transmission in Kaokoland beyond the limitations of my dataset.

As discussed in Chapter 2, *"Herpes Simplex Virus Type 2 Among Remote Pastoralists in Northwestern Namibia*," I did not find the predicted relationship between herpes and proximity to urban centers. Despite trying several analytical techniques, detailed in the methods section of that chapter, I was unable to show any significant relationship between urban proximity and herpes risk, though the results suggest that inaccessibility to treatment—which can be the result of remoteness or geographic barriers—may increase one's likelihood of acquiring an HSV-2 infection.

The most striking results from Chapter 2 come from the demographic distribution of HSV-2 infections. Older adults and women have much higher prevalence of HSV-2 than younger adults and men. This result is consistent with the results of other studies of HSV-2 infection patterns across high-risk populations, but in Kaokoland, women appear to bear a significantly higher risk than men than has been shown in other studies. I draw on my qualitative data to contextualize this in terms of local hygiene and sexual practices that simultaneously increases female risk and decreases male risk.

Finally, my original predictions assumed a relationship between men's wealth and likelihood of having gonorrhea, but it was with herpes—not gonorrhea—where I found a significant pattern. Wealthy men were far more likely than non-wealthy men to have acquired herpes. This demonstrates the long lasting impact of wealth on a Kaokoland man's ability to obtain and maintain sexual partnerships.

I did not find an effect of distance or wealth/resource stability on likelihood of having gonorrhea. As I outline in Chapter 3, "*High Prevalence of Neisseria gonorrhea in a Remote, Undertreated Population of Namibian Pastoralists*," there are unusual findings about gonorrhea in Kaokoland that reveal interesting patterns of this disease in an untreated population. Once I completed my diagnostic assays and saw the overwhelming number of positive gonorrhea cases in my study, I realized these results could not be explained in terms of the original predictions because there were so many more cases than I expected or have seen in the literature among other high-risk populations. Cases were evenly distributed across regions and wealth status, negating my predictions about associations with urban proximity and resource behavior. This chapter, therefore, became less about the human ecological correlates of gonorrhea infection and more about the surprising and previously unreported characteristics of gonorrhea in an undertreated population.

Because I used an in-house developed qPCR assay for my diagnostic, I was able to quantitate the amount of GC DNA in each sample. I found that most of the positive GC cases had very low quantities of GC DNA. This led to the conclusion that most of these low quantity infections were actually lingering infections that were previously of a higher titer but had not yet resolved.

This chapter further discusses the social factors that influence how likely people are to recognize GC symptoms and seek treatment for them. Treatment seeking behavior is very low in Kaokoland, which fits in with our finding of so many slowly diminishing, untreated infections. These findings speak to the inappropriateness of syndromic management for remote populations.

Chapter 4, "*Neisseria gonorrhoeae In a Rarely Treated, High-Activity Population: Using Empirical Data to Inform a Transmission Model*," was the natural outgrowth of chapter 3. The observation of such a high number of low-level infections generated many questions that I cannot answer with this dataset. How long does it take for a high quantity infection to diminish past the ID_{50} threshold (my delineation between high and low quantity infections)? What is the mean duration of these low quantity infections? Are these long-lasting, untreated infections helping to drive the high endemic levels of GC in the population (i.e. what are the mean transmission probabilities of the low quantity infections?) These questions can be answered, however, through analysis of an equation-based model of gonorrhea transmission.

In Chapter 4, I introduce a new mathematical model of *Neisseria gonorrhoeae* transmission under conditions with low condom use, high rates of partner concurrency, and little medical intervention. These conditions offer a close proxy of gonorrhea under natural conditions. This model draws strength from its inclusion of many empirically

derived parameter values. The model demonstrates that low quantity infections do play an important role in maintaining high endemic levels of gonorrhea. It also demonstrates that with the inclusion of the low quantity state of infection, asymptomatic cases persist several months longer than previously thought. Also, male-to-female transmission, for both high and low quantity infections, might have been underestimated in the past.

Finally, I conclude with a short summary of the significance of these findings, the lessons learned in conducting disease research that combines fieldwork in a remote setting with molecular diagnostics and computational analytics, and important future directions for work in Kaokoland.

CHAPTER 2: HERPES SIMPLEX VIRUS TYPE 2 AMONG REMOTE PASTORALISTS IN NORTHWESTERN NAMIBIA

Abstract

Though HSV-2 epidemiology has been described for many western and/or urban populations, disease burden has not been characterized for remote, non-western, undertreated populations. Using field-based interdisciplinary methods, we estimated HSV-2 prevalence and explored demographic, social and geographic correlates of infection among pastoralists in Kaokoland, Namibia. HSV-2 status was significantly associated with female gender (O.R. = 3.1, 95% C.I. = 2.00, 4.71), increasing age (by category, not year) for both men (O.R. = 7.5, 95% C.I. = 2.67, 20.85) and women (O.R. = 6.2, 95% C.I. = 2.48, 15.50), and, with increased wealth among men (O.R. = 5.1, 95% C.I. = 1.98, 13.09). There was considerable variation in prevalence by region. Higher risk among women can be explained, in part, by local hygiene practices and a preference for “dry” sex. Ethnographically contextualized epidemiologic studies of remote, vulnerable populations can provide essential information for limiting the introduction and spread of new infections.

Introduction

Little is known about risk factors for acquisition and transmission of sexually transmitted diseases (STD) in remote, vulnerable populations, but there are important reasons why they should not be neglected. First, we can make new observations about the epidemiologic characteristics of a pathogen by studying it in a different environment. Second, rapid changes in culture, mobility and the nature of resource use (Homewood,

2008), particularly in the form of sedentarization (Anderson & Broch-Due, 1999), among subsistence-living pastoralists can lead to new sources of vulnerability. Here we explore demographic, social and geographic risk factors for HSV-2 in a multi-tribal pastoralist community in Kaokoland, northwestern Namibia. The tribal societies of Kaokoland are facing social and environmental transitions (Friedman, 2000; Talavera, 2002) including sedentarization, which is already known to negatively impact health among east African pastoralists (Fratkin & Roth, 2004; Fratkin, Roth, & Nathan, 2004, 1999). These transitions could lead to new epidemiologic burdens, including novel sexually transmitted diseases such as HIV/AIDS, which is highly prevalent in neighboring regions of Namibia.

Study motivation

HSV-2 is one of the most common sexually transmitted diseases (STDs) worldwide and is the leading cause of genital ulcers (Corey & Wald, 2008; Schiffer & Corey, 2009). It is incurable and has lifelong infectivity. Symptoms are often mild; it is estimated that 90% of HSV-2 positive people are unaware of their status (Flemming et al., 1997; Hook & Leone, 2006). However, vertical transmission of HSV-2 during labor can cause severe disseminated and encephalitic infection in neonates (Corey & Wald, 2008). Neonatal morbidities and mortality as a result of HSV-2 infection is of greatest concern among developing nation populations where access to healthcare is unreliable.

The epidemiology of Herpes Simplex Virus 2 (HSV-2) is well characterized for western and industrialized societies (Looker, Garnett, & Schmid, 2008; Wald, 2004). This is not the case for non-western, subsistence-based societies. The often starkly different social norms, sexual partnerships and geographic mobility may result in different population patterns, which can bring new insights into the disease. HSV-2 is of global health concern, particularly in sub-Saharan Africa (Looker, et al., 2008), as positive HSV-2

status is associated with increased risk for HIV infection (Abu-Raddad et al., 2008). There are similarities between HSV-2 and HIV biology—e.g. lifelong infectiousness, viral shedding in the absence of symptoms—that may make HSV-2 particularly valuable for predicting the patterns of a future HIV epidemic (Abu-Raddad et al., 2008, 2010).

The epidemiological overlap between HSV-2 and HIV is relevant in Kaokoland. Although it has one of the lowest HIV rates in Namibia (e.g. HIV prevalence in Opuwo, the district capital, is nearly 8%), adjacent districts have HIV prevalence >15% (de la Torre et al., 2007; MoHSS Namibia, 2008). Geographic and cultural barriers have protected against HIV introduction in the past but, like many African pastoral communities, these boundaries are eroding and HIV remains a serious threat.

Social dynamics in Kaokoland

Kaokoland, a remote and sparsely populated landscape, is home to a dynamic and diverse tribal community. Resident tribal groups of Kaokoland include—but are not limited to—the Herero, Himba, Tjimba and Twa. The Herero and Himba are closely related and are culturally and economically dominant in Kaokoland. Herero settlements are concentrated in the southern areas of Kaokoland and are better connected to urban areas, diverse economic opportunities and government services (e.g. schools, clinics, etc) than those of the Himba who live in the northwestern areas of Kaokoland.

Our study focuses on the people living in the most rural and inaccessible areas of Kaokoland; places from which it is hardest to travel for healthcare and other services. These parts of Kaokoland are settled by the Himba and other tribes, including the Tjimba and Twa. It is this group of remotely living, subsistence-level pastoralists we refer to when we use the term “Kaokoland pastoralists.”

The Tjimba are generally thought to be a branch of the Himba tribe, living, until recently, in high altitude enclaves within Himba territory (Frank, 2000; Malan, 1974; Vedder, 1938). Himba and Tjimba people recognize their close kinship, as is demonstrated by the frequency of inter-marriages and sexual partnerships. Though many informants do not recognize a distinction between being Himba or Tjimba ("*We are the same, from the roots.*"), some Himbas we spoke to look down on the Tjimba as being lower status or backwards. Other tribal groups in Kaokoland, such as the Twa, do not share close ancestral ties with the Himba (Vashro, submitted) and are considered neither suitable marriage partners nor sex partners. Marriages between Tjimba and Twa people are not uncommon, however, which links Himbas, at least indirectly, to Twa people in the same sexual networks (Hazel, unpublished). It is less clear how much the Himba-Tjimba-Twa sex network connects with members of other local tribal groups (e.g. Hakaona, Zemba, Kuvale) and outsiders.

Marriage in Kaokoland, as in many pastoral societies, requires payment of a bride price (Borgerhoff Mulder, 1995; Goody & Tambiah, 1973; Homewood, 2008; Low, 2000). Therefore a man, or his family, must have some wealth to marry; very wealthy men can have multiple wives. Non-marital relationships may also involve some transfer of resources, informally and temporarily, from the male to female partner. Therefore, wealthy men often have greater prospects for obtaining wives and girlfriends than their less-wealthy counterparts.

There are many forms of accepted sexual partnerships among the Kaokoland pastoralists, particularly among the Himba. Despite strict control by family authority figures over marriage, both men and women have a fair amount of autonomy to select extra-marital partners (Scelza, 2011). Extra-marital relationships vary greatly. Some are very short-lived and virtually anonymous, while others last decades. Given the high

mobility of the pastoral lifestyle, contact patterns in any sexual partnership are inconsistent over the course of the relationship (Hazel, unpublished).

The cultural acceptance of multiple and concurrent sexual partnerships among the Himba, coinciding with a general distrust and dislike for condoms, has led to the assumption by local healthcare workers and activists that STD burden is high (Talavera, 2002). High rates of secondary sterility among the Herero led to similar suggestions by researchers (Pennington & Harpending, 1993). In neither case has disease burden actually been measured.

Geography and subsistence living in Kaokoland:

Life in Kaokoland is lived at the subsistence level. Cattle are the main currency and herd size reflects both wealth and status. In addition to herding cattle, people in Kaokoland herd goats, tend gardens (maize is the staple crop), and forage for wild fruits and tubers. Not everyone has access to each of these food production practices. Few families have sustainable herds of cattle or goats. Gardens are more evenly distributed among the population, but garden quality is highly variable. Those families who have neither livestock nor a productive garden rely mostly on foraged foods or handouts from neighbors.

All subsistence practices in Kaokoland require some mobility. People travel extensively, often in a patterned fashion, away from their home villages to graze cattle, to tend maize gardens (gardens may not be one's home village), to forage, or visit family and attend ceremonies (weddings, funerals, ancestor worship ceremonies). Traditional travel seldom leads Kaokoland residents beyond the Kaokoland boundaries, but mobility patterns are changing. People are not only migrating through traditional routes that connect home villages to cattle posts and other family sites; they are traveling to growing

urban areas and new regions where there are fewer family connections. Traders, tourists, non-governmental organizations and government workers have an increased presence in Kaokoland, and they offer a faster mode of transportation to new and different sites within and beyond Kaokoland. These changes may alter the pool of potential sexual partners and possibly lead to new sex networks.

Logistic challenges of epidemiologic studies among pastoralists

There are many logistic challenges to conducting epidemiologic studies in remote areas, perhaps explaining why these studies are rare. First, epidemiological research among a remote society involves collecting, storing and transporting biological samples under limiting conditions. Second, if the study population is nomadic, the data collection team must also be. Third, participants from remote, non-western societies are likely to be unfamiliar with and sensitive to disease testing or discussing matters of reproductive health and behavior. All of these may enhance the difficulty of getting a sufficiently large sample for accurately estimating prevalence. Finally, cultural context is essential for properly interpreting results. Therefore, locally informed, descriptive data about cultural norms and practices are required but can be prohibitively time consuming to collect.

To address these challenges, we conducted a quantitative epidemiologic study informed by qualitative anthropologic techniques. Though our sample size limits our analytic potential in some directions, we explore HSV-2 epidemiology in Kaokoland at an unusually close level. Our interdisciplinary approach offers unique insights into demographic, social and geographic aspects of disease risk, and has, we hope, valuable implications for future intervention efforts.

Methods

Field location and data collection sites

Data were collected from April to November, 2009, across 28 villages in Kaokoland, the northwestern section of the Kunene district. The sample villages were chosen based on results of a previous census (Hazel, unpublished) to represent the range of geographic (degree of remoteness), ecologic (type of subsistence that is supported) and economic (cumulative villages wealth, measured in herd size) variability among Himba and Tjimba villages in Kaokoland. Villages ranged in size from 5 to 1020 adults with the population size varying by season. Pastoralists are mobile and move across Kaokoland. Subsistence practices usually lead to more travel during the dry than the rainy and winter seasons. Therefore, we conducted a brief census upon arrival in a village to determine if there were sufficient individuals present to warrant data collection. If less than two adults were present and willing to participate, we moved to the next selected village, returning at a later point if possible.

It was very difficult to accurately estimate the response rate for this study. In the larger villages (n~1000), we directly invited only a small proportion to participate, but the word spread rapidly (as villagers were illiterate, posters and fliers were not used). This makes it difficult to determine the number invited to participate relative to those who did participate. By contrast, in small villages, the study team was able to visit all the homesteads and directly invite all adults so the response is known. The proportion of the village populations (based on our census) that participated ranges from 0.02 (largest villages) to 0.70 (mean = 0.33, median = 0.30).

Before establishing a village as a data collection site, the research team obtained permission from the local chief. Ethical approval was granted by the University of

Michigan Internal Review Board (HUM00025104) and by the Namibian Ministry of Health and Social Services.

Participant recruitment

Any culturally recognized adult (e.g. women ≥16, men ≥18), who in 2009 spent at least half a year in Kaokoland, was eligible to participate. Once the local chief granted permission, we met with groups of villagers to discuss the nature and purpose of the study. We recruited participants in two ways: 1) People came directly to us, expressing interest in being enrolled or 2) we visited people at their houses and encouraged them to enroll. No participants requested to be disenrolled from the study. Pastoralists are mobile, so we often recruited individuals from villages that they did not consider their home.

In total, 445 participants were enrolled. Several participants were removed from the analysis either because a) they reported living in a village for which we could not get accurate GPS coordinates (n=6); b) their home village is not in Kaokoland (n=2); c) they do not have a home village because they live in a city (n=10); d) or their HSV status was inconclusive (n=25). Our final sample included 402 participants.

HSV-2 status data

We determined HSV-2 status using the Biokit HSV-2 Rapid Test®, which uses whole blood from a finger prick to detect the presence of the HSV-2- specific IgG antibody. Each test result was compared to a photographic guide to positive spot identification provided by the Biokit Company to determine if it was positive, negative, or inconclusive. A digital photograph was taken and the test was discarded. Several months after the data collection period, the digital images were compared to the photographic guide and HSV-2 status was re-recorded for all participants. Participants with discordant records

(i.e. did not have two positive, two negative or two inconclusive records) were read a third time by an independent coder. If two out of three records were the same (e.g. first code = inconclusive, second code = positive, third code = positive), the majority record was chosen for the final status (e.g. final status = positive). Any participant whose test had three different records was marked as inconclusive.

Interview data

After completing the HSV-2 test, each participant answered questions from a structured interview on relevant demographic, social/behavioral and geographic data. The entire interaction took between 30-60 minutes. All interviews (including sample collection) were conducted in an isolated setting where no one could hear or see the interaction. Data collected included:

Demographic variables:

1) *Age range (People in Kaokoland do not know their exact age.)*
2) *Sex/gender*
3) *Tribal affiliation*

Social/behavioral variables:

1) *Wealth (i.e. livestock herd size. Participants were categorized into three categories based on their response: poor, intermediate wealth, wealthy.)*
2) *Marriage status (For men we also asked how many wives they have.)*
3) *Number of sex partners over the past six months (We asked several detailed questions about sex partnerships to triangulate and confirm total numbers.)*

Geographic/spatial variables:

1) *Home village*

2) *Frequency of travel to nearby cities*

3) *Reasons for travel*

Residence measures

Despite their mobility, all Kaokoland residents identify a particular village as home. For every participant, we obtained collected the name of their home village and the GPS coordinates for that village. Villages in Kaokoland are organized into regions. These regions are locally determined, based on traditional boundaries, and are not recognized by the state. All home villages in our dataset are located in one of five large regions: Omaanda, Ehama, Omunjandu, the Marianflus and Ozosemo. Twenty participants claimed a home village that was not in one of these regions. These participants were aggregated into a single region termed "Other."

Aggregating residence data

The mobility and low density of life in Kaokoland make it difficult to enroll large numbers of individuals from a single data collection site. In large villages, and in seasons when people congregate for ceremonies, participant recruitment is relatively easy. In small villages or during seasons when people disperse to tend to livestock, gardens, or forage, recruiting is more difficult. To minimize variability in village sample size, we collected data along "clusters" of neighboring villages that are ecologically and economically similar; data from these villages are easily aggregated. Village aggregation also allows us to increase village sample size while decreasing the number of village categories, both of which increases statistical power. We collected data in 28 villages, but 107 villages were named as a home village. After aggregating 107 home villages into 23 clustered "villages," there is still variability in sample size (range: 5 – 51, mean: 18.2, median: 18.5). Participants from six outlying villages that we could not cluster were removed from the analyses (n=6).

Measuring village-to-city distance

We defined a city or urban center as a place where there is state infrastructure—specifically clinics and schools—as well as shops and bars that require payment in Namibian dollars (a relatively novel currency for the Kaokoland pastoralists). We collected GPS coordinates for each Kaokoland urban center—Opuwo, Okanguati, Epupa and Etanga.

All participants were asked how often they travel to each of the four cities. We counted the frequency of each of these replies to determine which city is the most visited by members of each home village. We then calculated the shortest linear distance between a home village and its most traveled to city. When two cities were visited with equal frequency, we chose the closer city.

Qualitative data

We conducted open-ended interviews with focus groups, using factorial design structure (Bernard, 2006). Focus group interviews mainly explored cultural rules about sexual partnerships and sexual behavior, and attitudes about STDs. Open-ended group interviews gave us the opportunity to learn about culturally normative behaviors for highly sensitive topics that might be too uncomfortable for individuals to discuss personally (e.g. *Do people have oral sex? How are sexual encounters initiated?*).

We also conducted open-ended individual interviews, targeting chiefs, midwives and other influential people. In these interviews we sought detailed information about economic (e.g. how to measure herd wealth), ecologic (e.g. resource management), and traditional healing practices (e.g. how herpes is identified, explained and treated).

In general, we found that people in the Kaokoland community are comfortable talking about sexual behavior and sexual health, probably because of the relatively open cultural attitudes about sexual relationships and partner exchange.

Quantitative analyses

We conducted bivariate analyses to explore associations between our main effect variables and HSV-2 status. We then constructed a random-effects model to account for the very small sample sizes for home villages that were not data collection sites. Initial results showed that 24% of the variance is accounted for by differences between home villages. We subsequently added region to the model to see whether individuals from villages in the same region have similar risk compared to those from villages in different regions. When region was added as a main effect, variance in home village disappeared. We thus use region rather than home village to explore spatial and geographic influences on HSV-2 risk. Finally, we fit a multivariate logistic regression model of HSV-2 risk in Kaokoland. All analyses were conducted using R 2.11.1.

Results

The prevalence of HSV-2 in our sample of Kaokoland pastoralists was 35%. However, we found a strong association between increased HSV-2 risk and being female, increasing age, wealth, and geography. Because women are at much higher risk than men for HSV-2 (O.R. = 3.1, 95% C.I. = 2.00, 4.71), we stratified all crude associations by sex/gender.

Prevalence of HSV-2 was higher among women than men in every age category (figure 1), and increased with age (table 2.1). Among men and women there were no statistically significant associations with tribe. HSV-2 prevalence increased with wealth, and marital status among men. The trends were similar among women but not

statistically significant. There was no association with number of sex partners within the past six months among men or women.

Although there were no statistically significant differences by tribe, we did observe associations with region. Three regions—the Marianflus, Ozosemo, Omunjandu—had significantly higher HSV-2 prevalence than Omaanda. Ehama and "Others" did not have meaningfully higher HSV2 prevalence than Omaanda. The association with region remained after adjusting for age and gender.

Because city proximity might increase access to sexual partners, we considered whether regions whose villages were closer to frequently visited cities had higher prevalence of HSV-2. Using a logistic model (where we controlled for age, sex and wealth and region), we explored the relationship between village-to-city distance and HSV-2 prevalence, but found no association. As this null result could be due to a non-linear relationship between HSV-2 and urban proximity, we made a quadratic variable for village-to-city distance. We still found no association between HSV-2 risk and distance. Finally, we considered whether the relationship between village-to-city distance and HSV-2 prevalence was being obscured by regional differences. We tested for an interaction between region and distance using both the linear and quadratic form. In both cases, urban proximity was not a significant predictor of HSV prevalence.

A logistic model of HSV-2 prevalence in Kaokoland

Based on our bivariate associations and X^2 results, we fit a multivariate logistic model of HSV-2 prevalence, using age range, sex/gender, wealth status and region to predict presence of HSV-2 antibodies (table 2.2). The results were essentially the same as our crude associations stratified by gender.

Discussion

We estimated the prevalence of HSV-2 and its associated risk factors among a remote, pastoral group. To the best of our knowledge, this is the first estimate of any STD prevalence in Kaokoland and among any similarly remote pastoral groups in the literature. Our study illustrates how interdisciplinary approaches can yield novel, generalizable insight into the epidemiology of STDs among vulnerable populations.

Consistent with the literature, women in Kaokoland had higher rates of HSV-2 infection than men, though this difference decreases with each age category (figure 1). Most studies find a similar pattern (Looker, et al., 2008; Mertz, 1993; Wald, 2004; Watson-Jones et al., 2007), particularly in sub-Saharan Africa (Kirakoya-Samadoulougou et al., 2011; Smith & Robinson, 2002). Underlying biological differences account for some of the greater male-to-female transmission probability for HSV-2 and many other STDs (Mertz et al., 1992; Padian et al., 1987; Pertel & Spear, 2008), but higher prevalence among women can be exacerbated by local behaviors or practices that simultaneously decrease transmission probability for men while increasing it for women. In our logistic model (table 2.2), women's odds of HSV-2 infections are five times higher than men's. These odds are much greater than typically reported for nationwide and minority US populations (Bauer, Khobzi, & Coleman, 2010; Beydoun et al., 2010; Molina et al., 2011; Xu et al., 2006). Our qualitative data provide some additional insights.

Women are probably exposed to HSV-2 at younger ages than men because they are more likely to have high-risk partners: older, wealthy men. Age discrepant partnerships lead to earlier, faster acquisition of infection in women, especially in regard to HIV (Gregson et al., 2002; Leclerc-Madlala, 2008). In Kaokoland, such couplings occur through family-arranged marriage, as well as through female choice. During our open-

ended interviews, many women reported that wealthy men make desirable sex partners because they provide access—even temporarily—to basic (maize, sour milk) and luxury (beauty products, jewelry) resources.

Male and female hygiene practices could also exacerbate sex differences in HSV-2 prevalence. Himba and Tjimba males, like most other men in Kaokoland, were circumcised early in life. Reports on the impact of male circumcision for decreasing risk for HSV-2 are conflicting but many show a significant effect (Reynolds et al., 2004; Tobian et al., 2009; Weiss et al., 2006).

While circumcision could decrease HSV-2 risk for men, female beauty and hygiene practices might increase risk. Maintaining the Himba, Tjimba and Twa beauty aesthetic involves regular applications of a locally produced make-up comprised of ochre powder and milk fat. Every day, every inch of a woman's body is covered in a deep red foundation. This unique beauty regimen is not conducive to washing with water. Therefore, women clean their bodies daily—including their vaginas—not with water, but with a fragrant smoke made from burning local herbs. Female informants consistently report two aims of vaginal smoking. First, the smoke acts as a perfume, giving women a "*nice smell*." Second, smoking dries out the vaginal tissues. In our qualitative interviews, both men and women state a preference for dry ("*tough*") sex with minimal female fluids. Furthermore, women report the evening as the ideal time to smoke their bodies in anticipation of a visit from a husband or boyfriend.

Dry sex can lead to increased vaginal tearing, and thus may increase transmission probability. While several studies have shown an association with dry sex and increased risk for HSV-2 (Mehta et al., 2008; Watson-Jones et al., 2007) and HIV (Auvert et al., 2001), these findings, like those regarding the protective effects of male circumcision,

are not consistent (Sandala et al., 1995). Inconclusive results could be due to varying effects of different methods for vaginal drying on HSV-2 transmission.

HSV-2 risk is generally associated with lower socio-economic status, within and beyond Africa (Hargreaves et al., 2002; Stavraky et al., 1983; Wald, 2004) and possibly reflects limited access to preventative care, and poor knowledge of sexual health and disease. Kaokoland is a natural-fertility population where condoms are seldom used. People's degree of risk arises principally from the frequency of contacts and the relative riskiness of their potential partner networks. Wealthy men (those with a lot of livestock) have greater negotiating powers to obtain and maintain sexual partnerships, so it is not surprising that HSV-2 prevalence is high in the wealthiest category. The impact of wealth on HSV-2 prevalence was somewhat stronger in poorer areas, but the number of wealthy people in poorer regions was too small to draw robust conclusions.

Geographic patterns in HSV-2 risk

Although we found no significant association between simple distance and HSV2 prevalence, remoteness may still play an important role in shaping partner exchange patterns and, thus, risk for HSV-2. The three regions with the highest prevalences are all functionally remote, which may be limiting residents' access to sexual partners. The Marianflus, the remotest region in Kaokoland, has no nearby urban centers. Ozosemo and Omunjandu are nearer to urban areas and other regions but difficult terrain makes travel within and beyond those regions difficult. Omunjandu, for example, is adjacent to Ehama (a lower prevalence region), but a precipitous and rocky pass separates the regions. People from these regions are more likely to choose partners who are nearby and equally limited in their partner pool, resulting in a small pool of sexual partners with high turnover. Once the virus is established in this kind of network, it can spread very quickly. Most of the villages in the three high-prevalence regions are difficult to access.

Although we did not find any association between urban proximity and increased HSV-2 prevalence, our interview data indicate that a common reason participants go to cities is to drink alcohol and seek opportunities for casual sex. This seeming contradiction might be due to the demographic structure of urban sexual networks. Participants from the younger age categories are far more likely to report going to cities for sex and alcohol; 55% of under-25 year olds report these reasons, compared to 27% of people 26-35 years old. However, younger participants were also more likely to endorse consistent condom use, especially with anonymous or casual partners. Of all the participants who claim to use condoms consistently (10%), 56% were in the youngest age category. Though most people (52%) had a hostile or disinterested attitude toward condoms (*"Condoms cause disease." "It is not the [traditional] way."*), younger people were also least likely to endorse this attitude because they "*were afraid of disease,"* or have, *"heard of HIV."*

Study limitations

Working both remotely and cross-culturally presents many challenges and limitations to effective study design. A rapid test was the only feasible assay in this field setting, given the storage and transport limitations of remote work. Unfortunately, the Biokit HSV-2 rapid test as a stand-alone assay was shown after the completion of our data collection to have sensitivity and specificity lower than western blot among some east African populations (Lingappa et al., 2010; Ng'ayo et al., 2010). Thus, we probably underestimated HSV-2 prevalence. This underestimation would have been applied to the sample evenly and likely did not affect the pattern of disease distribution that we observed.

Lack of formal record keeping is also a problem. Kaokoland pastoralists do not know their exact age, but it can be estimated within a few years by using fertility history

(women) and cultural life-stage landmarks (men). This also affects measures of wealth (i.e. number of livestock). People fairly accurately estimate small herd sizes but tend to over or under estimate larger ones. Finally, given the high rate of partner exchange and the lack of stigma associated with partner concurrency, estimates of lifetime number of partners proved an unreliable variable. This is not to suggest that partnerships in Kaokoland are forgettable or not meaningful. When asked about current and recent partnerships, participants regularly answer questions about even fleeting partnerships in great detail, but they do not count lifetime numbers of partnerships in the same way as western cultures and, thus, have difficulty producing a reliable estimate.

Conclusions

Similar to other studies, female gender and increased age are associated with HSV-2 prevalence among the Kaokoland pastoralists. We speculate that the higher prevalence among females might be exacerbated in Kaokoland as a result of local hygiene practices and increased contact between young women and older males (who have higher prevalence). Additionally, there are ecological risk factors for HSV-2 in Kaokoland—increased wealth and region of residence—that are somewhat novel and might represent important behavioral and ecological trends in risk among other remotely living, reproductively isolated populations.

Our interdisciplinary approach offers two kinds of novel insights. First, by introducing epidemiologic techniques to a highly remote study population, we show that epidemiologic studies of vulnerable populations are both feasible and important. Given that many remotely living subsistence-based populations, including the Kaokoland pastoralists, are facing rapid cultural and environmental transitions, it is important to get reliable STD prevalence measures. Second, contextualizing a prevalence study with

descriptive cultural knowledge deepens our understanding of the association between disease and risk factor. In Kaokoland, there is concern that changes in mobility and urban proximity could introduce HIV/AIDS into a population with high partner exchange and little access to preventative care. Our hope is that a better understanding of current STD burden and risk, as offered by our study, will provide insights into preventing an HIV epidemic.

References

Abu-Raddad, L. J., Magaret, A. S., Celum, C., Wald, A., Longini Jr., I. M., Self, S. G., & Corey, L. (2008). Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. *PLoS ONE*, *3*(5), 1-15.

Abu-Raddad, L. J., Schiffer, J. T., Ashley, R., Mumtaz, G., Alsallaq, R. A., Akala, F. A., Semini, I., et al. (2010). HSV-2 serology can be predictive of HIV epidemic potential and hidden sexual risk behavior in the Middle East and North Africa. *Epidemics*, *2*(4), 173-182.

Anderson, D. M., & Broch-Due, V. (1999). *The Poor Are Not Us*. Oxford: James Currey Ltd.

Auvert, B., Buvé, A., Ferry, B., Caraël, M., Morison, L., Lagarde, E., Robinson, N. J., et al. (2001). Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. *AIDS*, *15,* S15-S30.

Bauer, G., Khobzi, N., & Coleman, T. (2010). Herpes simplex virus type 2 seropositivity and relationship status among U.S. adults age 20 to 49: A population-based analysis. *BMC Infectious Diseases*, *10*(1), 359-368.

Bernard, H. R. (2006). Research Methods in Anthropology: Qualitative and Quantitative Approaches (4th ed., p. 801). Lanham: Alta Mira Press.

Beydoun, H. A., Dail, J., Ugwu, B., Boueiz, A., & Beydoun, M. A. (2010). Socio-demographic and behavioral correlates of herpes simplex virus type 1 and 2 infections and co-infections among adults in the USA. *International Journal of Infectious Diseases*, *14, Supplement 3*(0), e154-e160.

Borgerhoff Mulder, M. (1995). Bridewealth and its correlates: Quantifying changes over time. *Current Anthropology*, *36*(4), 573-603

Corey, L., & Wald, A. (2008). Genital Herpes. In K. K. Holmes, P. F. Sparling, W. E. Stamm, P. Piot, J. N. Wasserheit, L. Corey, M. S. Cohen, et al. (Eds.), *Sexually Transmitted Diseases* 4th ed., (pp. 399-438). New York: McGraw Hill Medical.

de la Torre, C., Khan, S., Eckert, E., Luna, J., & Koppenhaver, T. (2007). *HIV/AIDS in Namibia: Behavioral and Contextual Factors Driving the Epidemic*. Windhoek, Namibia.

Flemming, D., McQuillan, G., Johnson, R., Nahmais, A. J., Aral, S. O., Lee, F. K., & St. Louis, M. E. (1997). Herpes simplex type 2 in the United States, 1976-1994. *New England Journal of Medicine*, *337*, 1105-1111.

Frank, T. (2000). Archaeological evidence from the early pastoral period in North-west Namibia. In M. Bollig & J.-B. Gewald (Eds.), *People, Cattle and Land: Transformations of a Pastoral Society in Southwestern Africa* 13th ed., (pp. 77-94). Köln: Köppe.

Fratkin, E. M., & Roth, E. A. (2004). As Pastoralists Settle: Social, Health, and Economic Consequences of Pastoral Sedentarization in Marsabit District, Kenya. New York: Kluwer Academic.

Fratkin, E. M., Roth, E. A., & Nathan, M. A. (2004). Pastoral sedentarization and its effects on children's diet, health, and growth among the Rendille of Northern Kenya. *Human Ecology*, *32*(5), 531-559.

Fratkin, E. M., Roth, E., & Nathan, M. A. (1999). When nomads settle: The effects of commoditization, nutritional change and formal education on Ariaal and Rendille pastoralists. *Current Anthropology*, *40*, 729-735.

Friedman, J. T. (2000). Mapping the Epupa Debate: Discourse and Representation in a Namibian Development Project. In G. Miescher & D. Henrichsen (Eds.), *New Notes on Kaoko* (pp. 220-235). Basel: Basler Afrika Biliographien.

Goody, J., & Tambiah, S. J. (1973). *Bridewealth and Dowry* (p. 171). Cambridge: Cambridge University Press.

Gregson, S., Nyamukapa, C. A., Garnett, G. P., Mason, P. R., Zhuwau, T., Caraël, M., Chandiwana, S. K., et al. (2002). Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *The Lancet*, *359*(9321), 1896-1903.

Hargreaves, J. R., Morison, L. A., Chege, J., Rutenburg, N., Kahindo, M., Weiss, H. A., Hayes, R., et al. (2002). Socioeconomic status and risk of HIV infection in an urban population in Kenya. *Tropical Medicine & International Health*, *7*(9), 793-802.

Homewood, K. (2008). *Ecology of African Pastoral Societies* (p. 292). Oxford, UK: James Currey Ltd.

Hook, E. W., & Leone, P. (2006). Time to translate new knowledge into practice: A call for a national genital herpes control program. *Journal of Infectious Diseases*, *194* (1), 6-7.

Kirakoya-Samadoulougou, F., Nagot, N., Defer, M.-C., Yaro, S., Fao, P., Ilboudo, F., Langani, Y., et al. (2011). Epidemiology of herpes simplex virus type 2 infection in rural and urban Burkina Faso. *Sexually Transmitted Diseases*, *38*(2), 117-123.

Leclerc-Madlala, S. (2008). Age-disparate and intergenerational sex in southern Africa: the dynamics of hypervulnerability. *AIDS*, *22*, S17-S25.

Lingappa, J., Nakku-Joloba, E., Magaret, A., Friedrich, D., Dragavon, J., Kambugu, F., Joloba, M., et al. (2010). Sensitivity and specificity of herpes simplex virus-2

serological assays among HIV-infected and uninfected urban Ugandans. *International Journal of STD & AIDS*, *21*(9), 611-616.

Looker, K. J., Garnett, G. P., & Schmid, G. P. (2008). An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bulletin of the World Health Organization*.

Low, B. S. (2000). *Why Sex Matters*. Princeton: Princeton University Press.

Malan, J. S. (1974). The Herero-speaking peoples of Kaokoland. *Cimbebasia*, *2*(4), 113-129.

Mehta, S. D., Moses, S., Agot, K., Agingu, W., Parker, C., Ndinya-Achola, J. O., & Bailey, R. C. (2008). Herpes simplex virus type 2 infection among young uncircumcised men in Kisumu, Kenya . *Sexually Transmitted Infections* , *84* (1), 42-48.

Mertz, G. J. (1993). Epidemiology of genital herpes infections. *Infectious Disease Clinics of North America*, *7*(4), 825-839.

Mertz, G. J., Benedetti, J., Ashley, R., Selke, S. A., & Corey, L. (1992). Risk Factors for the Sexual Transmission of Genital Herpes. *Annals of Internal Medicine*, *116* (3), 197-202.

MoHSS Namibia. (2008). Estimates and Projections of the Impact of HIV/AIDS in Namibia (p. 34). Windhoek, Namibia.

Molina, M., Romaguera, R. A., Valentine, J., & Tao, G. (2011). Seroprevalence of herpes simplex virus 2 among Hispanics in the USA: National Health and Nutrition Examination Survey, 2007–2008. *International Journal of STD & AIDS*, *22*(7), 387-390.

Ng'ayo, M. O., Friedrich, D., Holmes, K. K., Bukusi, E., & Morrow, R. A. (2010). Performance of HSV-2 type specific serological tests in men in Kenya. *Journal of Virological Methods*, *163*(2), 276-281.

Padian, N., Marquis, L., Francis, D. P., Anderson, R. E., Rutherford, G. W., O'Malley, P. M., & Winkelstein, W. (1987). Male-to-female transmission of human immunodeficiency virus. *JAMA*, *258*(6), 788-790.

Pennington, R., & Harpending, H. (1993). The Structure of an African Pastoralist Community: Demography, History and Ecology of the Ngamiland Herero. Oxford, UK: Clarendon Press.

Pertel, P. E., & Spear, P. G. (2008). Biology of Herpesviruses. In K. K. Holmes, P. F. Sparling, W. E. Stamm, P. Piot, J. N. Wasserheit, L. Corey, M. S. Cohen, et al. (Eds.), *Sexually Transmitted Diseases* 4th ed., (pp. 381-398). New York: McGraw Hill Medical.

Reynolds, S. J., Shepherd, M. E., Risbud, A. R., Gangakhedkar, R. R., Brookmeyer, R. S., Divekar, A. D., Mehendale, S. M., et al. (2004). Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *The Lancet. 363*(9414) 1039-1040.

Sandala, L., Lurie, P., Sunkutu, M. R., Chani, E. M., Hudes, E. S., & Hearst, N. (1995). "Dry sex" and HIV infection among women attending a sexually transmitted diseases clinic in Lusaka, Zambia. *AIDS*, *9 Suppl 1*, S61-68.

Scelza, B. A. (2011). Female choice and extra-pair paternity in a traditional human population. *Biology Letters* , *7* (6), 889-891.

Schiffer, J., & Corey, L. (2009). New concepts in understanding genital herpes. *Current Infectious Disease Reports*, *11*(6), 457-464

Smith, J. S., & Robinson, N. J. (2002). Age-specific prevalence of infection with herpes simplex virus types 2 and 1: A global review. *Journal of Infectious Diseases*, *186* (Supplement 1), S3-S28.

Stavraky, K. M., Rawls, W. E., Chiavetta, J., Donner, A. P., & Wanklin, J. M. (1983). Sexual and socioeconomic factors affecting the risk of past infections with herpes simplex virus type 2. *American Journal of Epidemiology*, *118*(1), 109-121.

Talavera, P. (2002). Challenging the Namibian Perception of Sexuality: A Case Study of the Ovahimba and Ovaherero Culturo-Sexual Models in Kunene North in an HIV/AIDS Context. Windhoek: Gamsberg Macmillan.

Tobian, A. A. R., Serwadda, D., Quinn, T. C., Kigozi, G., Gravitt, P. E., Laeyendecker, O., Charvat, B., et al. (2009). Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *New England Journal of Medicine*, *360*(13), 1298-1309.

Vedder, H. (1938). *Southwest Africa in Early Times*. London: Oxford University Press.

Wald, A. (2004). Herpes simplex virus type 2 transmission: Risk factors and virus shedding. *Herpes : The Journal of the IHMF*, *11*(Suppl 3), 130A-137A.

Watson-Jones, D., Weiss, H., Rusizoka, M., Baisley, K., Mugeye, K., Changalucha, J., Everett, D., et al. (2007). Risk factors for herpes simplex virus type 2 and HIV among women at high risk in northwestern Tanzania. *Journal of Acquired Immune Deficiency Syndrome*, *46*(5), 631-642.

Weiss, H. A., Thomas, S. L., Munabi, S. K., & Hayes, R. J. (2006). Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis . *Sexually Transmitted Infections*, *82*(2), 101-110.

Xu, F., Sternberg, M. R., Kottiri, B. J., McQuillan, G. M., Lee, F. K., Nahmias, A. J., Berman, S. M., et al. (2006). Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA 296*(8), 964-973.

Table 2.1: Crude associations between HSV-2 status and selected demographic and social variables among 402 participants in 28 village field sites in Kaokoland, Namibia 2009

		Men			Women		
		N	HSV-2 + n (%)	OR (95% C.I.)	N	HSV-2 + n (%)	OR (95% C.I.)
Age range							
	≤ 25	62	6 (13%)	1.0 (-, -)	78	17 (18%)	1.0 (-, -)
	26-35	61	10 (21%)	1.8 (0.62, 5.39)	56	32 (34%)	4.8 (2.25, 10.17)
	36-45	37	11 (23%)	3.9 (1.32, 11.84)	33	26 (28%)	13.33 (4.94, 35.96)
	≥ 46	45	20 (43%)	7.5(2.67, 20.85)	30	19 (20%)	6.2 (2.48, 15.50)
Tribe							
	Other	26	7 (15%)	1.0 (-, -)	14	5 (5%)	1.0 (-, -)
	Twa	10	1 (2%)	0.3 (0.03, 2.83)	13	6 (6%)	1.5 (0.33, 7.23)
	Tjimba	55	10 (21%)	0.6 (0.20, 1.82)	60	29 (31%)	1.7 (0.50, 5.62)
	Himba	114	29 (62%)	0.9 (0.35, 2.43)	109	54 (58%)	1.8 (0.56, 5.61)
Wealth status							
	Poor	119	21 (44%)	1.0 (-, -)	187	89 (95%)	1.0 (-, -)
	Intermediate	63	14 (30%)	1.3 (0.62, 2.85)	8	5 (5%)	1.8 (0.43, 7.90)
	Wealthy	23	12 (26%)	5.1 (1.98, 13.09)	2	0 (0%)	0.0 (0, -)[a]
Marital status							
	Single	94	11 (23%)	1.0 (-, -)	94	41 (44%)	1.0 (-, -)
	Married	111	36 (77%)	3.6 (1.72, 7.62)	101	52 (56%)	1.4 (0.78, 2.41)
Polygynous marriage							
	No	83	26 (74%)	1.0 (-, -)		-	-
	Yes	19	9 (26%)	2.0 (0.72, 5.43)		-	-
Number of sex partners in past 6 months							
	0	12	0 (0%)	0.3 (0.04, 2.50)[1]	18	10 (11%)	1.3 (0.84, 3.52)
	1	69	15 (32%)	1.0 (-, -)	112	55 (59%)	1.0 (-, -)
	2 - 5	75	19 (40%)	1.2 (0.56, 2.65)	61	26 (28%)	0.77 (0.41, 1.44)
	> 5	49	13 (28%)	1.3 (0.55, 3.05)	3	2 (2%)	1.6 (0.12, 20.99)

[1]Arbitrarily added 1 to account for 0 value in cell

Table 2.2: Logistic model of HSV-2 risk among 402 participants in 28 village field sites in Kaokoland, Namibia 2009

Variable		ß value for log odds	SE	OR	95% C.I.	p-value
Age						
	≤ 25	Ref		1.0		
	26-35	1.224	0.325	3.4	1.81, 6.52	0.0002
	36-45	1.969	0.367	7.2	3.54, 14.96	<0.0001
	≥ 46	1.938	0.361	6.9	3.42, 14.52	<0.0001
Sex						
	Male	Ref		1.0		
	Female	1.737	0.295	5.7	3.23, 10.30	<0.0001
Wealth status						
	Poor	Ref		1.0		
	Intermediate	0.364	0.368	1.4	0.69, 2.96	0.3
	Wealthy	1.071	0.507	2.9	1.07, 7.94	0.03
Region						
	Omaanda	Ref		1.0		
	Ehama	-0.0124	0.380	0.9	0.42, 1.86	0.7
	"Others"	0.597	0.655	1.8	0.47, 6.36	0.4
	The Marianflus	0.805	0.410	2.2	1.00, 5.03	0.05
	Ozosemo	0.804	0.035	2.2	1.13, 4.50	0.02
	Omunjandu	0.902	0.402	2.5	1.13, 5.47	0.02

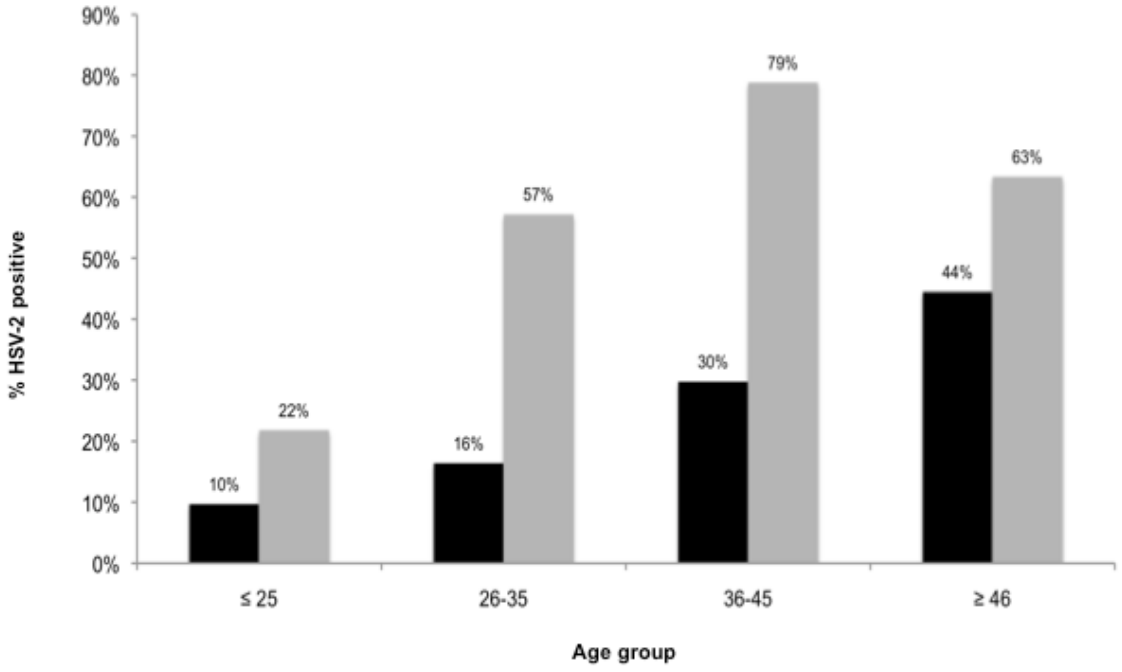
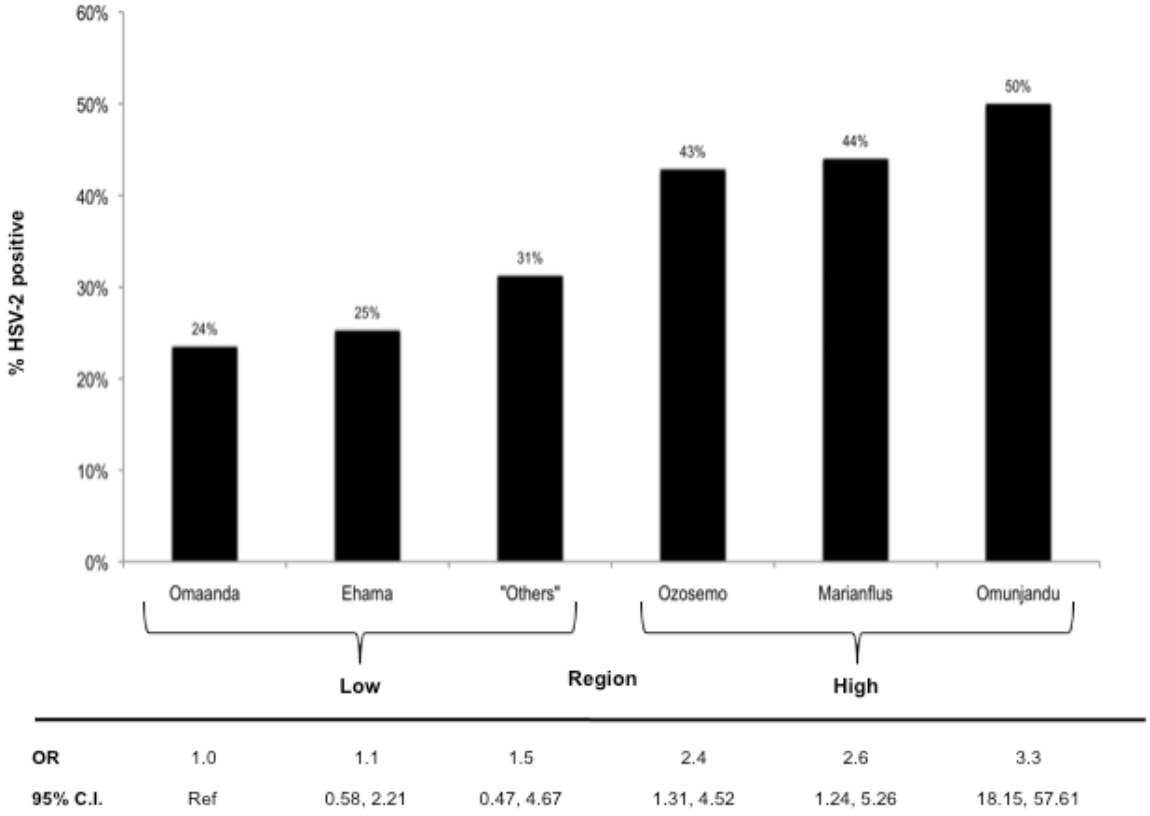


Figure 2.1: Prevalence of herpes simplex virus type 2 (HSV-2) is greater in women (gray) than men (black) at all age categories. HSV-2 risk is higher for women than men (O.R. = 3.1, 95% C.I. = 2.00, 4.74). For both men and women, overall prevalence increases with age but the difference is smallest in the oldest age category.



OR	1.0	1.1	1.5	2.4	2.6	3.3
95% C.I.	Ref	0.58, 2.21	0.47, 4.67	1.31, 4.52	1.24, 5.26	18.15, 57.61

Figure 2.2: Herpes simplex virus type 2 (HSV-2) prevalence shows a low/high dichotomy between regions. There are two patterns of risk across the main Kaokoland regions: A low risk group (<32% prevalence) and a high-risk group (>40%).

CHAPTER 3: HIGH PREVALENCE OF *NEISSERIA GONORRHOEAE* IN A REMOTE, UNDERTREATED POPULATION OF NAMIBIAN PASTORALISTS

Abstract

Background**:** The pastoralist communities in Kaokoland, Namibia, have long been presumed to have high gonorrhea prevalence. Healthcare is very difficult to access, so syndromic management is the norm. To estimate gonorrhea prevalence and social and ecological correlates of infection, we conducted a cross-sectional study.

Methods**:** We recruited 446 adults from 28 rural villages. Gonorrhea status was determined from urethral and vaginal swabs via qPCR assay. All participants answered a closed-ended interview about demographics, sexual behavior and symptom history.

Results**:** 16% of participants had high-level infections ($\geq ID_{50}$ dose) and 48% had low-level infections ($< ID_{50}$ dose). Women had higher prevalence than men of both high and low-level infections. High-level infections were temporally and spatially clustered, occurring among young adults in the Ehama region during the winter. Low-level infections were distributed homogenously—demographically, temporally, and spatially. Essentially all low-level infections and most high-level infections (men = 78%; women = 95%) were asymptomatic.

Conclusions**:** The epidemic-like nature of high-level gonorrhea cases suggests that intervention efforts can be focused on seasons of high social activity. The high proportion of low-level cases offers some new insights to the role of strain-specific

immunity and to the self-limiting qualities of gonorrhea. The overwhelming percentage of asymptomatic cases suggests that syndromic management is not an effective strategy for gonorrhea control in Kaokoland.

Introduction

Gonorrhea remains a public health problem, particularly among high sexual activity, resource poor populations. With the exception of antibiotic resistant strains (Bolan, Sparling, & Wasserheit, 2012), gonorrhea is treatable. However, across many populations as many as 67%-100% of all gonorrhea infections are asymptomatic (Detels et al., 2011), making them an important driver of transmission in persistent epidemics.

Social pressures (e.g. stigma), culture (e.g. hygiene and sexual behavior (Hazel et al., submitted)), and geography influence whether infected individuals will seek treatment. Rural South African women whose access to clinics is limited have low symptom recognition for gonorrhea and chlamydia (Wilkinson et al., 1999). If difficulty in accessing care influences the likelihood of recognizing serious symptoms, then syndromic management (despite its cost effectiveness) is unlikely to significantly reduce disease transmission or minimize the number of people who experience sequelae from untreated gonorrhea and chlamydia.

We studied gonorrhea among the isolated, semi-nomadic, subsistence-living pastoralists of Kaokoland (Frank, 2000; Malan, 1974; Vedder, 1938). Anthropologists and local healthcare workers have long suspected that gonorrhea burden is high in this region (Talavera, 2002) and among related tribes (Pennington & Harpending, 1993), because partner concurrency is common (de la Torre, et al., 2007), but condom use is rare (Hazel et al, submitted) and treatment—syndromic management exclusively—is difficult to access. In Kaokoland, we observed endemic gonorrhea in an environment that might

serve as a close proxy for conditions under which the gonorrhea-human host dynamic evolved. This allows us to make some inference into the biological and behavioral underpinnings of gonorrhea burden.

We also explored patterns of gonorrhea co-infection with chlamydia and identified demographic and ecological correlates of positive gonorrhea status. We believe our study is the first to estimate disease prevalence in this population and the first to report on gonorrhea in a population that is as geographically and culturally isolated as the Kaokoland pastoralists. Furthermore, because we use qPCR as a diagnostic assay, we can quantitate amounts of gonorrhea DNA in our samples to obtain a cross-sectional view of the range of infection.

Materials & Methods

Collection site and participant recruitment

Data were collected between April and November 2009 from 28 villages in Kaokoland, northwestern Namibia. The village study sites represent the ecological, geographic and economic diversity of the remotest regions of Kaokoland. The Himba tribe dominates these regions but Himbas live in close proximity with several other tribes, who were also included in the study. We refer to the tribes in our study collectively as the "Kaokoland Pastoralists." Data were collected over all three recognized seasons: the rainy season, the winter, and the dry season. Permission to conduct this research was given by the University of Michigan's Internal Review Board (HUM00025104) and the Namibian Ministry of Health and Social Services (MoHSS). We also received permission from the local chief before establishing a village as a study site.

We recruited any male or female volunteer who was a) a culturally recognized adult (e.g. women $\geq$16; men $\geq$18), and b) had resided in Kaokoland for at least half of the year, for

a total of 446 people. Our sample sizes for men and women were close to equal. Three people refused to collect a swab and 12 were excluded because they did not live full-time in Kaokoland, leaving a final sample size of 431. In accordance with the terms of MoHSS research approval, we took to the nearest clinic any village member who presented with bacterial STD symptoms or who reported a partner with symptoms for treatment, unless they refused.

Sample collection and storage

Our study focused on regions of Kaokoland that are so remote that they are not connected to a power grid. Therefore, we developed a sample collection protocol that did not require cold storage of any materials.

Male participants submitted a self-collected urethral swab sample; females submitted a self-collected vaginal swab sample. Self-collected swabs are as reliable as clinician-collected swabs (Chernesky et al., 2005) and our participants appeared to understand collection instructions clearly. We ensured participants had not urinated within the hour prior to sample collection and that women had not performed vaginal drying (a local practice (Hazel et al., submitted), within the past hour.

We stored sample material using Whatman® FTA cards (Piscataway, NJ). Upon contact with the chemical matrix in the FTA card, cells are lysed, proteins are denatured, and DNA is held stable. FTA technology allowed us to store our samples for several months while data collection continued. At the end of the data collection period, the FTA cards were shipped to the University of Michigan for diagnostic qPCR. Studies have confirmed the long-term viability of bacterial DNA stored in FTA cards (Rajendram et al., 2006). More recently, FTA cards have been demonstrated as an effective storage tool for molecular diagnosis of gonorrhea (Chi, e al., 2011).

qPCR Primer sets

We developed our own primer sets for gonorrhea (GC) and chlamydia (CT) diagnostics (table 3.1). For *Neisseria gonorrhoeae* detection, we selected a primer set that targets a conserved segment of the porin A pseudogene that is specific to *Neisseria gonorrhoeae* and does not have binding affinity for other species. Logistic limitations prevented us from running a second assay or developing a multiplex assay, so it is possible that we underestimated the number of gonorrhea cases in our study by targeting a single genetic region.

In light of the discovery of a new *Chlamydia trachomatis* variant in Sweden, wherein a deletion occurred at a highly conserved, and common diagnostic target site in the cryptic plasmid (Ripa & Nilsson, 2006), we designed a new primer set for our CT assay. We targeted an alternative conserved region of the cryptic plasmid (table 3.1) based on sequencing results by (Seth-Smith et al., 2009).

Finally, we ran all samples in an assay using universal bacterial primers (Nadkarni, et al., 2002), to ensure that each sample contained bacteria, minimizing the possibility that a GC-negative sample was actually a false negative due to collection, storage or DNA purification failures.

qPCR assays were performed using the Bio-Rad® CFX96 Real-Time System (Hercules, CA) with SYBR green master mix (Ssofast EvaGreen Supermix) in a total volume of 20µl. Optimal primer volume and qPCR conditions for our in-house primers are given in table 3.1. For CT and GC assays we ran standard curves from a 10-fold dilution series (10^8-10^2) using genomic DNA (GC) or cloned target DNA (CT) to quantitate starting concentrations. All samples were run in triplicate from which we calculated the average starting quantity. Any samples with a mean starting quantity of GC or CT DNA below 7.5

x 10^1 copies (our limit of detection for both the GC and CT assays) were considered too low to reliably call positive. These, along with samples that did not amplify were determined to be negative. Samples with a mean starting quantity $\geq 7.5 \times 10^1$ were considered positive.

Interview data

In addition to providing a self-collected swab, participants answered questions in a closed-ended, oral interview. The entire interaction took 30-60 minutes. Participants answered questions about their STD symptom and treatment history within the past six months, demographics (estimated age, tribal affiliation, marital status), residence (home village and region of Kaokoland in which the village is located), and the number of sex partners they had in the past six months.

Statistical analyses

We conducted bivariate analyses to explore associations between main effect variables and gonorrhea status. We used Fisher Exact tests to explore associations between gonorrhea status and self-reported symptoms. Data were analyzed using R 2.14.1.

Results

GC status by qPCR

Sixty-four percent of participant samples contained GC-specific DNA, but there was high variability in the amount of DNA present. We found no relationship between total bacterial concentration (estimated from the assays using universal primer) and GC concentration, confirming that low GC concentration was not a result of ineffective collection or attenuation of genomic material during storage.

Using the ID_{50} for gonorrhea—10^3 organisms—as our cut-off point (Todar, 2009), we divided GC-positive samples into high-level ($\geq 10^3$) and low-level ($<10^3$). The prevalence of low-quantity positive GC samples was 48%. The prevalence of high-quantity positive GC was 16%, for an overall prevalence of 64%. This categorization maps onto the distribution of DNA quantities from our samples because there is a dramatic drop off in the number of samples with quantities approximately more than 10^3 copies (figure 1).

Sex differences in prevalence

Because prevalence was higher in women than men for both high-level and low-level GC (table 3.2), we stratified our analyses by sex, but no patterns emerged. We therefore suspected that higher prevalence in women might be due to lower self-reporting of symptoms among women than men. Among people who reported having had gonorrhea-like symptoms in the past six months, there was no difference between men and women in their likelihood to seek treatment at the clinic ($X^2 = 0.03$, df = 1, p = 0.9). However, men were far more likely than women to report abnormal discharge ($X^2 = 13.9$, df = 1, p = 0.0002) and burning or itching during urination ($X^2 = 12.1$, df = 1, p = 0.0005).

Self-report of symptoms and GC status

We explored the relationship between having high or low-level GC and reporting gonorrhea-like symptoms. We asked all participants about abnormal discharge separately from questions about dysuria. However, since participant responses regarding these symptoms were highly correlated ($X^2 = 156.7$, df = 1, $p < 2.2^{-16}$) we grouped them when examining the relationship between symptom reporting and GC status. We removed from this analysis people who had been to the clinic within the last six months for treatment (n = 32; 78% were men) because treatment will presumably

clear most GC infections and obfuscate the relationship between having symptoms and being GC positive.

With the exception of men who had high-concentration cases of gonorrhea ($p = 0.02$), there was no relationship between being positive for GC and having symptoms (table 3.3). The percentage of women with high-level GC who reported symptoms was not significantly different than the percentage of GC-negative women who reported symptoms. This was also the case for both men and women who had low-level GC.

Seasonal variation and other variables

The nomadic way of life in Kaokoland leads to variability in population density across seasons. For every season in which recruiting took place, we selected villages in areas where there were at least 8-10 eligible individuals present. Consequently, there is a strong association between region and season of collection in our dataset ($X^2 = 14.6$, df = 1, $p = 0.0001$). Despite the confounding effects of season on region, when we stratified by region, most cases of high-level GC were collected during the winter (figure 2). This is particularly true for people in the youngest age group ($\leq$25 years old), living in the Ehama region (table 3.2).

For the most part, low-level GC cases were distributed evenly across populations, regions and collection season; however, their odds of having a low-level infection were significantly greater in the Ehama and Ozosemo (table 3.2).

Other variables, including tribal affiliation (Fisher Exact $p = 0.2$), marriage status ($X^2 = 0.3$, df = 2, $p = 0.8$), number of sex partners in the past six months (Fisher Exact $p = 0.9$), and co-infection with chlamydia (Fisher Exact $p = 0.2$), were not statistically significantly associated with GC prevalence.

Discussion

Using qPCR as a detection method for gonorrhea had two particular advantages that shaped the results of this paper. First, qPCR is more sensitive than conventional PCR. We had a limit of detection of 75 copies per 20µl sample, so we could detect very low-level infections and capture the widest possible prevalence in our dataset. (It is possible, that some of our lowest-level samples actually contained no live bacteria at the time of collection, and that what we were detecting in qPCR is the remnant DNA of dead cells from a cleared infection.) Second, qPCR amplifies *and* quantitates GC DNA present in the sample. This allowed to not only detect GC positive samples, but also to determine how much DNA was present in each sample. Quantitation allows us to explore the positive cases in more detail and to speculate about why GC prevalence is so high in Kaokoland.

Gonorrhea—high- and low-level—occurred frequently among Kaokoland pastoralists, affecting the majority (64%) of those screened. Though high-level cases were clustered demographically, spatially and temporally, low-level cases were distributed homogeneously. The vast majority of participants who had either high- or low-level GC reported no genitourinary symptoms. Our prevalence and percentage of asymptomatic infections are consistent with other studies in rural Africa (Wilkinson et al., 1999) and high activity populations (Detels et al., 2011) that were collected in less remote areas.

Local conditions and behaviors likely influence symptom recognition in Kaokoland. Dry sex and partner concurrency are nearly ubiquitous practices in the regions of Kaokoland where this study took place (Scelza, 2011; Talavera, 2002, Hazel et al., submitted). Frequent partner exchange and concurrency is associated with higher GC transmission risk for both men and women (Hooper et al., 1978; Platt, Rice, & McCormack, 1983),

and other non-STD conditions among women (Fethers, et al., 2008). There is evidence that dry sex increases transmission probability for non-HIV STDs for men (Beksinska, et al., 1999) and HIV in women (Auvert et al., 2001). Recognition of symptoms requires a meaningful distinction between what people regard as healthy (i.e. normal) and what people regard as signs of illness. If discomfort is normal, symptoms will be hard to recognize. This might explain why, among participants who report symptoms, GC and CT negative participants are just as likely to report genitourinary discomfort as participants who are positive for GC and/or CT.

Syndromic management without screening or partner outreach has little impact on the reduction of asymptomatic infections. However, due to expense and infrastructure requirements of lab-based diagnostics, most developing countries use syndromic management (WHO, 2007) to treat a suite of symptoms that are commonly caused by bacterial STDs. Even when symptoms are present, seeking treatment is not trivial for people living in remote areas. There are few clinics in Kaokoland and they are a far and expensive journey from many villages. This is especially true for women, who must leave children and put aside crucial provisioning duties to attend the clinic.

Detecting temporal patterns in GC epidemics is crucial for effective screen and outreach. Most of our high-level cases were detected in the winter. Seasonal patterns among gonorrhea epidemics have been observed elsewhere (Grassly, Fraser, & Garnett, 2005). In Kaokoland, the winter is the time of year when people are most liberated from the responsibilities of subsistence practices and when food is most abundant. It is therefore the preferred time of year for holding ceremonies. Access to sexual partners is greater and the number of contacts in a given period of time likely increases, explaining why we observed a concentrated spike in infections during the winter. A series of weddings and funerals occurred in July in the Ehama region, underlying the spike in infected samples

we collected. Given infrastructural and resource limitations to intervention efforts in Kaokoland, outreach could be concentrated in winter and could utilize local informational networks to identify the timing and location of ceremonies to target places of highest risk.

While broad immunity, acquired over many years of sexual activity (Plummer et al., 1989) and repeated exposure, may explain why high-level (i.e. high infectiousness) cases were concentrated among the youngest adults (who had the least exposure), it does not explain why low-level cases were distributed evenly across all age groups. Some low-level infections may be old infections of a previously higher titer that were not treated and have begun to diminish. Because we do not have repeated, longitudinal measures of individual infections, we do not know the time period over which infection levels decrease. Though these old infections must be less transmissible, they are highly prevalent and likely play an important role in maintaining endemic GC levels. Unfortunately, we found no equivalent data in the literature for comparison.

Significance and impact of research in small, remote populations

Our study has several limitations, which are difficult to avoid in studying remote, nomadic populations. These include the limited sample size per village, and a lack of infrastructure, necessitating collection and storage protocols for testing later. However, these do not seriously undercut the value of our results, which give insight into GC under natural conditions, and the limitations of syndromic management for remote populations.

Korenkamp et al (2002) suggest that in underserved populations, improving syndromatic management of STDs is unlikely to be effective in reducing gonorrhea prevalence; enhancing reproductive health education is also crucial. Our results are in agreement, with the added stipulation that access to treatment must be enhanced, especially for women who carry the largest burden of asymptomatic infection. Local knowledge of

patterns in movement and social functions can help focus treatment and prevention efforts more efficiently.

Vulnerable populations, like the Kaokoland pastoralists, currently face great morbidities and possible risk of a future HIV epidemic as the local culture and environment undergoes drastic transformation (Fratkin, Roth, & Nathan, 1999; Friedman, 2000). It will be critical for the health and survival of these communities to be able to make accurate predictions of future risk and transmission pathways and design more effective intervention and outreach.

References

Auvert, B., Buvé, A., Ferry, B., Caraël, M., Morison, L., Lagarde, E., Robinson, N. J., et al. (2001). Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. *AIDS*, *15*, S15-S30.

Beksinska, M. E., Rees, H. V., Kleinschmidt, I., & McIntyre, J. (1999). The practice and prevalence of dry sex among men and women in South Africa: a risk factor for sexually transmitted infections? *Sexually Transmitted Infections*, *75*(3), 178-180.

Bolan, G. A., Sparling, P. F., & Wasserheit, J. N. (2012). The emerging threat of untreatable gonococcal infection. *The New England Journal of Medicine*, *366*(6), 485-487.

Chernesky, M. a, Hook, E. W., Martin, D. H., Lane, J., Johnson, R., Jordan, J. a., Fuller, D., et al. (2005). Women find it easy and prefer to collect their own vaginal swabs to diagnose *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infections. *Sexually Transmitted Diseases*, *32*(12), 729-733

Chi, K., Chen, C., Ye, T., Nachamkin, E., & Ballard, R. (2011). The molecular diagnosis of rectal GC and CT infections using the FTA elute card for specimen collection and the real-time multiplex PCR for detection. *Sexually Transmitted Infections*, *87*(Suppl 1), A272.

de la Torre, C., Khan, S., Eckert, E., Luna, J., & Koppenhaver, T. (2007). *HIV/AIDS in Namibia: Behavioral and Contextual Factors Driving the Epidemic*. Windhoek, Namibia

Detels, R., Green, A. M., Klausner, J. D., Katzenstein, D., Gaydos, C., Handsfield, H. H., Pequegnat, W., et al. (2011). The incidence and correlates of symptomatic and

asymptomatic *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in selected populations in five countries. *Sexually Transmitted Diseases*, *38*(6), 1

Fethers, K. a, Fairley, C. K., Hocking, J. S., Gurrin, L. C., & Bradshaw, C. S. (2008). Sexual risk factors and bacterial vaginosis: a systematic review and meta-analysis. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *47*(11), 1426-35

Frank, T. (2000). Archaeological evidence from the early pastoral period in North-west Namibia. In M. Bollig & J.-B. Gewald (Eds.), *People, Cattle and Land: Transformations of a Pastoral Society in Southwestern Africa* (13th ed., pp. 77-94). Köln: Köppe.

Fratkin, E. M., Roth, E., & Nathan, M. A. (1999). When nomads settle: The effects of commoditization, nutritional change and formal education on Ariaal and Rendille pastoralists. *Current Anthropology*, *40*, 729-735.

Friedman, J. T. (2000). Mapping the Epupa Debate: Discourse and Representation in a Namibian Development Project. In G. Miescher & D. Henrichsen (Eds.), *New Notes on Kaoko* (pp. 220-235). Basel: Basler Afrika Biliographien.

Grassly, N. C., Fraser, C., & Garnett, G. P. (2005). Host immunity and synchronized epidemics of syphilis across the United States. *Nature*, *433*(7024), 417-421

Hooper, R. R., Reynolds, G. H., Jones, O. G., Zaidi, A., Wiesner, P. J., Latimer, K. P., Lester, A., et al. (1978). Cohort study of venereal disease, I: The risk of gonorrhea transmission from infected women to men. *American Journal of Epidemiology*, *108*(2), 136-144

Korenromp, E. L., Sudaryo, M. K., de Vlas, S. J., Gray, R. H., Sewankambo, N. K., Serwadda, D., Wawer, M. J., et al. (2002). What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *International journal of STD & AIDS*, *13*(2), 91-101

Malan, J. S. (1974). The Herero-speaking peoples of Kaokoland. *Cimbebasia*, *2*(4), 113-129.

Nadkarni, M. a, Martin, F. E., Jacques, N. a, & Hunter, N. (2002). Determination of bacterial load by real-time PCR using a broad-range (universal) probe and primers set. *Microbiology*, *148*(Pt 1), 257-66

Pennington, R., & Harpending, H. (1993). The Structure of an African Pastoralist Community: Demography, History and Ecology of the Ngamiland Herero (p. 268). Oxford, UK: Clarendon Press.

Platt, R., Rice, P. A, & McCormack, W. M. (1983). Risk of acquiring gonorrhea and prevalence of abnormal adnexal findings among women recently exposed to gonorrhea. *JAMA : the journal of the American Medical Association*, *250*(23), 3205-9

Plummer, F. A., Simonsen, J. N., Chubb, H., Slaney, L., et al. (1989). Epidemiologic evidence for the development of serovar-specific immunity after gonococcal infection. *The Journal of Clinical Investigation, 83*(5), 1472-1476

Rajendram, D., Ayenza, R., Holder, F. M., Moran, B., Long, T., & Shah, H. N. (2006). Long-term storage and safe retrieval of DNA from microorganisms for molecular analysis using FTA matrix cards. *Journal of Microbiological Methods*, *67*(3), 582-592

Ripa, T., & Nilsson, P. (2006). A variant of Chlamydia trachomatis with deletion in cryptic plasmid: Implications for use of PCR diagnostic tests. *Eurosurveillance*, *II*

Scelza, B. A. (2011). Female choice and extra-pair paternity in a traditional human population. *Biology Letters*, *7* (6), 889-891

Seth-Smith, H. M. B., Harris, S. R., Persson, K., Marsh, P., Barron, A., Bignell, A., Bjartling, C., et al. (2009). Co-evolution of genomes and plasmids within

Chlamydia trachomatis and the emergence in Sweden of a new variant strain. *BMC genomics*, *10*(1), 239

Talavera, P. (2002). Challenging the Namibian Perception of Sexuality: A Case Study of the Ovahimba and Ovaherero Culturo-Sexual Models in Kunene North in an HIV/AIDS Context (p. 111). Windhoek: Gamsberg Macmillan.

Todar, K. (2009). Gonorrhea. *The Microbial World*

Vedder, H. (1938). *Southwest Africa in Early Times*. London: Oxford University Press.

WHO. (2007) Training Modules for the Syndromatic Management of Sexually Transmitted Infections, 2nd Ed.

Wilkinson, D., Abdool Karim, S., Harrison, A., Lurie, M., Colvin, M., Connolly, M., & Sturm, A. (1999). Unrecognized sexually transmitted infections in rural South African women: A hidden epidemic. *Bulletin of the World Health Organization*, *77*(1), 22-28

Table 3.1: Primer sequences and qPCR conditions for in-house designed *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) assays

Target	Primer	Sequence	Conditions	Primer concentration
Chlamydia trachomatis				
Porin A pseudogene	GCporA_F	GAAAGTAATCAGATGAAACCAGTTC	98°C for 2 minutes	10mM/mL
	GCporA_R	CAAGAACAAAAAGAAAGCATCAT	98°C for 1 second, 57°C 1 second, 39x repeat	
Neisseria gonorrhoeae				
Cryptic plasmid	CTcryp_F	TGTCTGACGGTTCTTAAGCTGGGA	98°C for 2 minutes	10mM/mL
	Ctcryp_R	ATTGGTTGATCGCCCAGACAATGC	98°C for 1 second, 62°C 1 second, 39x repeat	

Table 3.2: Crude associations between gonorrhea status and selected demographic and ecological characteristics among 431 participants in 28 village field sites in Kaokoland, Namibia 2009

		High GC		Low GC	
	N	n (%)	cOR (95% C.I.)	n (%)	cOR (95% C.I.)
Sex					
Male	222	33 (15%)	1.0	94 (42%)	1.0
Female	209	**39 (19%)**	**1.9 (1.08, 3.35)**	111 (53%)	**1.9 (1.24, 2.91)**
Age range (oldest to youngest)					
≥ 46	81	11 (14%)	1.0	38 (47%)	1.0
36-45	76	7 (9%)	0.6 (0.19, 1.59)	32 (42%)	0.7 (0.37, 1.42)
26-35	124	19 (15%)	1.5 (0.60, 3.50)	67 (54%)	1.5 (0.80, 2.75)
≤ 25	150	35 (23%)	**2.2 (0.96, 4.88)**	68 (45%)	1.2 (0.67, 2.22)
Chlamydia					
Negative	397	63 (16%)	1.0	191 (48%)	1.0
Positive	34	9 (26%)	**1.9 (0.73, 4.70)**	14 (41%)	1.0 (0.42, 2.16)
Wealth					
Wealthy	27	3 (11%)	1.0	13 (48%)	1.0
Middle	77	10 (13%)	0.9 (0.22, 4.02)	28 (36%)	0.6 (0.24, 1.55)
Poor	327	59 (18%)	**2.1 (0.56, 7.76)**	164 (50%)	1.3 (0.58, 3.09)
Region					
Omaanda	113	14 (12%)	1.0	53 (47%)	1.0
Ehama	88	**37 (42%)**	**9.4 (3.92, 22.32)**	**38 (43%)**	**2.5 (1.21, 5.34)**
"Others"	16	2 (13%)	1.1 (0.20, 6.05)	8 (50%)	1.2 (0.37, 4.36)
The Marianflus	53	**2 (4%)**	**0.2 (0.04, 0.94)**	18 (34%)	0.5 (0.24, 1.00)
Ozosemo	101	10 (10%)	1.1 (0.43, 2.78)	61 (60%)	1.8 (0.98, 3.18)
Omunjandu	60	7 (12%)	0.9 (0.32, 2.47)	27 (45%)	0.9 (0.46, 1.76)
Season					
Rainy	67	4 (6%)	1.0	42 (63%)	1.0
Winter	156	**51 (33%)**	**5.1 (1.65, 16.05)**	53 (34%)	**0.5 (0.27, 0.97)**
Dry	208	17 (8%)	1.1, (0.34, 3.62)	110 (53%)	0.7 (0.37, 1.23)

Table 3.3: Association of chlamydia (CT), gonorrhea (GC), and CT & GC infections with self report of abnormal discharge or dysuria by gender among 431 participants in 28 village field sites in Kaokoland, Namibia, 2009

	Men				Women			
	N	Symptoms (%)	n	Fisher, 2-tailed	N	Symptoms (%)	n	Fisher, 2-tailed
CT-, GC-	79	7 (9%)		Ref	50	3 (6%)		Ref
CT+	9	1 (11%)		1.0	28	3 (11%)		0.7
GC low	80	9 (11%)		0.8	105	4 (4%)		0.8
GC high	27	6 (22%)		0.1	38	2 (5%)		1.0
CT+, GC low	2	0* (0%)		0.5	10	0* (0%)		1.0
CT+, GC high	2	1(50%)		0.4	7	0* (0%)		0.9

*Arbitrarily added 1 to account for 0 value in cell

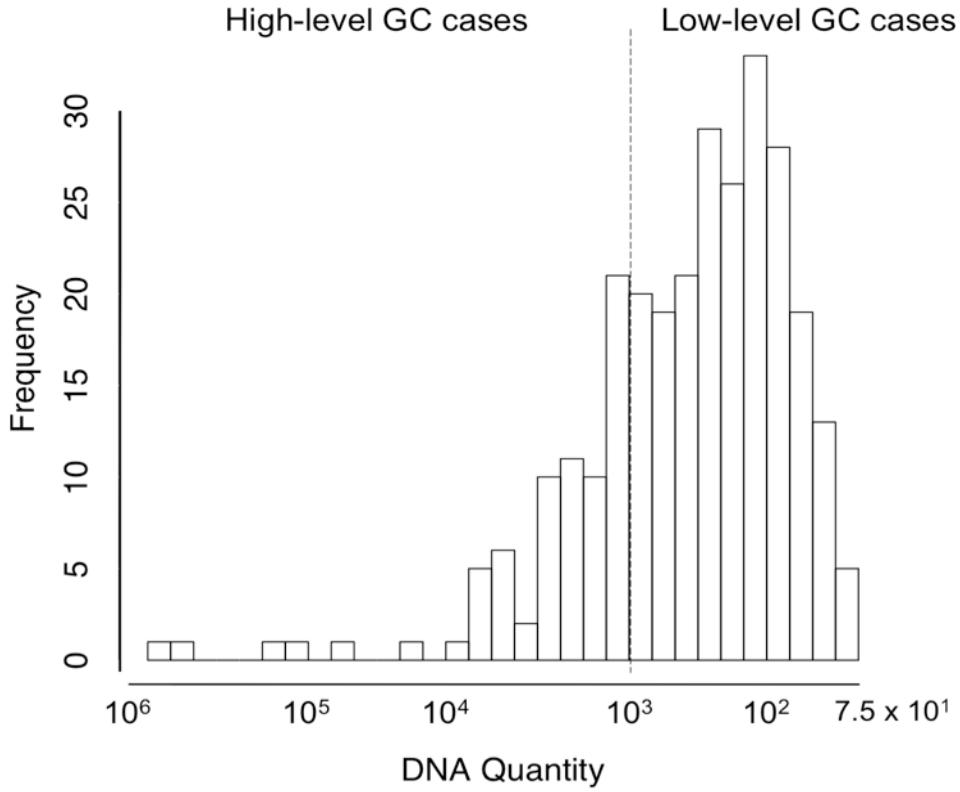


Figure 3.1: Histogram of DNA quantity in 431 urethral or vaginal samples from participants in Kaokoland, Namibia 2009. Quantities of 1000 copies or more were categorized as "high-level" infections, based on the definition of the ID_{50} dose for gonorrhea. This is very close to what appears to be a natural cut-off in our data.

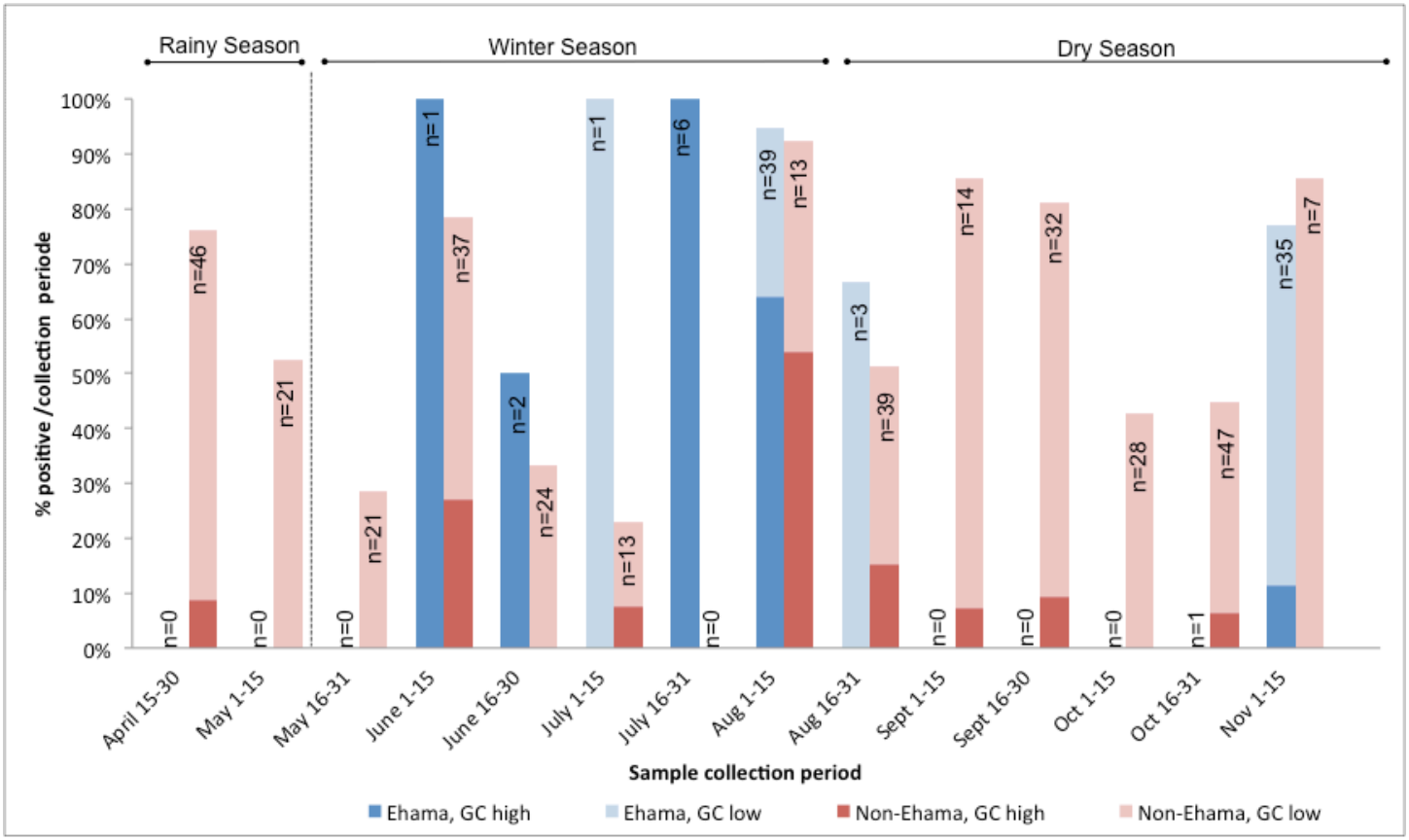


Figure 3.2: Prevalence of high-level gonorrhea (GC) cases is higher in the winter. Most cases occurred in Ehama (blue bars) and data collection in Ehama was most intense in the winter. However, winter is still significantly associated with high-level GC, when bivariate analyses are stratified by region (Ehama: O.R. = 21.6, 95% C.I. = 3.71, 180.6; Non-Ehama regions: OR = 1.9, 95% C.I. = 0.89, 3.89), though this association is not as strong for non-Ehama regions. Numbers indicate the total number of samples collected in either Ehama or non-Ehama regions for each two-week period.

CHAPTER 4: *NEISSERIA GONORRHOEAE* TRANSMISSION IN A RARELY TREATED, NON-WESTERN POPULATION: USING EMPIRICAL, CROSS-SECTIONAL DATA TO INFORM A COMPARTMENTAL MODEL

Abstract

Neisseria gonorrhea remains a serious burden in many high-activity, undertreated populations. Recent empirical work on gonorrhea prevalence among pastoralists in Kaokoland, Namibia found high prevalence of asymptomatic gonorrhea infections. The majority of these infections were low-level (i.e. below the ID_{50} dose). Using empirically collected data from the Kaokoland study on disease status, symptom history (self-report), and recent sexual contacts, we developed a gonorrhea transmission model that incorporates low-level infections as an additional disease status. We used the model to generate estimates for difficult-to-measure parameters as well as for parameters associated with low-level infections. We also aimed to describe the impact of these infections on overall prevalence patterns. Our results suggest that transmission probabilities are higher than previously estimated and that low-level infections are consistent with empirical findings that immunity to gonorrhea is strain-specific and incomplete. These results provide new insights to gonorrhea transmission where symptom reporting is low and treatment is difficult to access.

Introduction

There are many challenges to building an effective compartmental model of gonorrhea (GC) transmission, including lack of knowledge of the impact of asymptomatic infections, an

incomplete understanding of immune response to gonorrhea infection, and the difficulty of modeling the complexity of contact network structures.

The earliest models (Hethcote & Yorke, 1984; Yorke, Hethcote, & Nold, 1978) accounted for asymptomatic disease by adding another equation to represent a third health status (susceptible, symptomatic, asymptomatic) and variability in sexual contact frequencies by assuming two sub-groups, differentiated by sexual activity levels. The high activity group—responsible for the persistence of GC, despite R_0 values of apparently <1 across the rest of the population—is referred to as the "core" group (Hethcote, 1976; Nold, 1979). Though empirical evidence of core group transmission has been found (Rothenberg, 1983), there have been many debates about how it has been used. Since its development, core-group concept has been defined and applied in many different ways (Thomas & Tucker, 1996); this leads to a lack of consensus regarding its value in measuring, predicting, and intervening on real GC epidemics. Furthermore, Rothenberg et al. (1996) argue that the concept of a core group is too simplistic because it considers only individual risk behaviors and not confounding influences of risk associated with one's group membership or environment. For example, living in an area with high early adult mortality due to violence can limit the impact of never using condoms on risk for gonorrhea exposure.

In response to this, more recent models have expanded the complexity of contact patterns by questioning the assumption that contact between core and non-core group members is random, an assumption that is likely an oversimplification of reality. Garnett & Anderson (1993) define a type of assortative mixing that adds a single parameter (ε) to the model that defines what proportion of all contacts occurs between individuals of the same group (Garnett & Anderson, 1993). The concept of preferred mixing (Jacquez, et al., 1988; Simon & Jacquez, 1992) estimates the proportion of total contacts that are reserved for members of one's own group (r_i) and assumes that all other contacts (1-r_i) are random. One

advantage of preferred mixing over assortive mixing is that it allows for activity groups to have different amounts of within-group preference.

Despite the inclusion of greater biological and behavioral complexity in these models, they still struggled to reflect real epidemiologic patterns because of a lack of knowledge of appropriate parameter estimates. Garnett et al. (1999) responded to this problem by fitting a GC transmission model with parameter values drawn from empirical data. Their model describes the GC transmission dynamics from a clinic population in Newark, New Jersey. The model includes two infected/infectious states (symptomatic and asymptomatic), four sexual activity groups (instead of the simple "core" and "non-core" dichotomy), and an embedded expression for assortive sexual mixing among them. This model is informed by empirical data from the Newark clinic population, but also relies on data from the National Health and Nutrition Examination Survey (NHANES) dataset to estimate parameters for contact patterns. Ultimately, they find this empirically driven model only matches real world patterns when transmission probabilities and asymptomatic disease parameters are set unrealistically high. Also, they find that the model is highly sensitive to small changes in parameter values.

A model of GC transmission in Kaokoland, Namibia

We present a model of gonorrhea transmission among a remotely living, rarely treated population of semi-nomadic pastoralists in Kaokoland, northwestern Namibia, among whom we undertook a cross-sectional, empirical study of gonorrhea burden and sexual behavior in 2009. Like Garnett et al., our GC model includes four sexual activity groups and parameter estimates are based on empirical data.

We believe our model makes several improvements on Garnett et al.'s work. First, we recruited from of an entire population of sexually active adults within a closed sexual

network, not a subpopulation of symptomatic patients attending a clinic. Therefore, our estimates for several parameters—including proportion of asymptomatic infections (θ_k), number of contacts (c_{ki}), and preferred mixing (ri)—are backed by a richer dataset.

Second, we include a novel complexity, based on our empirical observations in the Kaokoland study: a third infected/infectious status that is exclusively asymptomatic, low bacterial load (i.e. < 10^3 copies/20µl reaction in qPCR assay), and high prevalence (Chapter 3 of this dissertation). In Kaokoland, where most GC infections are asymptomatic and people therefore seldom seek treatment, we assume that the duration of most infections is longer and diminishes in titer over time. Though the transmission probability of low-level infections is likely lower than that of high-level infections, their high prevalence suggests they are important in maintaining endemic levels of gonorrhea in this population. Because low-level infections are exclusively asymptomatic, we assume they are *at least* as long lived as asymptomatic high-level infections. By adding this additional disease status, we observe asymptomatic infections at a finer resolution that allows for nuance in duration and transmissibility across the life of the infection.

The contribution of modeling to the problem of high prevalence GC in Kaokoland

Because of the high prevalence of asymptomatic disease and a corresponding lack of antibiotic treatment, we saw more gonorrhea cases in Kaokoland in 2009, albeit mostly at low bacterial loads, than we anticipated. Sixty-four percent of participants (n=276) were GC positive; 48% of these cases were low-level, or below the ID_{50} of 1000 copies per sample (Todar, 2009; see Chapter 3 of this dissertation for detailed diagnostic methods).

Because our empirical work was cross-sectional, we are limited in terms of epidemiologic analytics in how much we can characterize low-level infections with our data. Therefore, we built a compartmental model to further explore transmission dynamics in Kaokoland in light

of our empirical findings. We can use this model to explore some basic assumptions about GC spread, particularly the notion of core groups and the natural history of untreated cases. These assumptions are based on data from disparate sources. This is unavoidable—one study cannot measure everything—but modeling GC transmission indicates which assumptions are valid, which must be reconsidered, and which are sensitive to context. With these contributions in mind, we explore several questions about endemic GC in Kaokoland in 2009 with our model.

Question 1: In a population where most people, not just a small core group, have multiple and concurrent partners, how does contact structure affect GC prevalence? Unlike many western populations, having multiple, concurrent partners is culturally acceptable and commonly practiced among the Kaokoland pastoralist tribal groups. Populations that broadly support partner concurrency challenge the notions of a GC-sustaining, high-activity "core" group and even the assumption of preferred mixing by activity level. Our empirical dataset includes data on recent sexual partners for all participants in the Kaokoland study. Thus, we have a unique ability to explore these questions of partner concurrency, the role of "core" groups, and preferred mixing in our model because we have partner network data for all participants.

Question 2: Are previous estimates of transmission probability accurate? One of the concerns raised by Garnett et al. (1999) was that they could only mimic endemic GC levels found the Newark, NJ study by setting transmission probabilities (β_1=0.8 and β_2=0.6) unrealistically high. We attempted to address that concern in our model, suspecting that an additional infectious status with transmission probability (albeit much lower) might help to drive overall prevalence. If we are correct, that could account for why Garnett et al. require higher β values to maintain GC prevalence in the model similar to that of the Newark population.

Question 3: What are the transmission characteristics of low-level infections? The observation of highly prevalent, asymptomatic, low-level GC cases in the Kaokoland empirical dataset was an unexpected finding that yielded more new questions than robust conclusions. For example: How long does it take for high-level infections to decrease below a quantity of 10^3? How long do low-level infections last before the resolve? We use our model to generate estimates of a) the rate at which high-level asymptomatic infections decrease into low-level infections (ψ_k), b) the transmission probability of low-level infections (β'_k) and, c) the duration of low-level infections before they resolve (γ_k).

Question 4: How does the addition of a low-level status of GC infection to the compartmental model impact the transmission dynamics and overall prevalence? These infections are highly prevalent in Kaokoland; this is likely to be true in any high activity population where a) a high proportion of the GC cases are asymptomatic and b) access to treatment is poor. With prevalence as high as 42% (men) and 53% women, low-level infections likely have an impact on overall transmission patterns and we use this model to explore that.

The distribution of GC in Kaokoland, as we see it in our 2009 dataset, is really just a snapshot of a dynamic process of transmission, self-limiting infection, and disease resolution. We identified an important stage of infectiousness (low-level asymptomatic infections) but lack empirical data to describe it further. Our model provides an opportunity to estimate these unknown characteristics of low-level GC infection (e.g. transmission, duration) under the biological and sociological conditions of Kaokoland.

These efforts will hone our future research questions and inform further data collection. Empirical validation of our model will deepen our understanding of the effects of GC in undertreated populations, and offer important information for more effective intervention and

treatment programs. The original fieldwork in Kaokoland was completed when treatment options were strictly limited to symptomatic people. This is still the case, but these studies—the empirical dataset and the theoretical modeling—have the potential to improve STD care to the Kaokoland communities and similarly remote, undertreated populations. With parameter estimates that are backed by empirical validation, we can build from our current model to predict future risk based on behavioral or epidemiologic transitions. This is an important future step because the Kaokoland pastoralists, like many remotely living subsistence-based populations, are facing economic, cultural, and environmental changes that are likely to have an impact on health and healthcare access (Fratkin & Roth, 2004).

Methods

An empirical study of Neisseria gonorrhoeae in Kaokoland, Namibia

This model is informed by an empirical dataset, collected over eight months in 2009 among the semi-nomadic, remotely living pastoralists of Kaokoland, in northwestern Namibia. These data were collected as part of an epidemiologic and behavioral study of sexually transmitted diseases that explored the characteristics of burden in a high activity, remote population with very limited access to treatment. Treatment is exclusively through syndromic management (Pettifor, et al., 1999; WHO, 2007). Urethral (male) and vaginal (female) swabs were tested for GC-specific DNA using qPCR, a highly sensitive molecular technique that enables quantitation of DNA. Twelve percent of men and 18% of women had GC infections with a DNA concentration $\geq 10^3$ (i.e. the ID_{50}) (Chapter 3 of this dissertation). The striking result from the Kaokoland study was the high prevalence of low-level GC DNA found: 42% of men's and 53% of women's samples had GC DNA quantities of $<10^3$ copies. 75 copies was the limit of detection. Details of the laboratory methods for GC detection are given in Chapter 3 of this dissertation.

The range of GC DNA quantities in our dataset is continuous. Thus, the binary distinction between high-level and low-level infection status is a somewhat arbitrary one that we defined to help describe qualitative differences among GC infections in this population. We detected so many infections, not only because GC is endemic in Kaokoland, but also because we used a highly sensitive qPCR diagnostic assay that can detect GC cases with DNA quantities down to 75 copies per sample.

Within this high-prevalence dataset—64% overall—we found great variability in DNA quantities (figure 4.1) that cannot be treated homogeneously. We chose 10^3 copies as a cut-off between high- and low-level gonorrhea because it is estimated to be the ID_{50}, or the dose at which 50% of experimental subjects become infected (Todar, 2009). In our empirical data, we see a distinct increase in frequency in samples with quantities that are slightly greater than 10^3 copies/20µl reaction (figure 4.1), indicating that approximately 10^3 copies is a meaningful distinction between infections types.

Description of the model

We present an ordinary differential equation model that describes the transmission dynamics of endemic gonorrhea in a high-activity, undertreated population in remote Namibia (figure 4.2). The model was built using MatLab R2011a.

Individuals in our model fall into one of four health categories: susceptible (X), symptomatic high-level infected (Y^{sh}), asymptomatic high-level infected (Y^{ah}), or asymptomatic low-level infected (Y^{al}). Participants with low-level GC infections were no more likely to report genitourinary symptoms than people who tested negative for gonorrhea and/or chlamydia; therefore we have no symptomatic low-level category in our model. Individuals in the model are categorized by sex ($_k$) and activity group ($_i$). Though partner concurrency is normative in Kaokoland, there is still wide variability in contacts per unit of time among participants. We

therefore follow Garnett et al. (1999) and allow four activity groups. These activity groups represent four levels of contact frequency, ranging from highest (*i=1*) to lowest (*i=4*) activity. Mean contact rate for each activity group can be different for men and women (i.e. $c_{1,i} \neq c_{2,i}$).

Heterosexual sex is assumed and non-vaginal modes of sexual contact (e.g. anal, oral) are omitted because these behaviors are culturally rejected and rarely practiced in the study population (Talavera, 2002; Hazel, unpublished). With a few exceptions (identified below), our parameter values come directly from the 2009 Kaokoland field study dataset. See Appendix A for the full model description and parameter values.

Parameter values

Population parameters

Entry/exit from population (μ): Because our model only considers sexually mature adults, we define our parameter of exit/entry from the population as an estimate of the number of adults entering/exiting the sexually active population. Entrants into the sexually active population are young adults who have experienced their first sexual encounter. We do not have thorough census or demographic information for this population, so we estimate the rate of entry into sexual activity from available data on the birth rate, minus the death rate for infants and children under five years old.

Birth and death rates for the rural pastoralists of Kaokoland are not well estimated. Most demographic data for this area include the urban areas of Kaokoland where healthcare is more accessible. One given estimate of Himba (the dominant tribe in rural Kaokoland) fertility is 4.7 total births/woman (Scelza, 2012), which is approximately 30.12 births/1000/year, or 0.0312 births/person/year. We then calculated the total child mortality to be 0.023 from data for the Kunene district for infant mortality (49.9 deaths/1000

births/year) and child-under-five mortality (71.2 deaths/1000/year), giving us an entry rate of μ = 0.0001/day.

Exit from the population is defined as a person no longer having sexual contacts, which could happen through cessation of sexual activity, migration or death. We assume that mortality rates for people over 5 years old and sexually active adults is very low, relative to early mortality (a reasonable assumption in this remote area of Kaokoland where HIV has not spread) and that emigration and immigration are also low enough to be discounted. Thus, we estimate exit from the population as the rate at which formerly sexually active people who expect to be active again stop sexual contact for at least six months (the length of time within which participants could accurately recall sexual contacts). New entrants into the population (young people who have recently had their sexual debut) and elderly people (who are considered less desirable as partners) were mostly likely to have no partners in the six-month preceding data collection. Other reasons that a sexually active participant was currently without partners include observation of a mourning period, post-partum abstinence, or temporarily living too far from partners (e.g. at a remote cattle post). From our empirical dataset, we found that the mean percent of formerly sexually active adults who did not have a sexual contact within the six months prior to data collection was 3% (range, by age and sex, was 1-6%), which comes to a rate of 0.00016. Because entry and exit rates in per day units are very similar, we use the same value, μ = 0.0001/day, for entry and exit.

Contacts ($c_{k,i}$): We estimate our contact parameter using the number of sex partners reported by study participants. All participants were asked to provide the names of all sexual contacts within the last six months—the longest range of time that participants could accurately recall contact information. For both men and women, we identified break points to divide the participants into four activity groups. The mean number of contacts for each activity group is the value we use for each $c_{k,I}$ (see Appendix A for values). Women

appeared to underreport, compared to men, so our estimates for female contacts from the data might be too low. The proportion of people in each activity group is not evenly distributed within (e.g. there are more people in $c_{k,i=2}$ and $c_{k,i=3}$ than the other activity groups) or between sexes (e.g. there proportion of men in $c_{1,i=1}$ is less than the proportion of women in $c_{2,i=1}$). These proportions are reflected in our initial conditions and do not change over time.

Actual number of sexual acts would provide a better estimate for this parameter but that is a difficult number to recall for the length of time in which we were interested. This level of detail is unlikely to be reliable in any population, and especially over a time period as long as six months. Therefore, like Garnett (1999), we use number of sex partners/unit of time instead of number of contacts. This means we assumed one contact per partnership, an assumption that likely frequently resulted in underestimates of the total number of sex acts per individual.

Unfortunately, it is rarely possible to obtain accurate estimates of sexual acts over long periods of time. To estimate the total number of sex acts, one must focus data collection on a small timeframe (e.g. one week or one month) but this generally sacrifices depth for breadth. High-resolution data for a short period of time might not be typical of a long-term pattern. This is especially likely to be true among the Kaokoland pastoralists and other similar semi-nomadic groups where subsistence behavior and seasonal variation can influence access to partners. Because the goal of the model is to understand long-term, endemic patterns of gonorrhea transmission, we prioritized simplified, broader estimates of sexual contact patterns over high resolution, narrow ones in our empirical dataset and parameter definitions.

Preferred mixing (r_i): This parameter estimates the proportion of contacts that are reserved for members of one's own activity group (Jacquez, et al., 1988). Preferred mixing allows us to explore the power of non-random contacts on GC transmission but does not require equal numbers of contacts between men and women (see Appendix A for $c_{k,i}$ and r_i values). The preferred mixing parameter also allows for different proportions of non-random mixing across activity groups, rather than the more simplistic assumption that everyone in the population assorts to the same degree (Hethcote & Yorke, 1984).

We were able to estimate r_i for the Kaokoland population from data we collected about recent sexual partnerships. Our sexual contact dataset includes the names of all contacts (n=1094) reported by every study participant (n=445). Most of these contacts were not participants and we have no further data for them. Many, however, were participants in our study (n=77); that means that for all partnerships between two study participants we know each of their total number of partners (c) within the past six months.

Using these partnerships, we built a matrix of these contacts (male-to-female by female-to-male) and calculated how many of the partnerships were between people of the same activity group. We compared our observed matrix to a matrix of expected values (i.e. a matrix of partnerships where the contact structure is completely random and people do not reserve any contacts for members of their own activity group). The expected-values matrix has a X^2 of 0; X^2 = 13.67 for the observed matrix. We calculated how much we needed to decrease the diagonals of the matrix (i.e. the cells that represent the number of contact between men and women of the same activity group) to make the observed matrix X^2 equal the expected values X^2 so that the resulting matrix would have lowest X^2 possible. These contacts represent the proportion of contacts that are reserved for members of one's own activity group and are not selected at random. These values are our parameter estimates for r_i.

Disease parameters

Transmission probability of symptomatic and asymptomatic high-level infections (β^h_k): This parameter (β) is the mean probability that a single contact with a person infected with a high-level infection will lead to a new infection. We cannot estimate this directly from our dataset because we do not have accurate estimates of the number of sex acts per person or the GC statuses of participants' contacts. However, values for gonorrhea transmission in the literature estimate male-to-female transmission at 0.5 (Platt, Rice, & McCormack, 1983) and female-to-male at 0.2-0.5 (Hooper et al., 1978). Garnett et al. (1999) could not maintain endemic GC in their model to match levels seen in Newark without increasing these probabilities to 0.8 and 0.6, respectively. Though they were concerned that these values were unreasonably high, we believe that these higher values may be close to reality for many populations. Platt et al. (1983) and Hooper et al.'s (1978) empirically derived estimates were based on culture detection methods, which are very insensitive compared to molecular assays that are now the standard. Additionally, in Kaokoland, GC transmission—especially male-to-female—is likely to be at the high end of realistic estimates because of the frequency of partner exchange, minimal condom use, and a preference for dry sex. Thus, we begin with the assumption that appropriate estimates for disease transmission lie somewhere in this higher range.

Transmission probability of asymptomatic low-level infections (β^l_k): We assume that low-level infections have a lower transmission probability than high-level infections. However, because our empirical work in Kaokoland was the first to report on the observance of high prevalence of low-level infections among an undertreated population, there are no reliable estimates for this parameter. We use our model to estimate values for low-level transmission probability.

Recovery from symptomatic high-level infection (σ_k): In the Kaokoland dataset, the vast majority of participants who reported having had symptoms in the prior six months sought treatment at a clinic. Only symptomatic people receive treatment because local STD care is through syndromic management; no screening or partner notification program exists. Thus, individuals in our model recover from symptomatic infection faster than they do from other categories of infection because they received antibiotics.

We identified participants who reported having had GC symptoms within the past six months (Chapter 3 of this dissertation). From these individuals' data, we estimated the number of days between symptom recognition and travel to the clinic. We separated this parameter by sex, because women in our study typically took longer to seek treatment. We estimated a duration average of 11.7 for men and 14.5 for women. These numbers are roughly estimated because people in our study population do not keep a specific record of dates. It takes several days after treatment begins (i.e. day of clinic attendance) for the antibiotics to completely clear the infection and we also found that there was variability in which antibiotics are dispensed during the 2009 data collection period (Hazel, unpublished). Therefore, our estimates for recovery from symptomatic high-level infection (σ_k) are likely low and oversimplified, but offer a starting point for calibrating the model.

Rate of movement from $Y^{ah}_{ki} \rightarrow Y^{al}_{ki}$ (ψ_k): This parameter estimates the rate at which asymptomatic high-level infections diminish into low-level infections. Like β^{l}_{ki}, this value is unknown because asymptomatic low-level infections had not been reported prior to the Kaokoland study. It has been assumed that untreated people are infectious for six months (Garnett et al., 1999), but this estimate was derived when culture was still the diagnostic gold standard. Low-level infections were not likely to be detectable and so previous values given for duration of infectiousness of untreated infections might actually be an estimate of

how long it takes for an untreated infection to diminish below the ID_{50} dose. We use our model to test this assumption.

Recovery from asymptomatic infection (γ_k): This is the rate at which low-level infections diminish to the point of complete resolution and an infected person becomes susceptible again. Because this parameter is part of movement in and out of the low-level infectious state, we again do not have reliable estimates for this parameter. We use our model to explore reasonable values.

Proportion of high concentration infections that are asymptomatic (θ_k): Very few men and even fewer women with high-level GC infections in the Kaokoland study reported symptoms. Given the lack of screening and partner notification programs in Kaokoland, people who do not perceive symptoms do not receive antibiotic therapy. These people stay infected and infectious longer than people who receive antibiotic treatment. The proportion of asymptomatic—and therefore untreated—individuals in a population will likely have a strong influence on transmission dynamics and endemic levels of GC.

All participants in the empirical study were asked whether they were currently experiencing a) abnormal discharge or b) dysuria (i.e. pain or itching during urination). Answers to these two questions were tightly correlated (Chapter 3 of this dissertation), so the variables were aggregated. Among participants with high-level GC infections, 78% of males and 95% of females were asymptomatic; this is a much higher rate of asymptomatic infection than usually reported in the literature, but studies among similarly rural (Wilkinson et al., 1999) and resource poor populations (Detels et al., 2011) find similarly low rates of symptom reporting.

Results & Discussion

Sensitivity analysis

We tested the sensitivity of the model to small increases in each parameter value (table 4.1). We individually increased each parameter by 1% and recorded the total number of males and females in each infection status at the end of each run. We calculated the percent difference between each of these runs relative to the base run and identified the parameter changes that caused the largest percent differences for each outcome.

We identified parameters that have the largest impact on endemic disease levels. A 1% increase in the proportion of high concentration, asymptomatic infections (θ_k) resulted in the largest shifts in endemic states in the model. For example, a 1% change in θ_1 resulted in a 4% increase in male symptomatic high-level infections. Based on local conditions, biological characteristics of individual epidemics, and accessibility of treatment, we expect values for θ_k to differ for different populations. Populations whose healthcare system has screening and partner notification programs might experience decreases in asymptomatic and untreated cases, resulting in dramatically different proportions of asymptomatic cases. Thus, the responsiveness of the model to θ_k seems reasonable.

With the exception of θ_1, no 1% increase in parameter value resulted in > a 1% change in outcome. The most impactful parameters, other than θ_k include transmission probabilities and values for moving in and out of the low-level infectious state.

Calibration and validation

We explored several key questions with this model. First we addressed the issue of how contact structure—or what we know of it—in Kaokoland differs in a society where concurrency and partner exchange are normative practices, not the behavior of only a small

subpopulation. Second, we revisit Garnett et al.'s (1999) conclusion that transmission probabilities over 0.5 are unlikely. Finally, we explored parameter values associated with the low-level infectious state and asked whether adding this disease status has a meaningful impact on endemic GC levels in this model.

Question 1: How does contact structure affect GC prevalence in Kaokoland? Does using a preferred mixing equation affect the outcome of endemic gonorrhea? We ran our model with r_i values that reflect the actual preferences for within-group contacts by each activity group from our dataset (calculations described above, final values in Appendix A). We then compared that run to one where all parameter values were the same except that r_i =0 for all activity groups (contact structure is completely random). When the contact structure is random, gonorrhea prevalence decreases (figure 4.3), albeit insignificantly (X^2=0.03, p=0.9).

This result seems counterintuitive. Randomness in the contact structure (i.e. individuals across activity groups contacting each other proportionally) increases disease prevalence, because high activity individuals are mixing with proportional likelihood with low activity individuals. Non-random mixing expressions were developed, in part, to represent the real-world complexity of network structures and reflect actual disparities in disease risk. However, in our model, we see very little difference between running the model with random and non-random contact. When we ran the model with complete self-preference (all r_i=1), our outcomes do not differ from the outcomes we get from using our empirically derived values (figure 4.3). In our sensitivity analyses, changes in r_i values did not yield large changes in endemic outcomes (table 4.1), which is consistent with these results.

In Kaokoland, where low-level GC infection prevalence is relatively high, and partner concurrency is common at all age groups, risk is spread equally across demographic characteristics (Chapter 3). (Women have higher prevalence but are also less likely to seek

treatment.) It may be that there is a prevalence threshold, beyond which, contact structure matters less, because so many people are infected. It may also be that contact rates in Kaokoland are relatively high for most activity groups (with the exception of lowest activity group ($c_{k,i=4}$<1 for both men and women), and this diminishes the impact of contact structure on disease risk across the population. Preferential mixing differs among activity groups: the highest activity group has the highest in-group preference ($r_{i=1}$=0.71), while there was relatively low in-group preference among the second highest activity group ($r_{i=2}$=0.17).

Question 2: Are male-to-female transmission probabilities higher than previously estimated? Regarding our parameters for high-level transmission probability, we were able to mimic endemic levels in Kaokoland with a reduced female-to-male transmission of β^h_2=0.5, but not when we lowered male-to-female transmission below Garnett et al.'s value of β^h_1=0.8 (figure 4.5). We used the model to estimate transmission probabilities for the low-level infected status as well. This is the first time this status has been presented in a model of gonorrhea transmission, so we used our calibration process to define reasonable estimates. Our final estimates for low-level transmission probabilities where β^l_1=0.4 and β^l_2=0.1.

When we ran the model with our starting estimates—Garnett et al's (1999) final values and β^l_1=0.2, β^l_2=0.1—we found that a) low-level prevalence was too low and b) high-level prevalence was too high (run 1, figure 4.4). We compared this outcome to prevalence when we run the model with the high-level transmission probabilities that were estimated by Hooper et al (1978) and Platt et al (1983). High-level prevalence (run 2, figure 4.4) decreased far below Kaokoland levels. Even when we keep values for β^h at Garnett et al.'s high values, if we do not increase low-level transmission as well, we cannot achieve prevalence that approaches Kaokoland levels (run 3, figure 4.4).

In runs 4-7 (figure 4.4), we attempted to refine our β values to find the estimates that lead to the closest match to the Kaokoland 2009 conditions. A β^h_1 value of less than 0.8 reduced female prevalence below real values. β^h_2 produces outcomes that closely match our empirical findings at a value of 0.5, when coupled with low-level transmission parameters.

Our starting values for male-to-female low-level transmission (β^l_1) was too low, but β^l_2 remained at 0.1. Increasing β^l_2 resulted in decreased prevalence, possibly because it resulted in more men remaining in the low-level infection status longer, and not returning to susceptibility for high-level infections. Alternatively, we had to increase our estimate for β^l_1 to achieve the low-level prevalence we observed in Kaokoland in 2009. Our final estimate for male-to-female transmission probability is (β^l_1=0.4).

This result suggests that differences in transmission risk between men and women persist among diminishing, lower transmissibility infections, which might help explain the greater prevalence of low-level infections among women in Kaokoland. This result also suggests that the β values estimated by Garnett et al. might not be unrealistically high. Some discussion of the existing empirical evidence for transmission probabilities is helpful here. These studies were conducted when the gold standard for GC diagnosis was culture (Hooper et al., 1978; Platt et al., 1983). Culture has largely been replaced by molecular techniques (e.g. our protocol for GC diagnosis in the empirical Kaokoland study), which are more sensitive and can detect GC DNA at much lower quantities. Therefore, it is likely that many cases were not detected in those early studies, reducing the transmission probabilities that they generated.

Hooper et al. also found that female-to-male transmission probability differed between two different demographic groups in their study, indicating that transmission probabilities are variable. Thus, it is also possible that among some high activity populations—especially

ones with high levels of partner exchange (Fethers, et al., 2008), low rates of condom use, and a preference for dry sex (Beksinska, et al., 1999)—transmission probabilities for both sexes are higher than previously estimated.

Our results indicate, not only that transmission probability for gonorrhea is greater than previously estimated, but also that it is context dependent. We do not assume that our estimates are universally appropriate; transmission probability is probably best represented by some range. The actually probability is some value in that range and is dependent upon many factors (e.g. bacterial load, infection duration, various behavioral characteristics). The parameters we provide here represent four means along a continuum of probability from our empirical work in Kaokoland.

Question 3: What are the transmission characteristics of low-level infection status? The high prevalence of low-level GC infections in Kaokoland (42% of men, 52% of women) motivated the construction of this model to define associated transmission characteristics of GC and explore its affect on overall prevalence in Kaokoland or other similarly undertreated populations with high endemic GC levels.

Our model output matched Kaokoland prevalence when we set parameter values where a) women were infectious at the asymptomatic, high-level stage longer than men and b) both men (γ_1=9 months) and women's (γ_2=12 months) asymptomatic high-level infections lasted longer than the six months typically estimated for untreated, asymptomatic infection. Also, women (ψ_2=9 months) remained in the low-level stage longer than men (ψ_1=7 months) before returning to susceptible status.

These numbers are far beyond estimates previously generated, but there are very few estimates from empirical data of the natural history of gonococcal infection, and none that were obtained in the absence of treatment where highly sensitive diagnostics were used to

diagnose and quantitate GC infections. A study of untreated, incarcerated women found that after four months of monitoring, less than half the participants became culture negative (Mahoney, et al., 1942). That means that infection duration is at least four months, but is likely longer. Most aspects of the study design suggest that disease duration was heavily underestimated. First, the study recruited already infected, symptomatic participants—days of infectiousness were lost at the beginning of the infection. Second, participants' GC was considered resolved when cultures became negative, even though all "cleared" participants still reported having symptoms—this insensitive diagnostic technique was likely not catching many infections.

There are also no reliable data for untreated GC duration for men. Handsfield et al. (1974) tracked asymptomatically infected men, but they were treated by day 165; this study demonstrates that infections last *at least* that long.

Most model-based research uses a six-month duration, which is derived from an attempt to find the duration of infection that would fit a population where the proportion of cases that are asymptomatic is 40-60% (Handsfield et al., 1974; Potterat, et al., 1983). These studies were conducted among urban populations in a clinic setting so we do not expect their proportions for asymptomatic cases to match the proportions found in highly remote populations.

Our estimates need to be backed up by other empirically-backed models and direct measures, but they do shed light on aspects of gonorrhea epidemiology that are very difficult to study—especially the impact of asymptomatic disease on driving transmission, particularly where gonorrhea infections are rarely treated and run a complete life course in the human hosts. These are the circumstances under which some research has suggested that immunity plays the strongest role (Plummer et al., 1989).

Question 4: What role do low-level infections play in overall gonorrhea prevalence?

Because low-level infections were highly prevalent among men and women—there were more men and women with these infections than there are GC negative people in our sample—we presumed they played an important role in driving overall transmission. In other words, we predicted that if we removed this compartment from our model, we would see a significant drop off in overall prevalence. However, we found that prevalence stayed the same but was comprised entirely of high-level infections, instead of mostly low-level infections.

After calibrating the model to match Kaokoland prevalence patterns (Appendix A), we ran the model with the same conditions, with the exception that people moved directly from being asymptomatic high-level to susceptible (figure 4.6). In these runs, overall prevalence remained the same, but the majority of these were high-level asymptomatic infections. Thus, when we remove the stage of low-level infections from the model, we see endemic levels of asymptomatic, high-level infections that are more prevalent than susceptibles (figure 4.7). Because high-level infections have a shorter duration—an infected person does not spend several additional months in the low-level infectious stage—individuals become susceptible to a new infection sooner. People's individual infections are shorter, but reinfection frequency increases and people spend more time in a state of high infectiousness. Given the high percentage of asymptomatic (i.e. untreated) cases in Kaokoland, this pattern would yield, not just more reinfections, but more opportunities for a single GC exposure to become severe (e.g. disseminated disease, pelvic inflammatory disease). Yet, this is not what we see in Kaokoland. Our model illustrates the impact of low-level infections on the prevalence of high-level infections and contributes to a long-held but patchy discussion on the importance of immunity in GC epidemiology.

Studies of similarly high-activity, low treatment populations do not report prevalences as high as we found in Kaokoland (Rahman et al., 2000; van den Hoek et al., 2001). Our model suggests that, without the added stage of low-level infection, prevalence of high-level infections in Kaokoland (and, presumably similar populations) would be much higher. Instead, we argue that high GC prevalence in undertreated populations is mostly comprised of long-duration, low-level infections, which have the effect of decreasing the number of opportunities an individual faces to become reinfected.

Model limitations and future directions

There are several limitations to conclusions we can draw from the key insights of our model. First, it is tempting to draw conclusions about immunity to GC from our model. These results and our empirical data from Kaokoland do not measure immunity but are consistent with previous observations of an incomplete immune response to gonorrhea infections. Plummer et al (1989) show that immunity is strain-specific and incomplete. Female sex workers were significantly less likely to be reinfected with the same strain of gonorrhea and the longer a woman engaged in sex work the less frequently she was infected. It has also been proposed that untreated infections will have a stronger immune response than those that resolve more quickly as a result of antibiotic intervention (Handsfield et al. 1974). Future work on this model would incorporate a compartment for partial immunity. This would be an important advancement on the model because it would allow us to make predictions about how specific intervention programs will affect population-wide acquired immunity. In a resource poor setting, where treatment is limited and erratic, immunity to disease can play a very important, protective role.

Also, while our model allows for low-level infections to generate from a) exposure from a contact with another low-level infection and b) a diminished asymptomatic high-level

infection, we do not allow for a new high-level infection to result from exposure to a low-level infection. However, this may be an important component of GC transmission, happening when a person with a low-level infection has sexual contact with a person who has never been exposed to that strain before. Since age-discordant couples are common in Kaokoland (Chapter 2 of this dissertation), it is very likely that many GC cases among the youngest adults were the result of contact with an older adult who has a low-level infection. It is necessary to further explore if these contacts are important for maintaining the 16% prevalence for high-level infections in Kaokoland.

Conclusions

We presented a new model of gonorrhea transmission that is the first to include a compartment for reduced-infectiousness disease status (figure 4.2, Appendix A). By supporting this model with a) extensive empirical, cross-sectional data about contact structure and b) sensitive, quantitative diagnostic GC assays, we were able to interrogate old assumptions about transmission probabilities and infection duration. In our model, non-random contact structure increased overall transmission, primarily by increasing the number of infectious men. Our model supports the estimates generated by previous modeling efforts (Garnett et al., 1999) for the transmissibility of high-level cases, further suggesting that the empirical estimates are not reliable. Finally, we described the transmission and duration of a new infectious stage of gonorrhea that is the result of untreated, unresolved asymptomatic infection. These explorations provide corroborating insights into the importance of immunity in shaping patterns of endemic GC.

References

Beksinska, M. E., Rees, H. V., Kleinschmidt, I., & McIntyre, J. (1999). The practice and prevalence of dry sex among men and women in South Africa: a risk factor for sexually transmitted infections? *Sexually Transmitted Infections*, *75*(3), 178–180

Detels, R., Green, A. M., Klausner, J. D., Katzenstein, D., Gaydos, C., Handsfield, H. H., Pequegnat, W., et al. (2011). The incidence and correlates of symptomatic and asymptomatic Chlamydia trachomatis and Neisseria gonorrhoeae infections in selected populations in five countries. *Sexually Transmitted Diseases*, *38*(6), 503–509

Fethers, K. a, Fairley, C. K., Hocking, J. S., Gurrin, L. C., & Bradshaw, C. S. (2008). Sexual risk factors and bacterial vaginosis: a systematic review and meta-analysis. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *47*(11), 1426–35

Fratkin, E. M., & Roth, E. A. (2004). As Pastoralists Settle: Social, Health, and Economic Consequences of Pastoral Sedentarization in Marsabit District, Kenya. New York: Kluwer Academic.

Garnett, G. P. G. P., & Anderson, R. M. (1993). Contact tracing and the estimation of sexual mixing patterns: The epidemiology of gonococcal infections. *Sexually Transmitted Diseases*, *20*(4), 181–191.

Garnett, G. P., Mertz, K. J., Finelli, L., Levine, W. C., & St. Louis, M. E. (1999). The Transmission Dynamics of Gonorrhoea: Modelling the Reported Behaviour of Infected Patients from Newark, New Jersey. *Philosophical Transactions: Biological Sciences*, *354*(1384), 787–797.

Handsfield, H. H., Lipman, T. O., Harnisch, J. P., Tronca, E., & Holmes, K. K. (1974). Asymptomatic gonorrhea in men: Diagnosis, natural course, prevalence and significance. *The New England Journal of Medicine*, *290*(3), 117–123.

Hethcote, H.W., & Yorke, J. A. (1984). Gonorrhea transmission dynamics and control. *Lecture notes in biomathematics* (no. 56.). Berlin: Springer.

Hethcote, Herbert W. (1976). Qualitative analyses of communicable disease models. *Mathematical Biosciences*, *28*(3-4), 335–356

Hooper, R. R., Reynolds, G. H., Jones, O. G., Zaidi, A., Wiesner, P. J., Latimer, K. P., Lester, A., et al. (1978). Cohort study of venereal disease, I: The risk of gonorrhea transmission from infected women to men. *American Journal of Epidemiology*, *108*(2), 136–144

Jacquez, J. a., Simon, C. P., Koopman, J., Sattenspiel, L., & Perry, T. (1988). Modeling and analyzing HIV transmission: The effect of contact patterns. *Mathematical Biosciences*, *92*(2), 119–199

Mahoney, J. F., Van Slyke, J., Wolcott, R. R., Thayer, J. D., & Nimelman, A. (1942). Culture studies in chronic gonorrhea in women. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases*, *26*, 38–47

Nold, A. (1979). The infectee number at equilibrium for a communicable disease. *Mathematical Biosciences*, *46*(1-2), 131–138

Pettifor, A., Walsh, J., Wilkins, V., & Raghunathan, P. (1999). How effective is syndromic management of STDs? *Sexually Transmitted Diseases*, *27*(7), 371–385

Platt, R., Rice, P. a, & McCormack, W. M. (1983). Risk of acquiring gonorrhea and prevalence of abnormal adnexal findings among women recently exposed to gonorrhea. *JAMA : the journal of the American Medical Association*, *250*(23), 3205–3209

Plummer, F. A., Simonsen, J. N., Chubb, H., Slaney, L., Kimata, J., Bosire, M., Ndinya-Achola, J. O., et al. (1989). Epidemiologic evidence for the development of serovar-specific immunity after gonococcal infection. *The Journal of Clinical Investigation*, *83*(5), 1472–1476

Potterat, J. J., Woodhouse, D. E., I, P. C., Markewich, G. S., & Fogle, J. S. (1983). Women contacts of men with gonorrhea: Case-finding yields. *Sexually Transmitted Diseases*, *10*(1), 29–32

Rahman, M., Alam, A., Nessa, K., Nahar, S., Datta, D., Alam, S., Mian, R. A., et al. (2000). Etiology of sexually transmitted infections among street-based female sex workers in Dhaka, Bangladesh. *Journal of Clinical Microbiology*, *38*(3), 1244–1246

Rothenberg, R.B. (1983). The geography of gonorrhea: Empirical demonstration of core group transmission. *American Journal of Epidemiology*, *117*(6), 688–694

Rothenberg, Richard B, Potterat, J. J., & Woodhouse, D. E. (1996). Personal risk taking and the spread of disease : Beyond core groups. *The Journal of Infectious Diseases*, *174*(Suppl 2), S144–S149

Scelza, B. A. (2012). Himba fertility and child mortality. http://www.philosophy.dept.shef.ac.uk/culture&mind/people/scelzab2/

Simon, C. P., & Jacquez, J. A. (1992). Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations. *SIAM Journal of Applied Mathematics*, *52*(2), 541–576

Talavera, P. (2002). Challenging the Namibian Perception of Sexuality: A Case Study of the Ovahimba and Ovaherero Culturo-Sexual Models in Kunene North in an HIV/AIDS Context (p. 111). Windhoek: Gamsberg Macmillan.

Thomas, J. C., & Tucker, M. J. (1996). The development and use of the concept of a sexually transmitted disease core. *The Journal of Infectious Diseases*, *174*(Suppl 2), S134–S143

Todar, K. (2009). Gonorrhea. *The Microbial World*.

WHO. (2007). Training Modules for the Syndromatic Management of Sexually Transmitted Infections, 2nd Ed.

Wilkinson, D., Abdool Karim, S., Harrison, A., Lurie, M., Colvin, M., Connolly, M., & Sturm, A. (1999). Unrecognized sexually transmitted infections in rural South African women: A hidden epidemic. *Bulletin of the World Health Organization*, *77*(1), 22–28.

Yorke, J. A., Hethcote, H. W., & Nold, A. (1978). Dynamics and control of the transmission of gonorrhea. *Sexually Transmitted Diseases*, *5*, 51–56

van den Hoek, A., Yuliang, F., Dukers, N. H., Zhiheng, C., Jiangting, F., Lina, Z., & Xiuxing, Z. (2001). High prevalence of syphilis and other sexually transmitted diseases among sex workers in China: potential for fast spread of HIV. *AIDS (London, England)*, *15*(6), 753–759

Table 4.1: Sensitivity analysis of all parameters in a model of gonorrhea transmission in Kaokoland, Namibia, 2009

				Susceptible men	Susceptible women	Symptomatic, High-level men	Symptomatic, High-level women	Asymptomatic, High-level men	Asymptomatic, High-level women	Asymptomatic, Low-level men	Asymptomatic, Low-level women
Baseline outcome values*				**488.18562**	**551.40615**	**4.14414**	**0.80775**	**224.58976**	**194.02916**	**283.08049**	**253.75694**
Parameter	**Starting value**	**+ 1%**									
r1**	0.71	0.7171	**n**	487.13216	550.33797	4.15267	0.80967	225.05203	194.49120	283.66314	254.36116
			% difference from baseline##	-0.00216	**-0.00194**	0.00206	0.00238	0.00206	0.00238	**0.00206**	0.00238
r2	0.17	0.1717		488.18234	551.35151	4.14417	0.80785	224.59120	194.05280	283.08229	253.78784
				-0.00001	-0.00010	0.00001	0.00012	0.00001	0.00012	0.00001	0.00012
r3	0.27	0.2727		488.45319	551.57108	4.14198	0.80745	224.47236	193.95784	282.93247	253.66362
				0.00055	0.00030	-0.00052	-0.00037	-0.00052	-0.00037	-0.00052	-0.00037
r4	0.5	0.505		488.47374	552.46203	4.14181	0.80585	224.46321	193.57228	282.92124	253.15985
				0.00059	**0.00191**	-0.00056	-0.00235	-0.00056	-0.00235	-0.00056	-0.00235
m	0.0001	0.000101		488.23670	551.45787	4.14483	0.80787	224.58926	194.02642	283.02922	253.70784
				0.00010	0.00009	0.00016	0.00015	0.00000	-0.00001	-0.00018	-0.00019
c11#**	0.074	0.07474		487.72613	550.76732	4.14786	0.80890	224.79138	194.30547	283.33463	254.11830
				-0.00094	-0.00116	0.00090	0.00142	0.00090	0.00142	0.00090	0.00142
c12	0.038	0.03838		487.76312	551.42929	4.14756	0.80771	224.77514	194.01914	283.31417	253.74386
				-0.00087	0.00004	0.00083	-0.00005	0.00083	-0.00005	0.00083	-0.00005
c13	0.0179	0.018079		487.21069	551.39424	4.15204	0.80777	225.01755	194.03431	283.61972	253.76369
				-0.00200	-0.00002	0.00190	0.00003	0.00190	0.00003	0.00190	0.00003
c14	0.0047	0.004747		487.91375	551.33265	4.14635	0.80788	224.70909	194.06099	283.23082	253.79848
				-0.00056	-0.00013	0.00053	0.00016	0.00053	0.00016	0.00053	0.00016
c21	0.0312	0.031512		487.51690	550.90785	4.14956	0.80864	224.88319	194.24469	283.45036	254.03882
				-0.00137	-0.00090	0.00131	0.00111	0.00131	0.00111	0.00131	0.00111
c22	0.0167	0.016867		488.16444	551.07922	4.14431	0.80834	224.59904	194.17056	283.09220	253.94189
				-0.00004	-0.00059	0.00004	0.00073	0.00004	0.00073	0.00004	0.00073
c23	0.0111	0.011211		488.08902	550.69570	4.14493	0.80903	224.63214	194.33644	283.13392	254.15884
				-0.00020	-0.00129	0.00019	0.00158	0.00019	0.00158	0.00019	0.00158
c24	0.0048	0.004848		488.20439	550.74775	4.14399	0.80893	224.58155	194.31399	283.07007	254.12933
				0.00004	-0.00119	-0.00004	0.00147	-0.00004	0.00147	-0.00004	0.00147
s1	0.0855	0.086355		488.21326	551.43049	4.10324	0.80768	224.59431	194.01345	283.08918	253.74838

Table 4.1 (continued): Sensitivity analysis of all parameters in a model of gonorrhea transmission in Kaokoland, Namibia, 2009

			0.00006	0.00004	-0.00987	-0.00008	0.00002	-0.00008	0.00003	-0.00003
s2	0.0707	0.071407	488.19141	551.41230	4.14407	0.79976	224.58602	194.02969	283.07849	253.75825
			0.00001	0.00001	-0.00002	**-0.00988**	-0.00002	0.00000	-0.00001	0.00001
g1	0.0055	0.005555	488.76918	550.76718	4.16310	0.81007	225.61725	194.58746	281.45047	253.83528
			0.00120	-0.00116	**0.00457**	0.00288	**0.00457**	0.00288	**-0.00576**	0.00031
g2	0.0055	0.005555	487.55847	552.09376	4.15444	0.81123	225.14771	194.86558	283.13938	252.22943
			-0.00128	0.00125	0.00248	0.00431	0.00248	0.00431	0.00021	**-0.00602**
bh1	0.8	0.808	487.26316	549.38672	4.15294	0.81258	225.06621	195.19058	283.51769	254.61012
			-0.00189	**-0.00366**	0.00212	**0.00599**	0.00212	**0.00599**	0.00154	**0.00336**
bh2	0.6	0.606	486.18846	550.56518	4.16564	0.80952	225.75481	194.45627	283.89109	254.16903
			-0.00409	-0.00153	**0.00519**	0.00220	**0.00519**	0.00220	**0.00286**	0.00162
bl1	0.2	0.202	488.34580	551.23072	4.14151	0.80686	224.44720	193.81595	283.06549	254.14647
			0.00033	-0.00032	-0.00063	-0.00110	-0.00063	-0.00110	-0.00005	0.00154
bl2	0.1	0.101	488.05369	551.55077	4.13986	0.80722	224.35756	193.90275	283.44890	253.73926
			-0.00027	0.00026	-0.00103	-0.00065	-0.00103	-0.00065	0.00130	-0.00007
th1	0.78	0.7878	486.31410	550.67571	3.97854	0.80923	225.77612	194.38485	283.93123	254.13021
			-0.00383	-0.00132	**-0.03996**	0.00183	**0.00528**	0.00183	**0.00301**	0.00147
th2	0.95	0.9595	487.7888	549.50991	4.15156	0.65171	224.99160	195.20170	283.47797	254.63668
			0.00124	**-0.00344**	0.00179	**-0.19317**	0.00179	**0.00604**	0.00140	**0.00347**
psi1	0.0055	0.005555	489.65766	552.71996	4.14831	0.80421	222.62887	193.17914	283.56516	253.29669
			0.00302	**0.00238**	0.00100	-0.00438	**-0.00873**	-0.00438	0.00171	-0.00181
psi2	0.0055	0.005555	489.57194	552.85543	4.12763	0.80821	223.69468	192.25287	282.60575	254.08348
			0.00284	**0.00263**	-0.00399	0.00058	-0.00399	**-0.00915**	-0.00168	0.00129

***:** These are the outcome values for endemic levels when the model is run with the initial parameter estimates.

****:** r_i where i=1-4. *i=1* is the highest activity group.

#: c_{ki} where *k=1-2*. *k*=1, men; *k=2*, women

##: Bolded values are the largest percent differences for each disease status

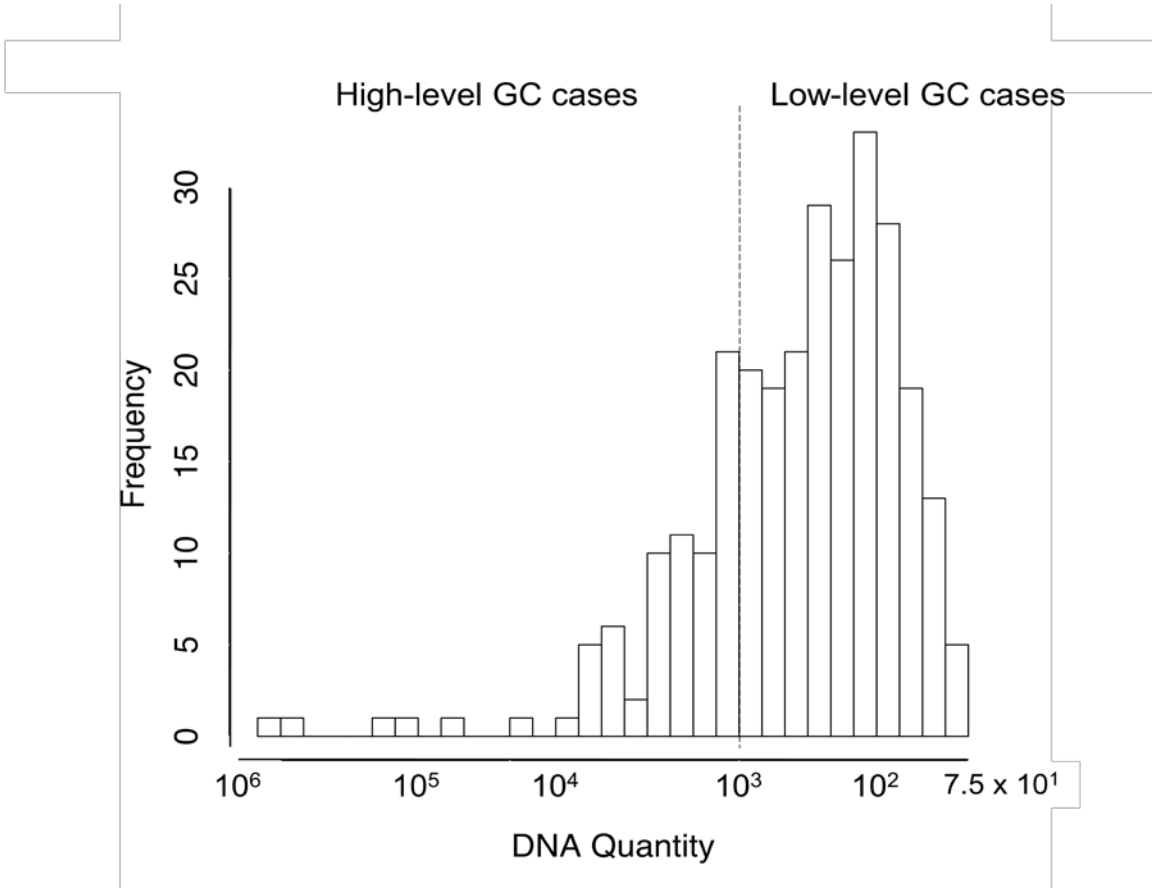


Figure 4.1: High-level/low-level dichotomy appears biologically meaningful. Quantities of 1000 copies or more were categorized as "high-level" infections, based on the definition of the ID_{50} dose for gonorrhea. This is very close to what appears to be a natural cut-off in our data.

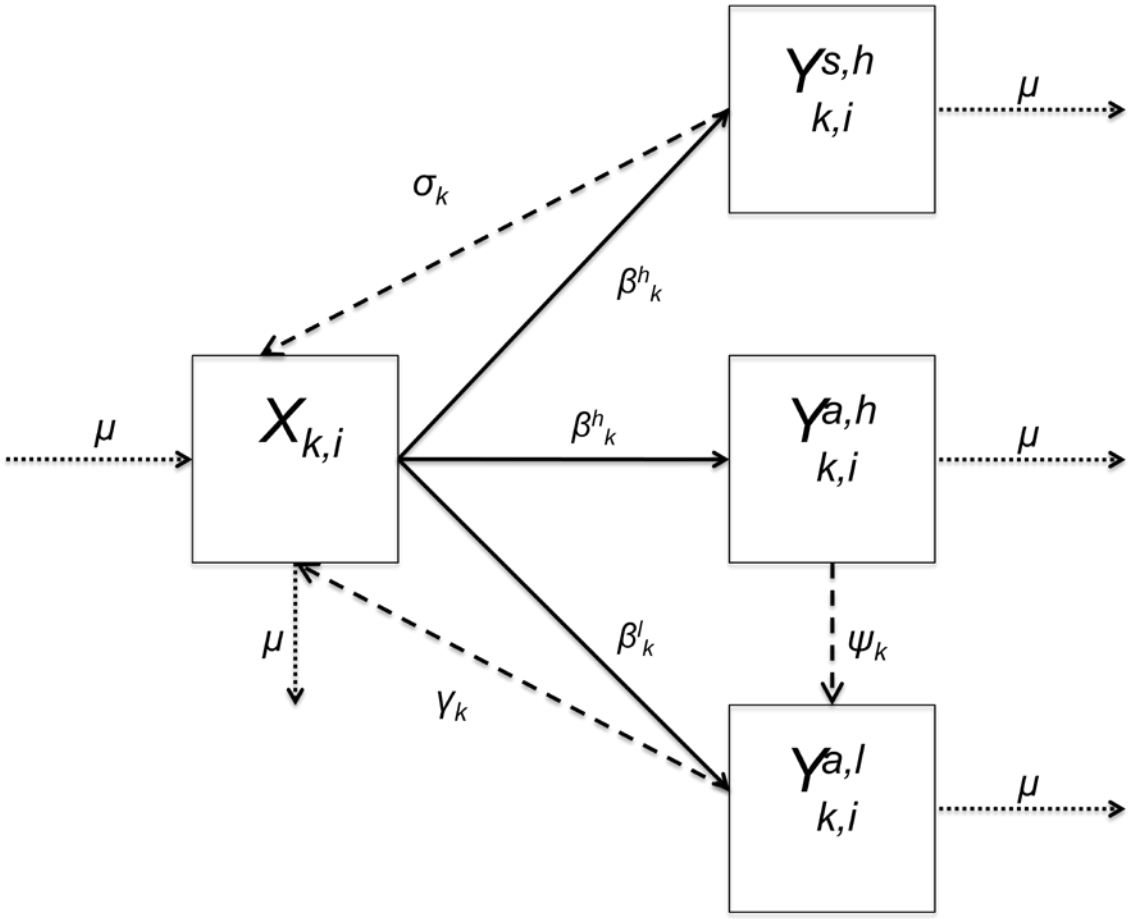


Figure 4.2: Diagram of the model of gonorrhea transmission in Kaokoland, Namibia 2009.

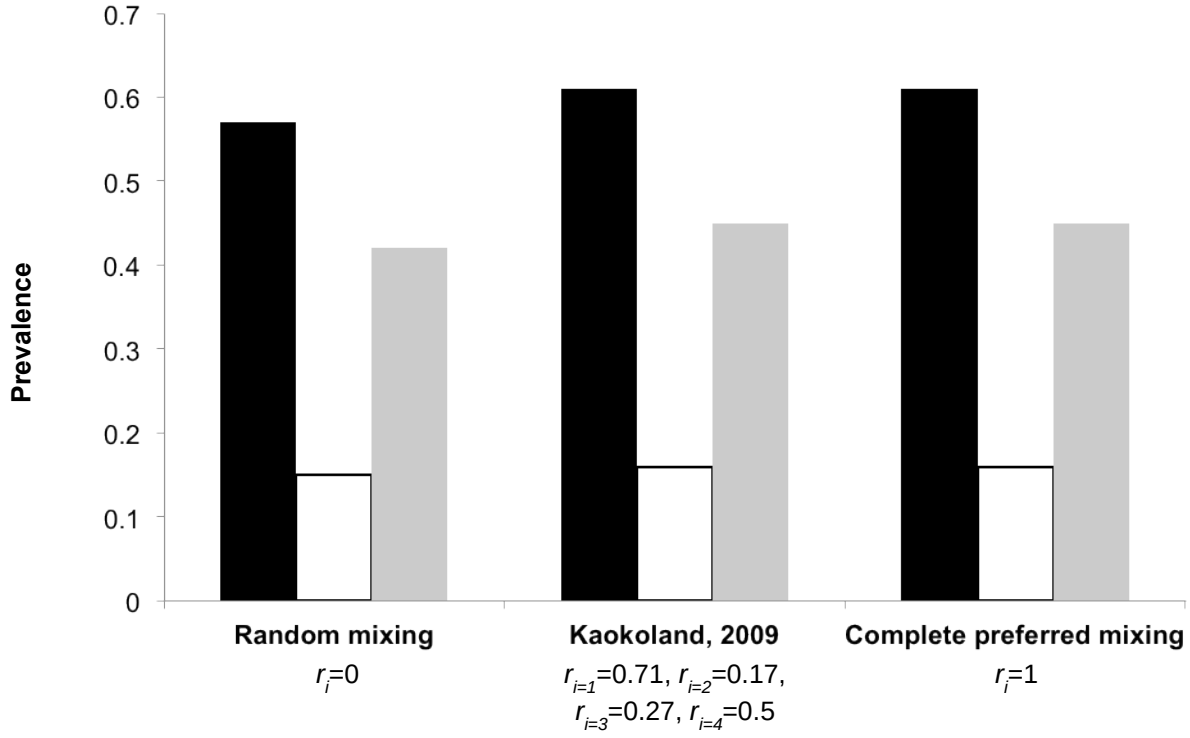
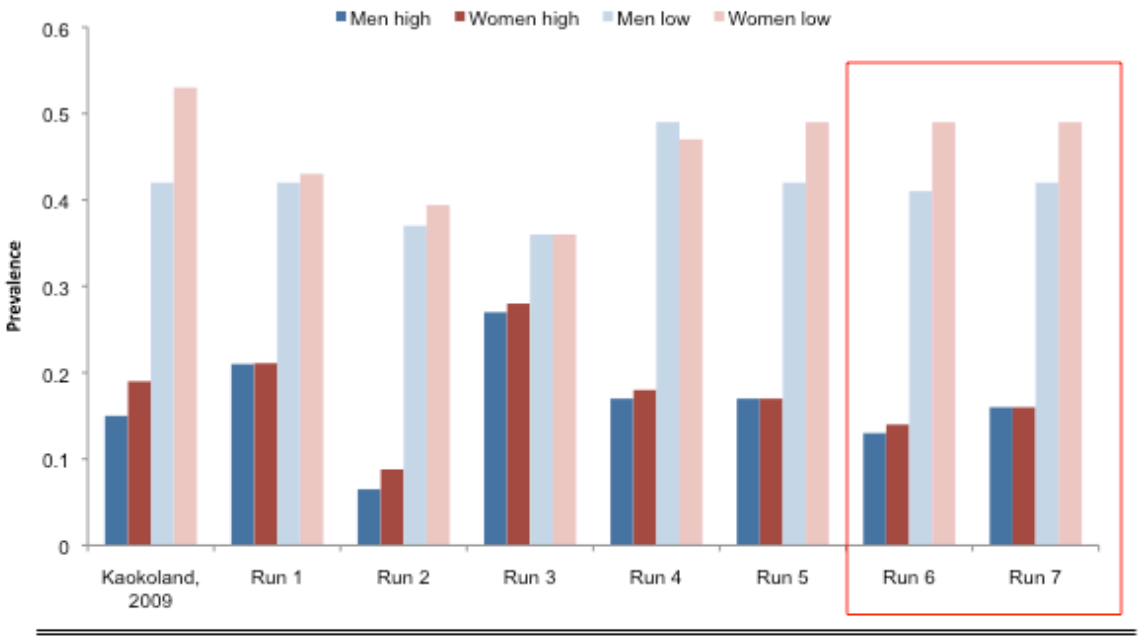


Figure 4.3: Prevalence is higher when contact structure is non-random. We ran the model a) where we assumed random mixing (r_i=0) and b) where we used our empirically derived estimates for r_i (see Appendix A for values). Trends were the same for men and women so prevalences are not reported by sex. Total prevalence (black) is slightly higher with preferred mixing than when contacts are random. This difference is due to a small increase in low-level infections (gray) with preferred mixing. High-level infections (white) do not change.



β^h_1	0.8	0.5	0.8	0.9	0.9	0.8	0.8
β^h_2	0.6	0.2	0.6	0.7	0.5	0.4	0.5
βI_1	0.2	0.2	0.0	0.3	0.4	0.4	0.4
β^l_2	0.1	0.1	0.0	0.2	0.1	0.1	0.1

Figure 4.4: Calibrating transmission probabilities for high- and low-level *Neisseria gonorrhea* infections. Transmission probabilities for high-level infections from our model are closer to Garnett et al (1999) estimates than those calculated in the literature. Low-level transmission probability estimates are lower than high-level estimates but maintain the same pattern of male-to-female being higher than female-to-male.

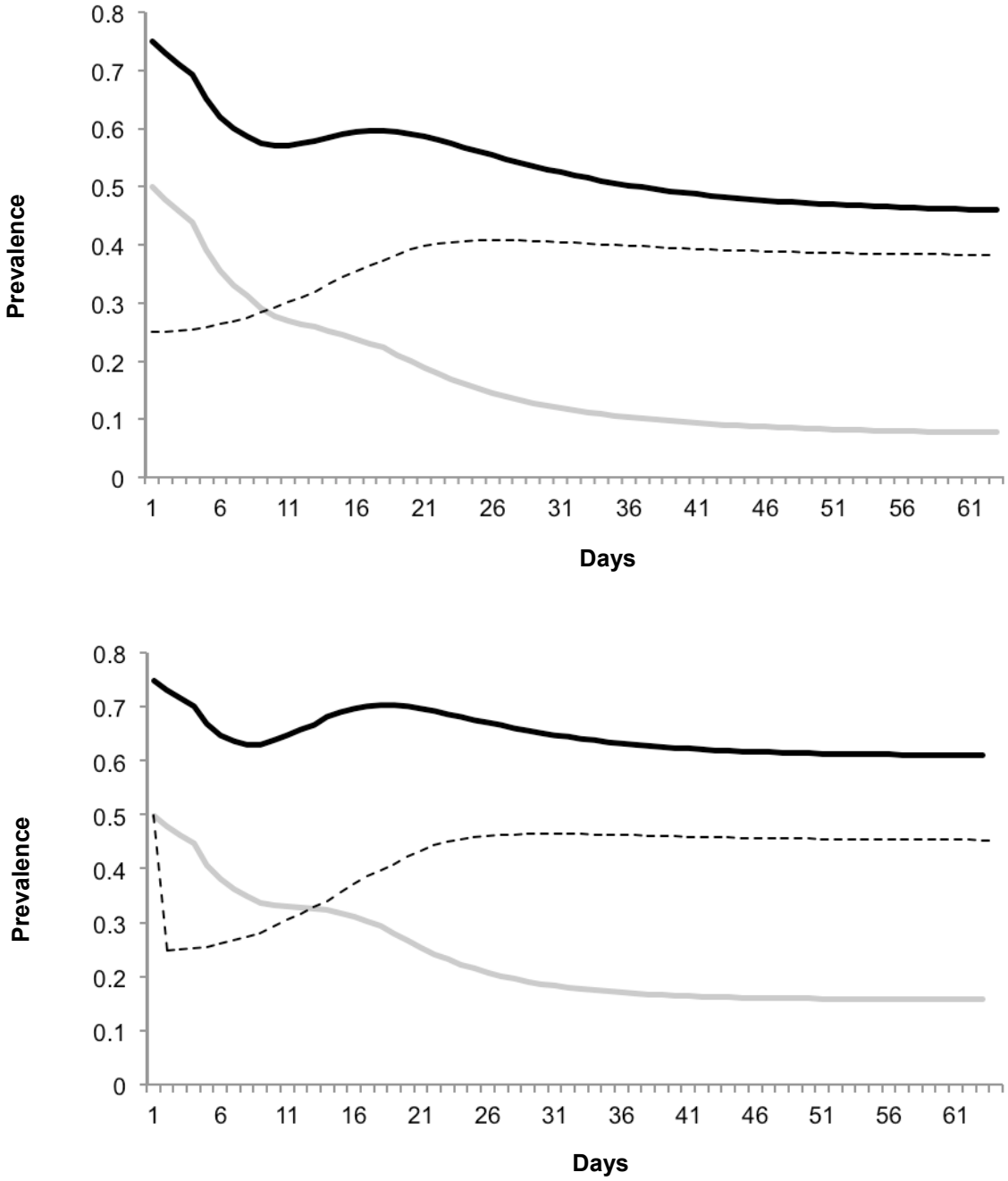


Figure 4.5: Transmission of high-level gonorrhea infections might be higher than previous empirical measures suggest. The top figure shows the prevalence outcomes when we run our model with high-level gonorrhea (GC) transmission probabilities as measured by Hooper et al. (1978) and Platt et al. (1983) (β^h_1=0.5; β^h_2=0.2). The bottom figure shows the prevalence when we increase transmission probabilities of high-level GC infections (β^h_1=0.8; β^h_2=0.5) Total prevalence (solid black) is below 50% with the empirical values and is over 60%—very close to total prevalence in Kaokoland in 2009—with the higher values. High-level GC prevalence (grey) is most impacted by these transmission differences, although low-level infections (dashed) also decrease slightly when high-level transmission values are low.

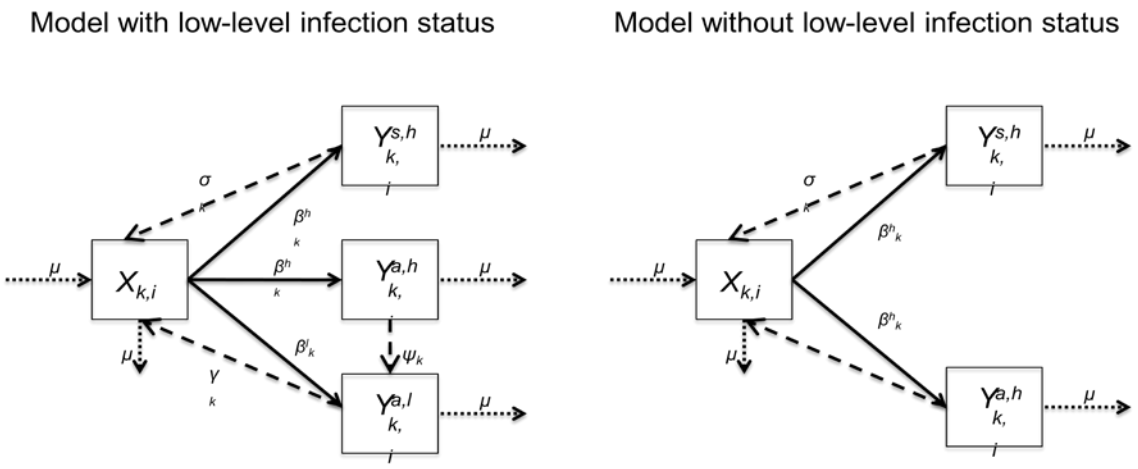


Figure 4.6: **A diagram of two model runs—with and without low-level infections.** To explore our question about the role of low-level infections in maintaining overall gonorrhea prevalence in Kaokoland, we compared outcomes from running our model (left) with outcomes from running the model after removing low-level infection status (right). When low-level status is removed, asymptomatic, high-level infections return directly to susceptible status.

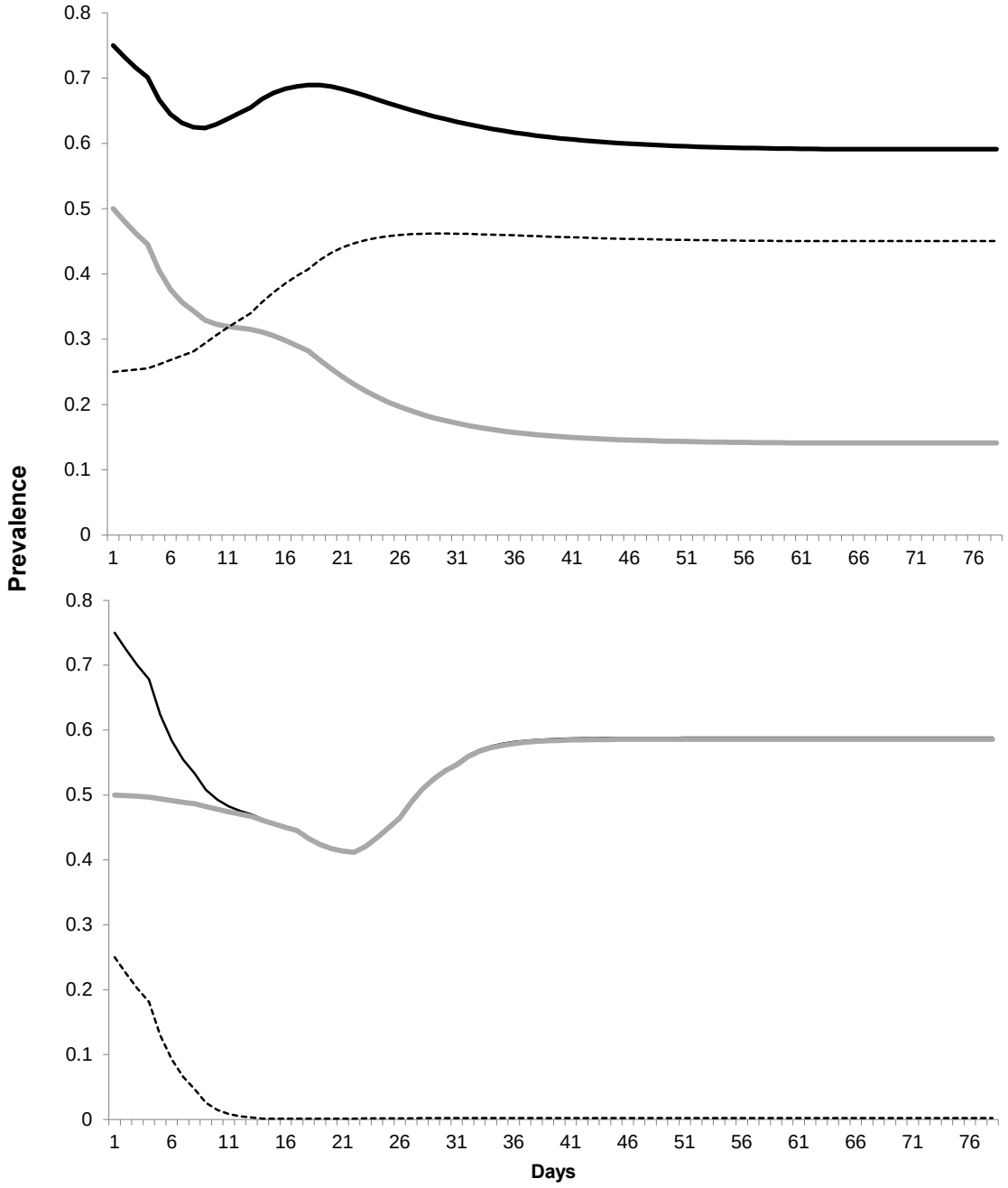


Figure 4.7: Removing low-level infections from the model increases high-level infections and does not reduce overall prevalence. The top figure shows prevalence patterns that match the Kaokoland conditions. Total prevalence (solid black) is just over 60% and is comprised of 48% low-level infections (dashed) and 16% symptomatic and asymptomatic high-level infections (gray). When low-level infections are removed (bottom), and die out from initial conditions, prevalence remains the same and is comprised almost entirely of asymptomatic high-level infections. Symptomatic infections increase as well but stay below 4% prevalence.

Appendix A

Section 1: The equations that define the model & table of parameter values

Susceptible

Full:

$$\frac{dX_{k,i}}{dt} = \mu N_{k,i} - \mu X_{k,i} - X_{k,i}c_{k,i}\left\{\begin{array}{l}\left[r_i\delta_{i,j=1} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right) + \beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=2} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right) + \beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \\ \left[r_i\delta_{i,j=3} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right) + \beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=4} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right) + \beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right]\end{array}\right\} + \sigma_k Y_{k,i}^{s,h} + \gamma_k Y_{k,i}^{a,l}$$

Short:

$$\frac{dX_{k,i}}{dt} = \mu N_{k,i} - \mu X_{k,i} - X_{k,i}c_{k,i}\left[\sum_h(\rho_{k',ij})\left(\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right) + \beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right)\right] + \sigma_k Y_{k,i}^{s,h} + \gamma_k Y_{k,i}^{a,l}$$

Symptomatic, high quantity

Full:

$$\frac{dY_{k,i}^{s,h}}{dt} = (1-\theta_k)X_{k,i}c_{k,i}\left\{\begin{array}{l}\left[r_i\delta_{i,j=1} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=2} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \\ \left[r_i\delta_{i,j=3} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=4} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right]\end{array}\right\} - (\mu+\sigma_k)Y_{k,i}^{s,h}$$

Short:

$$\frac{dY_{k,i}^{s,h}}{dt} = (1-\theta_k)X_{k,i}c_{k,i}\left[\sum_h(\rho_{k',ij})\left(\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right)\right] - (\mu+\sigma_k)Y_{k,i}^{s,h}$$

Asymptomatic, high quantity

Full:

$$\frac{dY_{k,i}^{a,h}}{dt} = \theta_k X_{k,i}c_{k,i}\left\{\begin{array}{l}\left[r_i\delta_{i,j=1} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=2} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \\ \left[r_i\delta_{i,j=3} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=4} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right]\end{array}\right\} - (\mu+\psi_k)Y_{k,i}^{a,h}$$

Short:

$$\frac{dY_{k,i}^{a,h}}{dt} = \theta_k X_{k,i}c_{k,i}\left[\sum_h(\rho_{k',ij})\left(\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right)\right] - (\mu+\psi_k)Y_{k,i}^{a,h}$$

Asymptomatic, low quantity

Full:

$$\frac{dY_{k,i}^{a,l}}{dt} = X_{k,i}c_{k,i}\left\{\begin{array}{l}\left[r_i\delta_{i,j=1} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=2} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \\ \left[r_i\delta_{i,j=3} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right] + \left[r_i\delta_{i,j=4} + (1-r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h(1-r_h)c_{k',h}N_{k',h}}\right)\right]\left[\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right]\end{array}\right\} + \psi_k Y_{k,i}^{a,h} - (\mu+\gamma_k)Y_{k,i}^{a,l}$$

Short:

$$\frac{dY_{k,i}^{a,l}}{dt} = X_{k,i}c_{k,i}\left[\sum_h(\rho_{k',ij})\left(\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right)\right] + \psi_k Y_{k,i}^{a,h} - (\mu+\gamma_k)Y_{k,i}^{a,l}$$

Parameter	Symbol	Definition	Men (k=1) preliminary values	Women (k=2) preliminary values	References
Preferred mixing	r_i	The proportion of total contacts that are reserved for members of the same activity group.	*i*=1: 5/7 = **0.71** *i*=2: 1/6 = **0.17** *i*=3: 4/15 = **0.27** *i*=4: 1/2 = **0.50**	*i*=1: 5/7 = **0.71** *i*=2: 1/6 = **0.17** *i*=3: 4/15 = **0.27** *i*=4: 1/2 = **0.50**	Jacquez et al, 1988; Hazel, 2009
Entry and exit from population	μ	Proportion of the population that enters and exits at each time step and leaves due to some reason besides a change in infection status.	**0.0001**	**0.0001**	Scelza, 2012; CIA world factsheet
Contacts	$c_{k,i}$	Mean number of sex partners within the past six months (per day).	i=1: (13.38*2/365)=**0.0743** i=2: (6.88*2/365)=**0.0382** i=3: (3.23*2/365)=**0.0179** i=4: (0.85*2/365)=**0.0047**	i=1: (5.62*2/365)=**0.0343** i=2: (3.0*2/365)=**0.0183** i=3: (2.0*2/365)=**0.0122** i=4: (0.87*2/365)=**0.0053**	Hazel, 2009
Recovery from symptomatic infections, $Y_{k,i}^{s,h} \rightarrow X_{k,i}$	σ_k	Mean number of days between onset of symptoms and receiving clinic treatment $(/year)^{-1}$.	(1/21)= **0.0476**	(1/24)=**0.0416**	Hazel, 2009
Recovery from asymptomatic, low quantity infections, $Y_{k,i}^{a,l} \rightarrow X_{k,i}$	γ_k	Mean number of days from the onset of infectiousness to the reduction of infection level below ID_{50} dose (e.g. $<10^3$) $(/year)^{-1}$.	(1/274)= **0.0037**	(1/365)= **0.0027**	No estimate available.
Transmission probability of high quantity infections	β_k^h	The probability that a susceptible person will be infected with GC during a single contact with a person with a high quantity GC infection.	**0.8** (from men to women)	**0.5** (from women to men)	Platt et al., 1983; Hooper et al., 1978; Garnett et al., 1999
Transmission probability of low quantity infections	β_k^l	The probability that a susceptible person will be infected with GC during a single contact with a person with a low quantity GC infection.	**0.4**	**0.1**	No estimates available.
Proportion of asymptomatic infections	θ_k	The proportion of the infected population that has a high quantity, asymptomatic infection at any point in time.	**0.78**	**0.95**	Hazel, 2009
Rate of movement from asymptomatic high quantity infection to low quantity infection, $Y_{k,i}^{a,h} \rightarrow Y_{k,i}^{a,l}$	ψ_k	Mean number of days a low quantity infection persists until it spontaneously resolves.	(1/212.75)= **0.0047**	(1/274)= **0.0037**	Garrnett et al., 1999; Grassly et al., 2005
Number of people in each activity group (Initial conditions)	$N_{k,i}$	The number of people in each activity group, based on proportion of population $N_{k,i}$, given a population size of 1000 men and 1000 women..	$\underline{N_{1,I} = 1000}$ *i*=1: **150** *i*=2: **220** *i*=3: **390** *i*=4: **240**	$\underline{N_{2,I} = 1000}$ *i*=1: **150** *i*=2: **150** *i*=3: **280** *i*=4: **420**	Kaokoland, 2009 dataset

Section 2: Description of the model

Susceptible

$$\frac{dX_{k,i}}{dt}$$

$$= \mu N_{k,i} - \mu X_{k,i} - X_{k,i} c_{k,i} \left[\sum_{h} (\rho_{k',ij}) \left(\beta_{k'}^{h} \left(\frac{Y_{k',j}^{s,h} + Y_{k',j}^{a,h}}{N_{k',j}} \right) + \beta_{k'}^{l} \left(\frac{Y_{k',j}^{a,l}}{N_{k',j}} \right) \right) \right] + \sigma_k Y_{k,i}^{s,h}$$

$$+ \gamma_k Y_{k,i}^{a,l}$$

$\frac{dX_{k,i}}{dt}$ = All susceptible people of *kth* sex, in the *ith* activity group.

Term: $\mu N_{k,i}$

Notation: 1.1

Description: Entry into the susceptible population through means other than clearing infection.

Explanation: This term generates entry of susceptible people from the *kth* sex and *ith* activity group into the population (e.g. sexual debut). People of the *kth* sex and *ith* activity group (N_{ki}) are multiplied by the rate at which people enter the population (μ).

Term: $\mu X_{k,i}$

Notation: 1.2

Description: Exit from the susceptible population through means other than new infection.

Explanation: This term removes people of the *kth* sex and the *ith* activity group from the susceptible population ($X_{k,i}$) by some means other than becoming infected (e.g. cease sexual activity). They are removed from the susceptible population at rate (μ), which is

set as equal to the rate of entry into the population. Since these people have left the population, they are not added to any of the infected populations.

Term: $X_{k,i}c_{k,i}$

Notation: 1.3

Description: Exit from the susceptible population through infection (as part of term 1.4)

Explanation: Term 1.3 generates the total number of contacts by people of the *kth* sex and the *ith* activity group. This term, when multiplied with multi-term 1.4 (described below), accounts for the people of *kth* sex in *ith* activity group who were removed from the susceptible population because they became infected with gonorrhea.

Term: $\sum_h(\rho_{k',ij})\left(\beta^h_{k'}\left(\frac{Y^{s,h}_{k',j}+Y^{a,h}_{k',j}}{N_{k',j}}\right)+\beta^l_{k'}\left(\frac{Y^{a,l}_{k',j}}{N_{k',j}}\right)\right)$

Notation 1.4

Description: Term 1.4 generates the proportion of new infections possible among people of the *kth* sex and the *ith* activity group. Term 1.4.1 ($\rho_{k',ij}$) is an equation that generates the proportion of contacts that are made by people of *kth* sex and the *ith* activity group with people of *k'th* sex and the *ith* activity group. The second set of brackets contains the probability of transmission. Both terms are described in detail below.

Explanation: In $\rho_{k',ij}$, sexual contacts occur across sex (*k* to *k'*) and activity groups (*i* to *j*), where *i=j* when mixing with a member of one's own activity group, and *i ≠j* when mixing outside of one's activity group. We sum over all probabilities of sex contacts with

people from the opposite sex (heterosexuality is assumed in this model) in *jth* activity groups. These contacts are then multiplied by the likelihood of having sexual contact with an infected person and the probability of transmission associated with that contact ($\boldsymbol{\beta}_{k'}^{h}$, $\boldsymbol{\beta}_{k'}^{l}$).

We repeat term 1.4 for each activity group ($j_{1\text{-}4}$). The sum of term 1.4 for all activity groups is multiplied by term 1.3 and provides an expected value for the rate at which people of the *kth* sex in the *ith* activity group leave the susceptible population due to acquiring a new gonorrhea infection. We break this large term into sub-units for further definition.

Term: $\boldsymbol{\rho_{k',ij} = r_i \delta_{i,j=1} + (1 - r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h (1-r_h)c_{k',h}N_{k',h}}\right)}$

Notation: 1.4.1

Description: This term dictates a) proportion of contacts with one's own activity group and b) which activity group is being contacted.

Explanation: Term 1.4.1 is the first segment of a larger term that determines how many contacts one has with each activity group. $\boldsymbol{r_i}$ is the key variable and it represents the proportion of total contacts that one reserves exclusively for members of one's own activity group (where *i=j*). This is called preferred mixing. $\boldsymbol{r_i}$ is defined for each activity group but does not differ between sexes (thus there is only an '*i*' subscript). All other contacts ($\boldsymbol{r_i}$) are drawn randomly from the population (meaning some of these ($\boldsymbol{r_i}$) contacts can still be among members of one's own activity group). The preferred mixing parameter ($\boldsymbol{r_i}$) is multiplied by a binary parameter ($\boldsymbol{\delta_{i,j}}$). When *i* = *j* (same activity group),

$\boldsymbol{\delta_{i,j}}$ = 1. When *i* ≠ *j* (different activity group), $\boldsymbol{\delta_{i,j}}$ = 0. When $\boldsymbol{\delta_{i,j}}$ = 0, term 1.4.1 cancels out and the addition of reserved/preferred contacts is removed from the $\boldsymbol{\rho_{k',ij}}$ term.

Term: $\boldsymbol{\beta_{k}^{h}}_{,}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)+\boldsymbol{\beta_{k}^{l}}_{,}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)$

Notation: 1.4.2

Description: Determines the probability of being infected with gonorrhea

Explanation: Now that contacts across activity groups have been calculated (1.4.1), we need to determine the transmission probability associated with these contacts (1.4.2). $\boldsymbol{\beta}$ is the probability that a sexual contact will lead to a transmission event. Gonorrhea transmission is higher from men to women than from women to men, so $\boldsymbol{\beta}$ gets a *k* subscript and a different value, depending on the direction of transmission (i.e. $\boldsymbol{\beta_{k}} \neq \boldsymbol{\beta_{k'}}$; or $\boldsymbol{\beta_{k=1}} > \boldsymbol{\beta_{k=2}}$). If we are looking at the probability for a person of the *kth* sex becoming infected, then we must use the transmission probability $\boldsymbol{\beta_{k'}}$. The probability of transmission from the opposite sex ($\boldsymbol{\beta_{k'}}$) is multiplied by the likelihood of having sex with an infected person. This likelihood is the number of infected people of the opposite sex (*k'*) in the *jth* activity group, divided by all the people of the opposite sex in the *jth* activity group.

Because our model assumes that transmission from a high quantity partner is greater than transmission from a low quantity partner, we have two $\boldsymbol{\beta_{k'}}$ values. Therefore, term 1.4.2 breaks into two pieces. Transmission probability for high quantity, opposite-sex contacts ($\boldsymbol{\beta_{k'}^{h}}$) is multiplied by the proportion of symptomatic and asymptomatic, high quantity, infectious, opposite-sex people in the *jth* activity group$\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)$. The transmission probability for low quantity, opposite-sex contacts ($\boldsymbol{\beta_{k'}^{l}}$) is multiplied by the

proportion of low quantity, infectious, opposite-sex people in the *jth* activity group $\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)$.

These two probabilities are added together and then multiplied against terms 1.4.1 and and 1.4.2 to get the total proportion of contacts that result in a new infection as a consequence of sexual contact with the *jth* activity group.

Terms 1.4.1, 1.4.2, are repeated and summed for contacts by each activity group. This final sum of expected values from contact with all activity groups is multiplied by term 1.3 ($\boldsymbol{X_{k,i}c_{k,i}}$) and represents the number of individuals who left the susceptible group due to acquiring a new infection.

Term: $\boldsymbol{\sigma_k Y_{k,i}^{s,h}}$

Notation: 1.5

Description: Re-entry into susceptible population after gonorrhea treatment.

Explanation: These are the people who return to the susceptible state because they received treatment for their gonorrhea. In our model, only symptomatic high quantity infecteds receive treatment. This value comes from the rate at which symptomatic people recover ($\boldsymbol{\sigma_k}$), multiplied by the number of symptomatic, high quantity people of the *kth* sex and the *ith* activity group ($\boldsymbol{Y_{k,i}^{s,h}}$). This value is simultaneously removed from the $\frac{dY_{k,i}^{s,h}}{dt}$ equation (term 2.3).

Term: $\boldsymbol{\gamma_k Y_{k,i}^{a,l}}$

Notation: 1.6

Description: Re-entry into susceptible population through spontaneous resolution of gonorrhea.

Explanation: These are the people who return to the susceptible state because their low quantity gonorrhea spontaneously resolved after some period of time. This value is generated by multiplying the rate at which low quantity gonorrhea resolves ($\boldsymbol{\gamma_k}$) by the number of low quantity cases of the *kth* sex in the *ith* activity group ($\boldsymbol{Y_{k,i}^{a,l}}$). The resolution rate for low quantity gonorrhea is unknown and not reported in the literature. We estimate this parameter as the number of high quantity, asymptomatic cases divided by the number of low quantity asymptomatic cases for each sex. These people are also removed from the low quantity, asymptomatic population (term 4.4).

Symptomatic, high quantity

$$\frac{dY_{k,i}^{s,h}}{dt} = (1-\theta_k)X_{k,i}c_{k,i}\left[\sum_h \left(\rho_{k',ij}\right)\left(\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right)\right] - (\mu+\sigma_k)Y_{k,i}^{s,h}$$

$\frac{dY_{k,i}^{s,h}}{dt}$ = All people with symptomatic, high quantity infections of the *kth* sex in the *ith* activity group.

Term: $(1-\theta_k)X_{k,i}c_{k,i}$

Notation: 2.1

Description: Entry into the high quantity, symptomatic population through new infections.

Explanation: This term estimates the proportion of men that move from susceptible to symptomatic, high-dose infectious. We multiply the number of susceptible people ($X_{k,i}$) of the *kth* sex in the *ith* activity group by the proportion of high-dose cases that are symptomatic ($1-\theta_k$) and the contact rate ($c_{k,i}$) for people of the *kth* sex in *ith* activity group. Since the proportion of people who are *asymptomatic* is determined by the value of θ_k, ($1-\theta_k$) gives us the proportion of symptomatic people. This term is multiplied by terms 2.2.1 – 2.2.2 and, together, these terms determine at what rate men move from the susceptible category to the high quantity, symptomatic category.

Term: $\sum_h \left(\rho_{k',ij}\right)\left(\beta_{k'}^{h}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)\right)$

Notation: 2.2

Description: Term 2.2 generates the proportion of new infections possible among people of the *kth* sex and the *ith* activity group. Term 2.2.1 ($\boldsymbol{\rho_{k',ij}}$) is an equation that generates the proportion of contacts that are made by people of *kth* sex and the *ith* activity group with people of *k'th* sex and the *ith* activity group. The second set of brackets contains the probability of transmission. Both terms are described in detail below.

Explanation: In $\boldsymbol{\rho_{k',ij}}$, sexual contacts occur across sex (*k* to *k'*) and activity groups (*i* to *j*), where *i=j* when mixing with a member of one's own activity group, and $i \neq j$ when mixing outside of one's activity group. We sum over all probabilities of sex contacts with people from the opposite sex (heterosexuality is assumed in this model) in *jth* activity groups. These contacts are then multiplied by the likelihood of having sexual contact with an infected person and the probability of transmission associated with that contact ($\boldsymbol{\beta_{k'}^{h}}$).

We repeat term 2.2 for each activity group ($j_{1\text{-}4}$). The sum of term 2.2 for all activity groups is multiplied by term 2.1 and provides an expected value for the rate at which people of the *kth* sex in the *ith* activity group leave the susceptible population due to acquiring a new gonorrhea infection. We break this large term into sub-units for further definition.

These terms were described in detail above. Below we indicate which terms from the $\frac{\boldsymbol{dX_{k,i}}}{\boldsymbol{dt}}$ equation correspond with the terms for $\frac{\boldsymbol{dY_{k,i}^{s,h}}}{\boldsymbol{dt}}$ equation.

Term: $\boldsymbol{\rho_{k',ij} = r_i \delta_{i,j=1} + (1 - r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h (1-r_h)c_{k',h}N_{k',h}}\right)}$

Notation: 2.2.1

Description & explanation: See term 1.4.1

Term: $\boldsymbol{\beta}_{\boldsymbol{k}'}^{\boldsymbol{h}}\left(\frac{Y_{k',j}^{s,h}+Y_{k',j}^{a,h}}{N_{k',j}}\right)$

Notation: 2.2.2

Description & explanation: See term 1.4.2, but the calculation for transmission of low quantity infections is removed from the symptomatic, high quantity infection equation.

Term: $(\boldsymbol{\mu}+\boldsymbol{\sigma}_{\boldsymbol{k}})\boldsymbol{Y}_{\boldsymbol{k},\boldsymbol{i}}^{\boldsymbol{s},\boldsymbol{h}}$

Notation: 2.3

Description: Exit from high quantity, symptomatic population

Explanation: This term represents the people of the *kth* sex in *ith* activity group who leave the state of being high quantity, symptomatically infected. These people ($\boldsymbol{Y}_{\boldsymbol{k},\boldsymbol{i}}^{\boldsymbol{s},\boldsymbol{h}}$) leave this state in two ways: either at the rate of exit from the population ($\boldsymbol{\mu}$) which is the same for both sexes and all activity groups or at the rate at which high quantity symptomatic infections are cleared through treatment with antibiotics ($\boldsymbol{\sigma}_{\boldsymbol{k}}$). The proportion of high quantity, symptomatic people who leave the population at rate ($\boldsymbol{\mu}$) are removed from the model because they are no longer in the population. The proportion of people who leave the high quantity, symptomatic state because they received antibiotics become susceptible again and are added to the susceptible population (term 1.5).

Asymptomatic, high quantity

$$\frac{dY_{k,i}^{a,h}}{dt} = \theta_k X_{k,i} c_{k,i} \left[\sum_h (\rho_{k',ij}) \left(\beta_{k'}^h \left(\frac{Y_{k',j}^{s,h} + Y_{k',j}^{a,h}}{N_{k',j}} \right) \right) \right] - (\mu + \psi_k) Y_{k,i}^{a,h}$$

$\frac{dY_{k,i}^{a,h}}{dt}$ = All people with asymptomatic, high quantity infections of the *kth* sex in the *ith* activity group.

Term: $\theta_k X_{k,i} c_{k,i}$

Notation: 3.1

Description: Entry into the high quantity, asymptomatic population through new infections.

Explanation: Term 3.1 estimates the proportion of people that move from susceptible to asymptomatic, high-dose infectious. We multiply the number of susceptible people ($X_{k,i}$) of the *kth* sex in the *ith* activity group by the proportion of high quantity cases that are asymptomatic (θ_k) and the contact rate ($c_{k,i}$) for people of the *kth* sex in *ith* activity group. This term is multiplied by terms 3.2.1 – 3.2.2 and, together, these terms determine at what rate people of *kth* sex in the *ith* activity group move from the susceptible category to the high quantity, asymptomatic category.

Term: $\sum_h (\rho_{k',ij}) \left(\beta_{k'}^h \left(\frac{Y_{k',j}^{s,h} + Y_{k',j}^{a,h}}{N_{k',j}} \right) \right)$

Notation: 3.2

Description: Term 3.2 generates the proportion of new infections possible among people of the *kth* sex and the *ith* activity group. Term 3.2.1 ($\boldsymbol{\rho_{k',ij}}$) is an equation that generates the proportion of contacts that are made by people of *kth* sex and the *ith* activity group with people of *k'th* sex and the *ith* activity group. The second set of brackets contains the probability of transmission. Both terms are described in detail below.

Explanation: In $\boldsymbol{\rho_{k',ij}}$, sexual contacts occur across sex (*k* to *k'*) and activity groups (*i* to *j*), where *i=j* when mixing with a member of one's own activity group, and *i ≠j* when mixing outside of one's activity group. We sum over all probabilities of sex contacts with people from the opposite sex (heterosexuality is assumed in this model) in *jth* activity groups. These contacts are then multiplied by the likelihood of having sexual contact with an infected person and the probability of transmission associated with that contact ($\boldsymbol{\beta_{k'}^{h}}$).

We repeat term 3.2 for each activity group ($j_{1\text{-}4}$). The sum of term 3.2 for all activity groups is multiplied by term 3.1 and provides an expected value for the rate at which people of the *kth* sex in the *ith* activity group leave the susceptible population due to acquiring a new gonorrhea infection. We break this large term into sub-units for further definition.

These terms were described in detail above. Below we indicate which terms from the $\frac{\boldsymbol{dX_{k,i}}}{\boldsymbol{dt}}$ equation correspond with the terms for $\frac{\boldsymbol{dY_{k,i}^{a,h}}}{\boldsymbol{dt}}$ equation.

Term: $\boldsymbol{\rho_{k',ij} = r_i \delta_{i,j=1} + (1 - r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h (1-r_h)c_{k',h}N_{k',h}}\right)}$

Notation: 3.2.1

Description & explanation: See term 1.4.1

Term: $\boldsymbol{\beta}_{\boldsymbol{k}}^{\boldsymbol{h}}{}_{\boldsymbol{'}}\left(\frac{\boldsymbol{Y}_{\boldsymbol{k}'\boldsymbol{,j}}^{\boldsymbol{s,h}}+\boldsymbol{Y}_{\boldsymbol{k}'\boldsymbol{,j}}^{\boldsymbol{a,h}}}{\boldsymbol{N}_{\boldsymbol{k}'\boldsymbol{,j}}}\right)$

Notation: 3.2.2

Description & explanation: See term 1.4.2, but the calculation for transmission of low quantity infections is removed from the asymptomatic, high quantity infection equation.

Term: $(\boldsymbol{\mu}+\boldsymbol{\psi}_{\boldsymbol{k}})\boldsymbol{Y}_{\boldsymbol{k,i}}^{\boldsymbol{a,h}}$

Notation: 3.3

Description: Exit from high quantity, asymptomatic population

Explanation: This term represents the people of the *kth* sex in *ith* activity group who leave the state of being high quantity, asymptomatically infected. These people ($\boldsymbol{Y}_{\boldsymbol{k,i}}^{\boldsymbol{a,h}}$) leave this state in two ways: either at the rate of exit from the population (**$\boldsymbol{\mu}$**) which is the same for both sexes and all activity groups or at the rate at which high quantity asymptomatic infections revert to low quantity infections without treatment. The proportion of high quantity, asymptomatic people who leave the population at rate μ are removed from the model because they are no longer in the population. The proportion of people who leave the high quantity, asymptomatic state because their infection reverted to a low quantity infection are added to the low quantity, asymptomatic population (term 4.3).

Asymptomatic, low quantity

$$\frac{dY_{k,i}^{a,l}}{dt} = X_{k,i}c_{k,i}\left[\sum_{h}(\rho_{k',ij})\left(\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right)\right] + \psi_k Y_{k,i}^{a,h} - (\mu + \gamma_k)Y_{k,i}^{a,l}$$

$\frac{dY_{k,i}^{a,l}}{dt}$ = All people with low quantity infections of the *kth* sex in the *ith* activity group. **In our model, all low quantity infections are asymptomatic.**

Term: $\mathbf{X_{k,i}c_{k,i}}$

Notation: 4.1

Description: Entry into the low quantity, asymptomatic population through new infections.

Explanation: This term estimates the proportion of people that move from susceptible to asymptomatic, low quantity infectious state. We multiply the number of susceptible people ($X_{k,i}$) of the *kth* sex in the *ith* activity group by the contact rate ($c_{k,i}$) for people of the *kth* sex in *ith* activity group. This term is multiplied by terms 4.2.1 – 4.2.2 and, together, these terms determine at what rate people move from the susceptible category to the low quantity, asymptomatic category.

Term: $\sum_h(\rho_{k',ij})\left(\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)\right)$

Notation: 4.2

Description: Term 4.2 generates the proportion of new infections possible among people of the *kth* sex and the *ith* activity group. Term 4.2.1 ($\rho_{k',ij}$) is an equation that generates the proportion of contacts that are made by people of *kth* sex and the *ith*

activity group with people of *k'th* sex and the *ith* activity group. The second set of brackets contains the probability of transmission. Both terms are described in detail below.

Explanation: In $\boldsymbol{\rho_{k',ij}}$, sexual contacts occur across sex (*k* to *k'*) and activity groups (*i* to *j*), where *i=j* when mixing with a member of one's own activity group, and *i ≠j* when mixing outside of one's activity group. We sum over all probabilities of sex contacts with people from the opposite sex (heterosexuality is assumed in this model) in *jth* activity groups. These contacts are then multiplied by the likelihood of having sexual contact with an infected person and the probability of transmission associated with that contact ($\boldsymbol{\beta^{l}_{k'}}$).

We repeat term 4.2 for each activity group ($j_{1\text{-}4}$). The sum of term 4.2 for all activity groups is multiplied by term 4.1 and provides an expected value for the rate at which people of the *kth* sex in the *ith* activity group leave the susceptible population due to acquiring a new gonorrhea infection. We break this large term into sub-units for further definition.

These terms were described in detail above. Below we indicate which terms from the $\frac{\boldsymbol{dX_{k,i}}}{\boldsymbol{dt}}$ equation correspond with the terms for $\frac{\boldsymbol{dY^{a,l}_{k,i}}}{\boldsymbol{dt}}$ equation.

Term: $\boldsymbol{\rho_{k',ij} = r_i \delta_{i,j=1} + (1 - r_i)\left(\frac{(1-r_j)c_{k',j}N_{k',j}}{\sum_h (1-r_h)c_{k',h}N_{k',h}}\right)}$

Notation: 4.2.1

Description & explanation: See term 1.4.1

Term: $\beta_{k'}^{l}\left(\frac{Y_{k',j}^{a,l}}{N_{k',j}}\right)$

Notation: 4.2.2

Description & explanation: See term 1.4.2, but the calculation for transmission of high quantity infections is removed from the asymptomatic, low quantity infection equation.

Term: $\psi_k Y_{k,i}^{a,h}$

Notation: 4.3

Description: Entry into low quantity, asymptomatic population through diminishing, untreated asymptomatic gonorrhea infection.

Explanation: This term represents the rate at which high quantity, asymptomatic people of *kth* sex in the *ith* activity group move from the state of being high quantity infected to low quantity infected. High quantity, asymptomatic people of the *kth* sex in the *ith* activity group ($Y_{k,i}^{a,h}$) revert to a low quantity infection at a rate of ψ_k. These people are also removed from the high quantity, asymptomatic population (term 3.3).

Term: $(\mu + \gamma_k)Y_{k,i}^{a,l}$

Notation: 4.4

Description: Exit from low quantity, asymptomatic population

Explanation: This term represents the people of the *kth* sex in *ith* activity group who leave the state of being low quantity, asymptomatically infected. These people ($Y_{k,i}^{a,l}$) leave this state in two ways: either at the rate of exit from the population (μ) which is the same for both sexes and all activity groups or at the rate at which low quantity infections

clear entirely and those people become susceptible again ($\boldsymbol{\gamma_k}$). The proportion of low quantity, asymptomatic people who leave the population at rate μ are removed from the model because they are no longer in the population. The proportion of people who leave the low quantity, asymptomatic state because their infection cleared are added to the susceptible population (term 1.6).

CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS

Summary

My findings reveal that the overall viral and bacterial sexually transmitted disease (STD) burden is very high in remote Kaokoland. I identified several aspects of burden that are both likely to be both unusual compared to the settings of most previous work and valuable for disease intervention efforts in remote, untreated populations.

There are several possible explanations for why herpes and gonorrhea prevalence showed the patterns they did. First, there could be a sample bias that resulted from using a convenience sampling method. We were limited to using this approach because of the nomadic and remote structure of Kaokoland livelihoods. A convenience sample could have led to a bias toward infected people, though given the high proportion of participants who reported no symptoms, I do not think this had a large effect.

Second, given the logistic difficulty of recruiting participants, the overall sample size is small, as in most anthropological studies. In some cases, statistically insignificant results could be due to low statistical power rather than a true lack of association between main effect and outcome variables—that is, there may still be biological significance.

My results may well reflect real patterns of disease distribution and risk. More studies of this kind in other populations, as well as further, more in-depth, studies in Kaokoland will

go far in helping us learn more about the behavioral and environmental correlates of STD risk in understudied, remote populations.

Environmental influences of STDs in Kaokoland: current and future

Though I did not find any effect of "distance" on risk for herpes or gonorrhea, there were important geographical and environmental correlates for both diseases. Herpes appears to have the highest prevalence in the most remote regions of Kaokoland. In some cases, remoteness is purely due to distance (e.g. Marianflus region), but in other cases (e.g. the Ozosemo and Omunjandu regions) remoteness results from inaccessibility due to physical environmental barriers rather than distance *per se*. People in these regions appear to be traveling beyond their resident regions less than their counterparts in accessible areas; thus their partner pools are smaller. I suggest that this creates a situation for rapid transmission of HSV-2.

Contrary to the association between remoteness and HSV-2 infection, I found that cases of high-level gonorrhea were more prevalent where there was considerable human traffic. The environmental effect for gonorrhea was both spatial—prevalence was higher where people were congregate—and temporal—people congregate more at times of the year when the subsistence burden is lower.

These findings reveal that two very common and important STDs can have very different patterns of spread if their biological characteristics are dissimilar in important ways (see Chapter 1). This means that disease intervention programs must have multiple strategies for prevention and education, including targeting different localities, at different times of the year, with different messages about risk and prevention.

The environmental influences I found in herpes and gonorrhea infections of 2009 might be starkly different from the way environment affects such burdens in the future. The physical and social environments of Kaokoland are changing dramatically. Longtime residents are changing their modes of travel (e.g. hitchhiking opportunities are increasing rapidly) and traveling more frequently outside their traditional corridors (e.g. to urban areas). Meanwhile, people from densely populated areas of Namibia are migrating to Kaokoland for economic opportunities and more land. What is now known about current disease burden strongly suggests that future research in Kaokoland should focus on these early shifts to identify new spatial and temporal trends in disease risk. Furthermore, the lifestyle in Kaokoland—traditionally and among new residents—is largely semi-nomadic. Research that looks more deeply at the role of migratory pathways could be very useful in predicting future routes of disease transmission.

Demographic and behavioral influences in STDs in Kaokoland: current and future

HSV-2 was highly prevalent throughout Kaokoland, especially among women and older adults; this parallels a common finding in HSV-2 epidemiology studies in many populations. Other demographic findings regarding HSV-2 risk were more unusual, but make sense in the remote pastoralist setting of Kaokoland. I found that wealthy men, who have higher social status and typically more sex partners, have significantly more HSV-2 than less wealthy men. In a culture in which partner exchange and concurrency are normative, but STD prevention is rare, it is the wealthier members of society (most of whom are men), not the poorer ones, who have the highest disease burden. Disease is more common among women—not a unique finding—but the statistical odds for women, compared to men, may be particularly high among women in Kaokoland because of differences in female and male hygiene practices and a cultural preference for dry sex.

While some demographic patterns of gonorrhea burden emerged, I found no correlation between risk and wealth. This is possibly due to prevalence having been so high—so many people were infected, it overwhelmed resource influences. Interactions between invading gonococci and the host immune system are not well understood, but are generally thought to be strain-specific and incomplete. My work did not generate data that speaks directly to the issue of immunity, but the results, coupled with insights from the mathematical model, suggest that immunity, acquired incrementally with each infection with a new strain, plays an important role in endemic gonorrhea in untreated populations. Therefore, age and frequency of exposure have a much stronger impact on gonorrhea distribution than resource status.

If we are to minimize symptoms and morbidities from gonorrhea, we need more accessible and effective healthcare. Syndromic management is ineffective in a remotely living population because people are more likely to be asymptomatic and, thus, not seek treatment. However, improved access might diminish the protective patchwork of immunity that Kaokoland pastoralists appear to develop over the course of their adult lives, because immune response is likely to be strongest from infections with longer durations (i.e. untreated infections). In other words, improvements to STD treatment need to be meaningful and consistent to be worth the loss of acquired immunity. Future research should focus on the parallel aims of encouraging meaningful, sustainable improvements in treatment while gaining empirical data on the actual biological and immunological underpinnings of gonorrhea.

Limitations and ways forward

The diagnostic techniques I used to measure herpes and gonorrhea status were not the most sensitive available, but met the logistic restrictions of working in a remote setting

with little infrastructure. My diagnostic techniques may have underestimated both herpes and gonorrhea prevalence, but would not have affected the *pattern* of disease prevalence I observed. These limitations were unavoidable at the time the project was designed. For example, the low sensitivity of the HSV-2 rapid test in Africa, compared to western blot, was not known at the time I began data collection. The small size of my research team (my translator and myself) severely limited the amount of data that we could collect in a period of time. Collecting data on a sensitive topic in a migratory, sparsely populated community is inescapably challenging, but these limitations are greater for smaller research teams.

This research produced valuable information about serious diseases in a neglected population. There are other remotely living, underserved populations, not just in Namibia, Africa and developing nations, but even in comparatively wealthy, industrialized societies. This research demonstrates its value—I hope—in showing that understanding disease burden and unmet needs at a very local level is possible for hard to reach populations.