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Estimating the Prevalence of Hepatitis C in Sub-Saharan Africa

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ESTIMATING THE PREVALENCE OF HEPATITIS C IN SUB-SAHARAN AFRICA

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To Mom

Essentially, all models are wrong, but some are useful.
– George E. P. Box (1987)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Hepatitis C (HCV) is a virus transmitted via contact with contaminated products such as razor-blades or by engaging in high-risk activities (i.e., such as sexual or injecting drug-use activities). Today, there are an estimated 115 million people world-wide living with HCV. Despite recent advancements in antiviral treatments that can ameliorate (or even cure) HCV, treatment remains laborious and costly and is often unavailable in resource-poor areas such as Sub-Saharan Africa (SSA). The primary aim of this study was to estimate the prevalence of HCV in SSA.

A meta-analysis was conducted on the HCV epidemic in SSA. A literature search for evidence of HCV in SSA was conducted and was limited to articles, abstracts, and conference proceedings published in English, Spanish, or French from January 2000 through December 2013. Linear and generalized-linear mixed effects models were used to estimate the pooled prevalence of HCV in SSA as a function of the population at-risk, region of SSA, year of publication, and the assay used to detect viremia. In these models, the estimates were weighted by their inverse variance and pooled separately using no transformation, a canonical logit transformation, and double-arcsine transformation. These three transformation approaches were compared on precision, model fit, and publication bias.

The overall pooled prevalence estimate of HCV in SSA ranged from 3.80% to 5.83% depending on the transformation used. For all three methods, however, prevalence of HCV

varied among those at-risk for infection ($p < .001$) and by region of SSA ($p < .001$). In fact, the prevalence of HCV among those at-risk for infection *depended* on region of SSA ($p < .001$). Conversely, this study was unable to show that prevalence depends on publication year ($p > .05$) or diagnostic assay ($p > .05$) under all three transformation methods. Regarding the optimal transformation, prevalence of HCV in SSA tended to be lowest when estimated under a canonical logit transformation and highest when estimated using no transformation of the raw effect sizes. Regarding precision and model fit, confidence intervals for all prevalence estimates were severely overlapping under the three transformation methods, yet normality, linearity, and residual plots consistently revealed that the canonical logit approach was superior when compared to the double-arcsine transformation and raw estimation method.

When estimating the pooled prevalence of HCV in SSA, this study did not identify meaningful differences between the logit and double-arcsine transformations. That is, they were generally comparable in precision and had severely overlapping confidence intervals for all moderator analyses. However, model fit statistics suggest that the canonical logit approach provided a better fit to the data than the double-arcsine transformation or raw estimation method. I caution future researchers considering no transformation of the raw prevalence estimates. When no transformation was used, the pooled prevalence estimate of HCV in SSA was inflated as measured by standardized residuals, individual study variances were severely attenuated, publication bias estimates were quite severe and, in some instances, the study predicted prevalence estimates well below zero. For this reason, I recommend using the canonical logit transformation for meta-analyses of HCV in Sub-Saharan Africa.

CHAPTER ONE

INTRODUCTION

Hepatitis C Virus (HCV) is a blood-borne virus with a known cure. While it is commonly diagnosed using an HCV antibody test, the prodromal phase of the virus is lasting - meaning affected individuals can lead healthy lives and be asymptomatic for decades before experiencing initial symptoms including elevated liver enzymes, somnolence, muscle soreness, joint pain, and abnormally dark urine (Chen & Morgan, 2006). In the United States, there are roughly 200,000 new cases of HCV per year with a nationwide prevalence of approximately 2.7 to 3.9 million individuals (Layden et al., 2014). In fact, the US prevalence of HCV is estimated to be approximately five times higher than the prevalence of human immunodeficiency virus (HIV).

Following World War II, HCV predominately spread within the home using shared blood-contaminated products (e.g., razor blades) and outside the home via intravenous drug use and high-risk sexual activity (Lavancy, 2009). Today, an estimated 115 million people world-wide live with HCV (Gower, Estes, Blach, Razavi-Shearer, & Razavi, 2014). Left untreated, these individuals will eventually experience severe liver damage leading to liver cancer, liver transplantation, or death.

Importantly, HCV is treatable. The use of antiviral medications such as interferon alfa-2b, pegylated interferon alfa, and Ribavirin effectively suppress viral replication, while even

newer antiviral medications such as Sofosbuvir and Simeprevir can cure some HCV genotypes. However, these treatments are labor-intensive for providers and costly for patients (Loy, Benyashvili, Adams, Pavkov, O'Mahoney, & Cotler, 2016). In fact, these medications are so expensive that they remain unavailable in resource-poor areas (Lemoin, Eholie, & Lacombe, 2015). Because there is no vaccination available to prevent infection, education about the virus and how it spreads remain the primary methods to reduce its spread (Mora et al., 2016). This is particularly true in Africa where genetic research suggests that HCV originated more than 600 years ago (Layden et al., 2014). Alarmingly, sub-Saharan Africa accounts for 20% of the global HCV infection rate where more than 21 million people live with HCV. In this region, Epidemiologists require frequent updates about the incidence and prevalence of the virus to develop and evaluate the medical, behavioral, and social interventions meant to forestall it. The prevalence estimates these professionals require are specific to African region (Western, Eastern, Central, and Southern sub-Saharan Africa) and stratified by risk status, including blood donors, those from the general population, and those at high-risk for infection.

The need for accurate and nuanced HCV prevalence estimates is clear: The true world-wide prevalence of Hepatitis C is variable, ranging from 108 million individuals affected in 1990 to, as noted above, 115 million people living with the virus in 2014 (Gower et al., 2014; Mohd-Hanafiah, Groeger, Flaxman, & Wisersma, 2013). While prevalence of HCV certainly depends on the time-period in which it is estimated (Rothman, Greenland, & Lash, 2008), discrepancies in these global estimates are also partially due to researchers' methodological choices,

including their applied inclusion and exclusion criteria and whether their sampling plan includes or excludes special populations (such as blood donors). This variability is even more pronounced in Sub-Saharan Africa where recent meta-analyses revealed that the prevalence of HCV in sub-Saharan Africa is variable, ranging from 2.98% to 3.94% over similar time periods. These estimates are even more dispersed when stratified by African region and risk strata (Mora et al., 2016; Rao, Johari, du Cros, Messina, Ford, & Cooke, 2015).

There is an additional methodological decision that affects prevalence estimates – one that has not been investigated within the sub-Saharan African population: The decision of which transformation to use on the raw prevalence estimates. Generally, during any meta-analysis of prevalence (or proportions) a decision is made to free the raw estimates from their 0-1 boundary using a transformation (Agresti, 2002). The choice of transformation affects the standard error estimate of the pooled prevalence statistic which correspondingly affects the precision of our understanding of the epidemic (Barendregt, Doi, Lee, Norman, & Vos, 2013). This choice cannot be underestimated, because different transformations may result in conflicting conclusions that obscure the true infection rate. No study has sought to investigate how these methodological choices affect our understanding of HCV prevalence estimates in Sub-Saharan Africa.

Therefore, the purpose of this study is twofold: The primary objective of this dissertation is to estimate the true seroprevalence of Hepatitis C in sub-Saharan Africa among the four main regions of SSA, population risk strata, year of study, and among the diagnostic

assays used to detect the virus. The secondary objective is to estimate how certain we are about these HCV prevalence estimates in Sub-Saharan Africa. That is, the secondary objective is to compare these prevalence estimates when the standard error is computed using no transformation, the traditional or canonical logit transformation, and the double arcsine transformation (Barendregt et al., 2013). The specific aims are as follows:

Prevalence of HCV varies by risk strata. Rao et al. (2015) identified 185 articles measuring the prevalence of Hepatitis C among individuals at low-risk and high-risk for the virus. They found that among those at low-risk for infection, prevalence of HCV was as low as 1.99% (95% CI: 1.86 - 2.12). Conversely, among high-risk individuals such as injecting drug users, the prevalence was as high as 11.87% (95% CI: 7.05% - 16.70%). The hypothesis in this study is that the prevalence of Hepatitis C is lowest among blood donors and that prevalence will increase, sequentially, among individuals from the general population, those living with a chronic illness, and those at high risk for infection. Further, for each risk strata, the HCV prevalence estimates will be more certain as measured by their precision and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Prevalence of HCV varies by geographic region. In their meta-analysis, Rao et al. (2015) found that prevalence was highest in Central Africa at 6.76% (95% CI: 5.98% - 7.55%) which decreased to 4.34% (95% CI: 3.99% - 4.70%) in West Africa, and was lowest in Southeast Africa (0.91%, 95% CI: 0.80 - 1.02%). Using geographic coordinates described by the World Health

Organization, the hypothesis in this study is that prevalence is highest in Central Africa but decreases, sequentially, among those in Western Africa, Eastern Africa, and Southern Africa. Further, the estimates for each region are hypothesized to be more certain as measured by their precision and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Prevalence estimates for the low and high-risk HCV infection groups depend on geographic region. Madhava, Burgess, and Drucker, (2002), Mohd-Hanafiah et al. (2013), and Rao et al. (2015) concluded that the prevalence of hepatitis C among low and high-risk groups *depends* on the African region in which they live. For example, in their meta-analysis, Rao et al. found that the prevalence of HCV among low-risk individuals was alarmingly high in Central Africa (6.89%) and West Africa (3.72%) but lower in Southeast Africa (0.67%). Conversely, among high-risk individuals defined as patients with liver disease, multiple blood transfusions, hemodialysis, renal transplants, sickle-cell disease, or injecting drug users, Rao et al. found that this conclusion flipped: Prevalence was highest in Southeast Africa (12.62%), followed by West Africa (10.70%) and Central Africa (8.42%). Therefore, the hypothesis in this study is that there is a significant interaction between risk strata and geographic region. Further, the estimates for each risk cohort stratified by region are hypothesized to be more certain as measured by their precision and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Prevalence of HCV varies by article year. Prevalence is a biased statistic. Unlike an exhaustive census of infections or infection rate over time (incidence), prevalence estimates offer only an ephemeral snapshot of the HCV burden at a specific moment (Rothman et al., 2008). For this reason, the time periods that capture available data may be salient moderators of the epidemic. The hypothesis in this study is that prevalence of HCV is highest among articles published between 2000 and 2004 but decease, sequentially, among articles published between 2005 and 2009 followed by articles published between 2010 and 2013. A negative association between increasing year and HCV prevalence is anticipated in response to ongoing efforts to suppress the spread of the virus. As before, we also hypothesize that these estimates are more certain as measured by their precision and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Lastly, *prevalence of HCV varies by assay type*. Beyond the temporal, geographic, and population risk effects, prior research suggests that the serologic assay used to determine HCV status affects prevalence estimates due to variation in false positivity rates (Candotti et al., 2001; Layden et al., 2014; Mullis et al., 2013; Scheiblauer et al., 2006; Seremba et al., 2010). For this reason, the type of assay used to detect the virus may be an important moderator of HCV prevalence. The hypothesis in this study is that prevalence varies among articles using rapid screen, second generation, third generation, and fourth generation assays. Further, the estimates for each assay are hypothesized to be more certain as measured by their precision

and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Understanding how prevalence varies by region, risk strata, year of study, and diagnostic assay may provide meaningful information to Epidemiologists and other researchers in Sub-Saharan Africa. Further, determining which transformation method provides superior measurement of the prevalence of hepatitis C can tighten our understanding of the epidemic, where even a difference of 1% could indicate thousands of affected individuals. As such, the rationale for this investigation is timely and aptly aligns with the social justice mission of Loyola's school of education.

CHAPTER TWO

LITERATURE REVIEW

This chapter reviews the key literature summarizing the hepatitis C virus, its global burden, and its deleterious effects in sub-Sharan Africa, some of which was previously discussed by the author and his colleagues in Mora et al. (2016) where the canonical logit transformation results described in this dissertation were published. This chapter also summarizes and critiques currently established statistical methods for the meta-analysis of Hepatitis C prevalence estimates in Sub-Saharan Africa and concludes with a summary of how this dissertation adds to a growing consensus on a preferred method.

Hepatitis C Virus

Hepatitis C Virus (HCV) is a blood borne pathogen causing a slow, life-long infection that ultimately leads to chronic liver disease, cirrhosis, liver cancer, or death (Lavanchy, 2009; Mora et al., 2016). While new highly effective anti-viral treatments are available, they are costly – estimated at approximately $84,000 for a 12-week course of treatment (The 64th Annual Meeting of the American Association for the Study of Liver Diseases, 2014). Worse, because the virus primarily affects the liver, an individual living with HCV may eventually require a liver transplantation which carries additional risks, including infection and organ rejection.

Globally, these specific treatments (i.e., anti-viral medications and liver transplantation) are not always readily available, particularly in resource-poor areas (Lemoin et al., 2015). With

no available vaccine to prevent infection, treatment and disease prevention remain the primary methods to reduce global disease burden (Layden et al., 2014; Mora et al., 2016). In areas such as sub-Saharan Africa, for example, healthcare providers and Epidemiologists require routine updates on the prevalence of HCV to effectively promote prevention strategies. Therefore, investigating methods to estimate the prevalence of this deadly infection in sub-Saharan Africa is both sensible and necessary.

Global Disease Burden

There are significant discrepancies in recent HCV global burden estimates. For example, as cited in Mora et al. (2016), Mohd-Hanafiah et al. (2013) estimated that 185 million individuals worldwide were HCV antibody seropositive – a 52% increase from 1990. One year later, Gower et al. (2014) estimated that only 115 million individuals worldwide were seropositive.

Such discrepancies in the prevalence of HCV may be partially due to researchers' applied inclusion and exclusion criteria, and this is particularly true when researchers oversample blood banks or minors who tend to have lower HCV prevalence estimates (Mora et al., 2016; Rao et al., 2015). Additionally, *prevalence* itself is a biased statistic that obscures our understanding of the epidemic. Unlike a census (which is a complete accounting of the infections in a community at given point in time) or incidence (which represents the rate of new infections over time), prevalence is an ephemeral statistic that offers only a brief time-dependent estimate of the HCV burden (Rothman et al., 2008). Accordingly, the time periods that capture the available

data may be salient moderators of the disease burden and suggests that any meta-analysis investigating the prevalence of HCV should use article year as a moderating variable for the time periods of the included studies (Gower et al., 2014; Mohd-Hanafiah et al., 2013; Mora et al., 2016; Rao et al., 2015; Rothman et al., 2008). This could be particularly true in Sub-Saharan Africa, where ongoing efforts to suppress the virus may influence prevalence estimates.

Disease Burden in Sub-Saharan Africa

Despite differences in their estimates, both Mohd-Hanafiah et al. (2013) and Gower et al. (2014) reveal that sub-Saharan Africa suffers from an alarming HCV disease burden. Further, our true understanding of the prevalence rate in sub-Saharan Africa is profoundly limited by a lack of robust primary research, including limited population-based studies with adequate sampling strategies meaning there is significant uncertainty when estimating the true disease burden in this region (Layden et al., 2014; Mora et al., 2016).

More specifically, a recent meta-analysis revealed a pooled HCV seroprevalence of 2.98% across Sub-Saharan Africa (Rao et al., 2015), but Madhava et al. (2002), Mohd-Hanafiah et al. (2013), and Rao et al. (2015) identified significant variability across geographic regions within these areas (i.e., Central, Southeastern, and Western Africa) and risk groups (e.g., blood donors, pregnant women, those with an existing liver disease, substance users, and children). More specifically, Rao et al. identified 185 articles measuring the prevalence of Hepatitis C among individuals at low-risk for the virus. These individuals were pregnant women, blood donors, students, and patients seeking care for non-hepatic illnesses. In this population, the

prevalence was alarmingly high in Central Africa (6.89%) and West Africa (3.72%) but lower in Southeast Africa (0.67%). Conversely, among 21 articles measuring high risk individuals defined as patients with liver disease, multiple blood transfusions, hemodialysis, renal transplants, sickle-cell disease, or injecting drug users, Rao et al. found that HCV prevalence *flipped*: It was highest in Southeast Africa (12.62%), followed by West Africa (10.70%) and Central Africa (8.42%). This is the very definition of an interaction. Clearly, geographic region and risk stratification affect our true understanding of the disease burden and suggests that any meta-analysis of HCV in Africa may need to stratify risk cohort estimates by geographic region.

In fact, the profound variability in published estimates suggests an overall disease burden statistic may not be appropriate or accurate, and our true understanding of the prevalence may depend on several important moderators (Mora et al., 2016). Beyond the geographic and risk strata effects, prior research also suggests that the serologic assay used to determine HCV status may affect prevalence estimates due to variation in false positivity rates (Candotti et al., 2001; Layden et al., 2014; Mullis et al., 2013; Scheiblauer et al., 2006; Seremba et al., 2010). Using 381 samples from limited resource areas (including Egypt and South Africa), Scheiblauer et al. (2006) analyzed the sensitivity (i.e., the probability the test is positive when the patient is truthfully HCV positive) and specificity (i.e., the probability the test is negative when the patient is truthfully HCV negative) of 44 different assays capable of detecting HCV. Among these 44 assays, only 30 (68%) met criteria established by the World Health Organization for diagnostic accuracy. This suggests that in a meta-analysis of HCV prevalence,

the type of assay used in each article may be a profound mediator of our true understanding of the epidemic.

Because these parameters may greatly impact disease estimates, it is important for prevalence estimates to account for the geographic region of Sub-Saharan Africa, study risk strata, year of study, and diagnostic assay used. Rarely have studies adjusted prevalence estimates to account for these effect modifiers, particularly when they are estimated under three competing statistical transformations.

Meta-Analysis of Prevalence Estimates

The choice of statistical transformation matters. This is because the raw mathematics of any meta-analysis synthesizing prevalence rates (or proportions) across multiple articles presents an additional limitation: Poor estimation of the standard error of the pooled prevalence statistic (Barendregt et al., 2013). Because any single estimate of prevalence is simply the number of positive cases over the number sampled (at the time the sample is taken), this ratio essentially follows a binomial distribution where the variance of any given study is:

$$\mathrm{Var}(p_i) = \frac{p_i(1-p_i)}{N_i}$$

Here, p_i is the proportion positive in article i, and N_i is the number of individuals sampled in that article. Summing over all articles (and other evidence), the **raw** pooled prevalence estimate becomes a sum of ratios:

$$\text{Pooled prevalence } (P) = \frac{\sum_i \frac{p_i}{Var(p_i)}}{\sum_i \frac{1}{Var(p_i)}}$$

where that the inverse variance weight of each article is noted in the denominator of the pooled prevalence statistic. The standard error (SE) of this raw pooled prevalence estimate is:

$$\text{SE}(P) = \sqrt{\sum_i \frac{1}{Var(p_i)}}$$

yielding a confidence interval for the precision of the population estimate equal to:

$$\text{CI}(P) = P \pm Z_{\alpha/2}\,\text{SE}(P)$$

Where, $Z_{\alpha/2}$ is commonly set to 1.96, for example, to estimate a two-sided 95% confidence interval (Agresti, 2002; Barendregt et al., 2013).

There are at least two concerns with the raw approach. First, p_i may be biased because it is bounded between 0 and 1 making it a poor effect size. That is, without using some transformation, it is possible to estimate a pooled prevalence estimate outside of the 0 to 1 range (Agresti, 2002; Barendregt et al., 2013). Second, Agresti (2002) and Barendregt et al. (2013) show that when p_i is too small (as it is among those at low risk for the virus) or too big (as it is among intravenous drug users), the variance of p_i approaches zero.

This later problem is concerning, because when a study's variance is small it receives more weight towards the pooled prevalence statistic. That is, studies with a prevalence estimate closer to 0 (or to 1) will receive a large weight while studies with prevalence in the middle of the 0 – 1 scale will receive a small weight. This is particularly concerning in the meta-

analysis of Hepatitis C prevalence in sub-Saharan Africa, where we expect prevalence estimates in most studies to be closer to zero rather than the middle of the scale.

For this reason, most researchers transform the raw study prevalence estimates before calculating a pooled prevalence statistic. Barendregt et al. (2013) discuss two methods commonly used to resolve these biases: One approach is to free each prevalence statistic from its 0 – 1 range using a canonical logit transformation. Then, for each study, the effect size is estimated as:

$$t = \ln(p_i) = \ln\left(\frac{p_i}{1 - p_i}\right)$$

And each study's variance is subsequently estimated as:

$$\mathrm{Var}(t) = \frac{1}{N_i p_i} + \frac{1}{N_i(1 - p_i)}$$

The meta-analysis then proceeds in the usual manner described above to estimate the transformed pooled prevalence estimate (*T*). Subsequently, this point estimate is returned to its 0 – 1 scale using a back transformation as described by Barendregt et al. (2013) and Agresti (2002):

$$\text{Back Transformed Pooled Prevalence } (P_T) = \frac{\exp(T)}{\exp(T) + 1}$$

In fact, the canonical logit approach was used to publish preliminary results for this dissertation (Mora et al., 2016). While this transformation provides an acceptable approach to the meta-analysis of prevalence data, Barendregt et al. (2013) argue that it merely reverses the

variance estimation problem mentioned above for the raw (or untransformed approach): Namely, they argue that the canonical logit transformation results in an overestimation (rather than underestimation) of each study's variance when the observed prevalence statistic is small or large. That is, under a logit transformation, a small study with prevalence near the middle of the metric (e.g., a study of prisoners or sex workers in sub-Saharan Africa) may outweigh a large study with prevalence closer to 0% (e.g., a study of blood donors in sub-Saharan Africa).

A third approach aims to ameliorate variance instability using a double-arcsine transformation. For each article *i*, the prevalence estimate is first transformed according to Barendregt et al. (2013):

$$z_i = \sin^{-1}\sqrt{\frac{n_i}{N_i+1}} + \sin^{-1}\sqrt{\frac{n_i+1}{N_i+1}}$$

Here, z_i is the double-arcsine transformed prevalence statistic for study *i*, n_i is the number of individuals affected in article *i*, and N_i is the number of individuals sampled in the article. Unlike the raw or canonical logit approach, the variance of a double-arcsine transformed pooled prevalence estimate requires no information about the prevalence rate. Instead, it merely capitalizes on the article's sample size as described by Barendregt et al. (2013):

$$\mathrm{Var}(z_i) = \frac{1}{N_i + 0.5}$$

The meta-analysis then proceeds in the usual manner described above to estimate the double-arcsine transformed pooled prevalence estimate (*Z*). Under this transformation, the true back transformation to the original 0 – 1 scale is admittedly complex:

$$\text{Back Transformed Pooled Prevalence } (P_Z) = 0.5\left\{1-\text{sgn}(\cos Z)\left[1-\left(\sin Z+\frac{\left(\sin Z-\frac{1}{\sin Z}\right)}{N}\right)^2\right]^{0.5}\right\}$$

However, it is important to note that Barendregt et al. (2013) state that the back transformation can be simplified with only a minimal loss in accuracy using a simplified reverse transformation:

$$\text{Back Transformed Pooled Prevalence } (P_Z) = \left(\sin\frac{Z}{2}\right)^2$$

Summary

The literature summarizing Hepatitis C globally as well as in Sub-Saharan Africa indicates that the prevalence of HCV likely depends on geographic region as well as the population sampled (Madhava et al., 2002; Mohd-Hanafiah et al., 2013; Mora et al., 2016; Rao et al., 2015). The literature also suggests that prevalence of HCV is fluid and depends on the time in which the data is collected (Rothman et al., 2008). Therefore, the wide dispersion in estimates of HCV prevalence in sub-Saharan Africa may be engendered not only by investigators' sampling strategies but also by their meta-analytic methods, particularly the methods employed to estimate the pooled prevalence estimates. The primary objective of this investigation is to estimate the true seroprevalence of Hepatitis C in sub-Saharan Africa among the four main regions of SSA, population risk strata, year of study, and among the diagnostic assays used to detect the virus. The secondary objective of this dissertation is to estimate how certain we are

about these HCV prevalence estimates in Sub-Saharan Africa. That is, the secondary objective is to compare these prevalence estimates when the standard error is computed using no transformation, the traditional or canonical logit transformation, and the double arcsine transformation (Barendregt et al., 2013; Trikalinos, Trow, & Schmid, 2013).

The central hypotheses are that prevalence varies by region of Africa with prevalence being lowest in Southern Africa and increasing sequentially in Eastern Africa, Western Africa, and Central Africa; that prevalence varies by risk strata with HCV estimates being lowest among blood donors and increasing sequentially among individuals from the general population, those living with a chronic illness, and those at high-risk for infection; that prevalence varies by the type of assay used; and that prevalence varies by article year with HCV estimates being highest among early articles and decreasing among articles published at later intervals due to applied epidemiological interventions meant to forestall the virus.

I also hypothesize that the pooled prevalence estimates for those at high-risk and low-risk for infection *depends* on WHO defined geographic African region. That is, the pooled prevalence estimates for those at low-risk and high-risk for infection are hypothesized to be different depending on whether the articles used to calculate such estimates sampled mainly from Central versus Southern Africa. Finally, I hypothesize that for all estimates, the canonical logit and double-arcsine approaches will result in tighter 95% confidence intervals and less publication bias when compared to an approach using no transformation.

CHAPTER THREE

METHODS

This chapter summarizes the research questions and methods used to address them. More specifically, it summarizes how the literature was searched for evidence of the Hepatitis C virus epidemic in sub-Saharan Africa (SSA), how the data was captured and recorded for each article, the statistical analyses used to estimate the pooled prevalence estimate of Hepatitis C in sub-Saharan Africa, and the approach used to compare the estimates under three competing transformations: No transformation, a canonical logit transformation, and double arcsine transformation. The five aims with their respective hypotheses are as follows:

1. Prevalence of HCV varies by risk strata. The hypothesis is that the prevalence of Hepatitis C is lowest among blood donors and increases, sequentially, among individuals from the general population, those living with a chronic illness, and those at high risk for infection. Further, for each risk strata, the HCV prevalence estimates are hypothesized to be more certain as measured by their precision and publication bias estimates when they are estimated under a canonical logit or double-arcsine transformation than under no transformation.
2. Prevalence of HCV also varies by region of Africa. Using geographic coordinates described by the World Health Organization, the hypothesis is that the prevalence of HCV is lowest in Southern Africa followed by Eastern Africa and Western Africa. It is

also hypothesized the prevalence of Hepatitis C is highest in Central Africa. Further, the estimates for each region are hypothesized to be more certain as measured by their precision and publication bias estimates when they are estimated under a canonical logit or double-arcsine transformation than under no transformation.

3. The pooled prevalence estimates for each risk strata *depend on* geographic region. That is, I hypothesize a significant interaction effect between risk strata and geographic region for the pooled prevalence estimate as described in Rao et al. (2015). Further, the estimates for each risk cohort stratified by region are hypothesized to be more certain as measured by their precision and publication bias estimates when they are estimated under a canonical logit or double-arcsine transformation than under no transformation.
4. Prevalence of HCV varies by article year. Due to efforts to forestall the transmission of HCV in SSA, the hypothesis is that the prevalence rates decline as article year increases. That is, prevalence is hypothesized to be highest among articles published between 2000 and 2004 but decrease, sequentially, among articles published between 2005 and 2009 followed by articles published between 2010 and 2013. Further, the estimates for each year are hypothesized to be more certain as measured by their precision and publication bias estimates when they are estimated under a canonical logit or double-arcsine transformation than under no transformation.

5. Finally, the prevalence of HCV is hypothesized to vary by the type of assay used to detect the virus. It is hypothesized that prevalence varies among articles using rapid screening, second generation, third generation, and fourth generation assays. Further, the estimates for each assay are hypothesized to be more certain as measured by their precision and publication bias estimates when estimated under a canonical logit or double-arcsine transformation than under no transformation.

Literature Search

The literature search for this dissertation was previously conducted between 2012 and 2015 and was aptly described in Mora et al. (2016), where the HCV prevalence results under the canonical logit transformation were published. This is a continuation of that prior publication.

As stated in Mora et al. (2016), the search for published articles and abstracts reporting HCV prevalence in Sub-Saharan Africa relied on specific search engines, including: Medline, Ovid, EMBASE, Google Scholar, PubMed, and Academic Search Complete/EBSCO using keywords “Hepatitis C AND Sub-Saharan Africa,” “HCV AND central Africa,” “HCV AND eastern Africa,” “HCV AND western Africa,” “HCV AND southern Africa,” and “HCV AND prevalence AND Africa.” When articles or abstracts were identified for inclusion, snowball sampling was used to find additional evidence from references in the published material.

Regarding the inclusion and exclusion criteria, Mora et al. (2016) states that the data capture was limited to articles that sampled from mainland countries in Sub-Saharan Africa that

were published between January 2000 and December 2013. These dates were selected to align with other meta-analyses of Hepatitis C in Africa in order to compare published estimates. There were no inclusion criteria. However, there were two exclusion criteria: First, only publications printed in English, Spanish, and French were retained. This was because there are over 1,000 languages spoken in Sub-Saharan Africa, but most research is published in one of these three languages (Bowden, 2008). Second, articles without original data were excluded out of necessity as were articles without HCV prevalence estimates.

Data Capture

HCV prevalence estimates and the absolute numbers used to generate these estimates were previously recorded for each study using double-data entry by five of the author's colleagues as described in Mora et al. (2016). An electronic query system (i.e., Research Electronic Data Capture or REDCap) flagged data entry discrepancies (Harris et al., 2009). When discrepancies were identified, two researchers reviewed the entries and agreed on which entry was correct. Studies were grouped into one of four Sub-Saharan regions using boundaries described by the World Health Organization, namely Central, Eastern, Western, or Southern Africa (UN/DESA, 2012). Publication year, and the highest generation diagnostic assay used (i.e., screening, second, third, or fourth generation assay) were also recorded.

As described in Mora et al. (2016), each sample was grouped into a population risk cohort representing either blood donors; those at high risk for infection (i.e., studies of prisoners and prison guards, adults and children with sickle cell disease, hospital workers, sex

workers, intravenous drug users, and hemodialysis patients); individuals with comorbid HIV infection; those with a chronic Illness (e.g., individuals with diabetes, those with a chronic liver disease, or patients admitted to a healthcare facility); or pregnant women, studies of household members, adults, outpatients, healthy children, and infants who were grouped into a fifth category representing the general population. This provided the following data dictionary available for this dissertation:

Table 1. Data Dictionary

Variable	Label	Measurement Level
study_id	Study ID	Nominal
article_id	Article ID	Nominal
author	Author	Nominal
year	Article Year	Scale
year_rc	Article Year: 2000-2004, 2005-2009, or 2010-2013	Ordinal
region	Study Region: Central, Eastern, Southern, or Western Africa	Nominal
cohort	Risk Strata: Blood Donors, Chronic Illness, General Population, High Risk, or HIV	Nominal
assay	Type of Assay Used: Screening or Second, Third, or Fourth Generation	Nominal
positive	Number HCV Positive in the Study	Scale
n	Total Sample in the Study	Scale
effect	Raw Study Prevalence	Scale

Note: This information is recorded on 221 studies nested within 185 articles

Statistical Analyses

All analyses for this dissertation were conducted using SAS software version 9.4 (SAS Institutes, Cary, NC) and the metafor package for *R* (Viechtbauer, 2010). For each of the five hypotheses, three different approaches for estimating average prevalence as an *effect size*

were compared: An estimate of average prevalence using no transformation, an estimate of average prevalence using a canonical logit transformation, and an estimate of average prevalence using a variance-stabilizing double arcsine transformation.

Effect Sizes

In any meta-analysis, there are usually three common goals (Field & Gillett, 2010). The first is to estimate the average and variance of a population effect. This usually means researchers synthesize raw or standardized mean differences between two cohorts over articles or other published evidence. If the outcome is nominal, researchers instead synthesize categorical effect sizes such as risk differences, risk ratios, odds ratios, or hazard ratios. A secondary goal is to estimate the variability in these effect sizes across the included studies. When the estimates are homogenous, researchers use this evidence to advocate for models that make few assumptions (i.e., fixed effects meta-analysis). However, over 20 years of research suggests that estimates across many diverse articles are rarely homogenous (Hedges & Pigott, 2001). Therefore, the third goal of most meta-analyses is to explain the heterogeneity using regression models (i.e., moderator analysis).

This dissertation is no different. However, instead of synthesizing traditional effect sizes such as mean differences, risk differences, risk ratios, odds ratios, or hazard ratios between two or more study cohorts, this study focuses on synthesizing proportions. These proportions are estimates of the prevalence of hepatitis C in Sub-Saharan Africa as reported in 221 studies published between 2000 and 2013. Because the dissertation synthesizes proportions rather

than difference scores, there is no consensus on which method is best for estimating the variability (or variance) of the true overall pooled proportion (or population prevalence estimate).

One goal of this study is to contribute information to that debate. Therefore, this study synthesizes proportions as the effect size using three different transformations: An estimate of average prevalence of HCV in sub-Saharan Africa using no transformation, an estimate of the average prevalence using a canonical logit transformation, and an estimate of average prevalence using a variance-stabilizing double arcsine transformation. The study hypothesizes that the canonical logit and double-arcsine transformations will result in a tighter estimate of the variance of the pooled prevalence statistic and a more accurate moderator analysis.

No Transformation

The first approach uses no transformation (i.e., a raw approach) and merely capitalizes on the raw prevalence estimate for each study (p_i). Recall from Chapter Two, this prevalence estimate essentially follows a binomial distribution where the variance of any given study is:

$$\mathrm{Var}(p_i) = \frac{p_i(1-p_i)}{N_i}$$

Here, p_i is the proportion positive in article i, and N_i is the number of individuals sampled in that article. Summing over all articles (and other acquired evidence), the raw pooled prevalence estimate becomes a sum of ratios:

$$\text{Pooled prevalence } (P) = \frac{\sum_i \frac{p_i}{Var(p_i)}}{\sum_i \frac{1}{Var(p_i)}}$$

where the inverse variance weight of each article, ubiquitous in most meta-analyses, is noted in the denominator of the test statistic. The standard error (SE) of this raw pooled prevalence estimate is:

$$\text{SE}(P) = \sqrt{\sum_i \frac{1}{Var(p_i)}}$$

yielding a confidence interval for the precision of the population estimate equal to:

$$\text{CI}(P) = P \pm Z_{\alpha/2}\,\text{SE}(P)$$

Canonical Logit Transformation

The second approach uses a canonical logit transformation. This method was used for the results previously published in Mora et al. (2016). Recall from Chapter Two, that the logit transformation formula for each study *i* applies a natural logarithm transformation to the raw prevalence statistic (p_i):

$$t_i = \ln(p_i) = \ln\left(\frac{p_i}{1-p_i}\right)$$

And each study's variance is estimated as:

$$\text{Var}(t_i) = \frac{1}{N_i p_i} + \frac{1}{N_i(1-p_i)}$$

Summing over all articles (and other acquired evidence), the pooled prevalence estimate becomes a sum of the logit transformed ratios:

$$\text{Pooled prevalence } (P_T) \text{ under logit transformation} = \frac{\sum_i \frac{t_i}{Var(t_i)}}{\sum_i \frac{1}{Var(t_i)}}$$

where, again, the inverse variance weight of each article, ubiquitous in most meta-analyses, is noted in the denominator of the test statistic. As before, the standard error (SE) of this transformed pooled prevalence estimate is:

$$\text{SE}(P_T) = \sqrt{\sum_i \frac{1}{Var(t_i)}}$$

yielding a confidence interval for the precision of the population estimate equal to:

$$\text{CI}(P_T) = P_T \pm Z_{\alpha/2}\,\text{SE}(P_T)$$

Double-Arcsine Approach

The final approach applies a double-arcsine transformation for each study i:

$$z_i = \sin^{-1}\sqrt{\frac{n_i}{N_i+1}} + \sin^{-1}\sqrt{\frac{n_i+1}{N_i+1}}$$

where its variance requires no information about the prevalence statistic – only the study sample size (*N*i)*:*

$$\text{Var}(t_i) = \frac{1}{N_i + 0.5}$$

Summing over all articles (and other acquired evidence), the transformed pooled prevalence estimate becomes a sum of transformed ratios:

$$\text{Pooled prevalence } (P_z) \text{ under double arcsine transformation} = \frac{\sum_i \frac{z_i}{Var(z_i)}}{\sum_i \frac{1}{Var(z_i)}}$$

where, as before, the inverse variance weight of each article is noted in the denominator of the test statistic. The standard error (SE) of this transformed pooled prevalence estimate is:

$$\text{SE}(P_z) = \sqrt{\sum_i \frac{1}{Var(z_i)}}$$

yielding a confidence interval for the precision of the population estimate equal to:

$$\text{CI}(P_z) = P_z \pm Z_{\alpha/2}\,\text{SE}(P_z)$$

Importantly, for all three approaches, the transformed pooled prevalence estimates are weighted using the inverse of the summation of the between and within study variances, which is the denominator of the pooled prevalence statistics (as described by Hedges & Vevea, 1998):

$$\text{Pooled prevalence } (P) \text{ under no transformation} = \frac{\sum_i \frac{p_i}{Var(p_i)}}{\sum_i \frac{1}{Var(p_i)}}$$

$$\text{Pooled prevalence } (P_T) \text{ under logit transformation} = \frac{\sum_i \frac{t_i}{Var(t_i)}}{\sum_i \frac{1}{Var(t_i)}}$$

$$\text{Pooled prevalence } (P_z) \text{ under double arcsine transformation} = \frac{\sum_i \frac{z_i}{Var(z_i)}}{\sum_i \frac{1}{Var(z_i)}}$$

Each point estimate is then back-transformed to the original raw prevalence metric as described in Chapter Two and in Barendregt et al. (2013).

Moderator Analysis

Regarding the moderators noted in the data dictionary above, study aims 1 through 5 required a regression approach to compare each level of the moderator on the pooled prevalence statistic.

Under no transformation, weighted linear mixed-effects models with identity links were used to estimate the pooled raw prevalence estimate within population cohorts, SSA regions, type of assay used, and publication year. In these univariable models, each moderator (i.e., population cohort, region, type of assay used, and publication year) represented a fixed effect while random intercepts were allowed for each study contributing to the estimate. For example, let Y_{it} denote the prevalence of HCV for moderator *t* in article *i*. Further, let X_{it} be the value of the moderator for that article. Conditional on a random article effect (γ_i), a linear mixed effects approach models the average prevalence for a given value of the random effect and moderator. It has the form:

$$\mu_{it} = \gamma_i + \alpha + \beta X_{it}$$

which states that the average prevalence for article *i* and moderator *t* is a function of a random article effect (γ_i) that accounts for sampling different populations across articles, a fixed effect intercept term (α) which is the expected prevalence rate when *Xit* = 0, and a fixed effect beta

term (β) which represents the increase or decrease (slope) of HCV prevalence for moderator *t* in article *i*.

Admittedly, a linear mixed effects model is a poor model for estimating any HCV prevalence rate in sub-Saharan Africa because, among other reasons, it is possible to estimate a pooled prevalence estimate outside of the 0 – 1 range (Agresti, 2002). However, a non-transformation option is available in most meta-analysis software packages, including metafor (Viechtbauer, 2010). Because one goal of the study is to compare precision under competing transformations, I report pooled estimates that synthesize non-transformed study estimates in this dissertation as well as pooled estimates that capitalize on a logit and double-arcsine transformation.

Under the logit transformation, weighted random-effects binomial *generalized* linear mixed models were used to estimate prevalence within population cohorts, SSA regions, type of assay used, and publication year. It has a similar form as the linear mixed effects model above except that it includes a logit link function [$g(.)$] to free the prevalence estimate for article *i* and moderator *t* from its 0-1 range to estimate average prevalence:

$$g(\mu_{it}) = \gamma_i + \alpha + \beta X_{it}$$

The model terms are same as before. The only new piece is the logit-link function, which assumes the conditional distribution of the data is binomial (i.e., disease present versus absent). Using SAS, the prevalence of HCV among blood donors versus the general population may be programmed as:

```
PROC GLIMMIX data=meta METHOD=REML;
CLASS binary_risk study_id;
MODEL positive/n = binary_risk / dist=binomial link=logit solution cl;
WEIGHT wstar;
RANDOM intercept / type=un subject=study_id;
LSMEANS binary_risk / pdiff cl ilink;
RUN;
```

where *wstar* is the inverse variance weight and the *ilink* option back transforms the estimates to the raw prevalence metric as described in Barendregt et al. (2013). Under a logit transformation, the exact same approach is used for all other moderators noted in the data dictionary table above to compare moderators on the prevalence of Hepatitis C. Statistical interactions were assessed using multivariable random-effects binomial models. For example, a weighted binomial random-effects model was used to assess whether there was a significant region-by-cohort interaction. In this model, region, cohort, and their interaction served as fixed effects while random intercepts were allowed for each study contributing estimates.

For the last approach, the double arcsine transformation was applied to each article's prevalence estimate and the variance of each article was estimated as described above using SAS Version 9.4. The transformation syntax is:

```
DATA meta_2;
SET meta;
z = (arsin(sqrt(positive / (n + 1))) + arsin(sqrt((positive + 1) / (n + 1))));
variance = 1/(n+0.5);
RUN;
```

Because I no longer capitalize on a canonical logit link, the transformed prevalence estimate now follows a normal distribution and a random effects *linear* mixed regression model was

used to determine the pooled prevalence estimate as a function of each moderator noted in the data dictionary above. Under this transformation, the prevalence of Hepatitis C among blood donors and the general population in Sub-Saharan Africa, for example, were compared using SAS syntax:

```
PROC MIXED data=meta ORDER = DATA METHOD=REML COVTEST;
CLASS binary_risk study_id;
MODEL z = binary_risk  / solution cl ddfm=contain outp=predicted;
RANDOM study_id;
PARMS (1) (1) / hold=2;
WEIGHT wstar;
RUN;
```

Here, the PARMS statement is used by SAS to hold the within-study variances fixed when estimating the fixed-effects parameter estimates, and the use of restricted maximum likelihood method (REML) was recommended by van Houwelingen, Arends, and Stijnen (2002). In fact, the REML method is used for all analyses for consistency. The transformed pooled parameter estimate (*z*) is returned to its 0 – 1 scale using the more complex but accurate back transformation described in Chapter Two:

$$\text{Back Transformed Pooled Prevalence } (P_Z) = 0.5\left\{1-\text{sgn}(\cos Z)\left[1-\left(\sin Z+\frac{\left(\sin Z-\frac{1}{\sin Z}\right)}{N}\right)^2\right]^{0.5}\right\}$$

which is coded in SAS as:

```
DATA predicted;
SET predicted;
IF cos(z) > 0 then sgn = 1;
else sgn = -1;
```

```
z = 0.5 * (1 - sgn * (1 - (sin(z) + (sin(z) - 1 / sin(z))/ N)**2)**0.5);
RUN;
```

Where *N* is replaced with an integer representing the total number of observations (or sum of negative and positive cases) sampled.

Transformation Comparisons

For all five aims, each prevalence estimate was tabled with its 95% confidence interval. These intervals were compared under all three transformations and, when they do not overlap, I conclude that the choice of transformation gains internal and statistical validity (Payton, Greenstong, & Schenker, 2003). This means that non-overlapping confidence intervals signal conflicting conclusions about the pooled prevalence estimate. Under these conditions, if the analysis were repeated many times, 95% of the time the true prevalence of HCV under one transformation would exclude the rate found under a competing transformation. Such conflicting conclusions may indicate severe bias in the pooled prevalence estimate that is directly dependent on the choice of transformation.

Additionally, in this study the confidence interval widths under all three transformations were directly compared using a precision statistic described by Barendregt et al. (2013). That is, for each approach, I subtracted the lower end of the back-transformed 95% confidence interval from its upper end, and this statistic shows how confident we are in the pooled prevalence estimate under each transformation. For this statistic, values closer to zero indicate greater precision and a superior transformation method.

Regarding model fit, this study used normal quantile-quantile (QQ) plots to assess the normal distribution assumption of the data under each transformation. These figures plot the quantiles of the observed prevalence distribution (y-axis) against the expected quantiles if the prevalence data is in fact normally distributed (x-axis). When the model fits well, the studies are normally distributed and fall on a straight line with a slope of 1.00 that goes through the (0, 0) coordinate point of the plot (Wang & Bushman, 1998).

Under each transformation, this dissertation also relied on residual and leverage bubble plots to identify studies that pull-on the estimated average prevalence. That is, I plotted leverage or hat values (x-axis) against studentized residuals (y-axis) and made the size of the bubble proportional to Cook's outlier diagnostic score (Viechtbauer & Cheung, 2010). Studies that were overly influential had larger radii with studentized residuals exceeding an absolute value of $z = 3.00$.

Regarding publication bias, this dissertation used two approaches. First, the study compared publication bias among the three competing transformations using Light and Pillemer (1984) funnel plots and subsequently using Begg and Mazumdar (1994) correlation coefficients. Light and Pillemer (1984) plots were used to compare the asymmetry of overall prevalence among all three transformation methods. These scatter plots plot the transformed prevalence estimates for each study on the x-axis with their inverted standard error on the y-axis. Whereas asymmetry in a funnel plot *may* indicate publication bias, when there is no

publication bias present 95% of the included studies scatter within the 95% confidence interval of the funnel (i.e., and the corresponding plot is symmetric).

However, a more formal test for publication bias was used to compare all transformed pooled prevalence estimates in this study using Begg and Mazumdar's (1994) rank correlation test. This tau correlation coefficient tests whether the included study prevalence estimates are related to their sample sizes. If the correlation coefficient is negative and significantly different from zero, it means the meta-analysis is missing studies with low prevalence merely because the sample sizes for those missing studies were too small for publication and were suppressed. Admittedly, Begg and Mazumdar indicate their formal test for publication bias is underpowered to detect such bias when there are fewer than 25 articles contributing to the correlation estimate. This limitation is acknowledged in Chapters Four and Five when appropriate.

Lastly, for all moderator analyses in this study, I capitalize on Viechtbauer's (2010) R-package *metafor* to compute explained and unexplained heterogeneity statistics. These statistics were also compared under the raw regression approach, canonical logit approach, and double-arcsine approach.

I use R^2 to estimate the proportion of variability in the dispersion of the pooled prevalence statistic that is directly due to the fixed effects in the model (e.g., at-risk population cohort, region of SSA, article year, and assay type). Here, higher R^2 values indicate a superior transformation method. Conversely, I use I^2 as an inconsistency index (or heterogeneity index) for all moderator analyses. Hedges and Olkin (1985) and Raudenbush and Bryk (2002) describe

I^2 as a statistic bounded between 0-1 that estimates the total variability in the pooled prevalence estimate that is due to differences among the included studies (i.e., between-article error). Generally, an I^2 statistic close to zero means that all heterogeneity observed in the meta-analysis was due to sampling error, whereas an I^2 close to unity means that all variability observed in the meta-analysis was due to heterogeneity between studies (Viechtbauer, 2010; Hedges & Olkin, 1985; Raudenbush & Bryk, 2002). Here, lower I^2 values indicate a superior transformation method (i.e., less inconsistency across articles), and I^2 values of 25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively.

Summary

This chapter summarized the research questions and methods used to address them. More specifically, it summarized the literature review for the meta-analysis, how the data was captured and recorded for each article, the statistical analyses used to estimate the pooled prevalence estimate of Hepatitis C in sub-Saharan Africa, and the approach used to compare the estimates under three competing methods to determine which methodology offers superior confidence in the pooled prevalence estimate: No transformation, a canonical logit transformation, or double arcsine transformation. Chapter Four describes the results and presents them using standard tables, forest plots, and Light and Pillemer (1984) funnel plots. Chapter Five concludes the dissertation with a discussion of the results and contributions to the consensus on which transformation offers the optimal approach for estimating the prevalence of Hepatitis C in Sub-Saharan Africa.

CHAPTER FOUR

RESULTS

In this chapter, I describe the results of the literature search for this dissertation which is a meta-analysis of the prevalence of Hepatitis C in sub-Saharan Africa. I also compare results from pooling individual prevalence estimates across the included articles using the three competing transformations described in Chapter Three: The double-arcsine transformation, the canonical logit transformation, and no transformation. I compare these estimates among articles that sample blood donors, those living with human immunodeficiency virus (HIV), individuals from the general population, individuals living with a chronic illness, and those at high-risk for infection. I also compare these pooled prevalence estimates among articles sampling from African regions described by the World Health Organization (WHO), including Central, Eastern, Southern, and Western Africa.

I further describe a meaningful, significant interaction between the five population cohorts and the region of Africa in which they live. That is, in this chapter I show that the estimated prevalence of HCV for each population cohort *depends* on WHO defined African region. I also compare the pooled prevalence estimates under each transformation by article year as well as the assay used to detect the HCV virus. Finally, this chapter concludes with a description of the variability in prevalence estimates across articles (i.e., heterogeneity) and provides a summary of the overall results.

Inclusion and Exclusion

This section reports the results of the literature search for the dissertation, which was previously reported in Mora et al. (2016). The search identified 361 published articles and abstracts for the analysis. Using WHO defined boundaries, 69 of these references were excluded because they sampled from the Northern Africa region. Additionally, 15 articles were excluded because they were printed in a language other than English, Spanish, or French, and another 68 articles were excluded because they had incomplete data. A final set of 24 articles were excluded because they were duplicate studies. This left 185 articles comprising *k* = 221 independent studies available for this dissertation (see Figure 1).

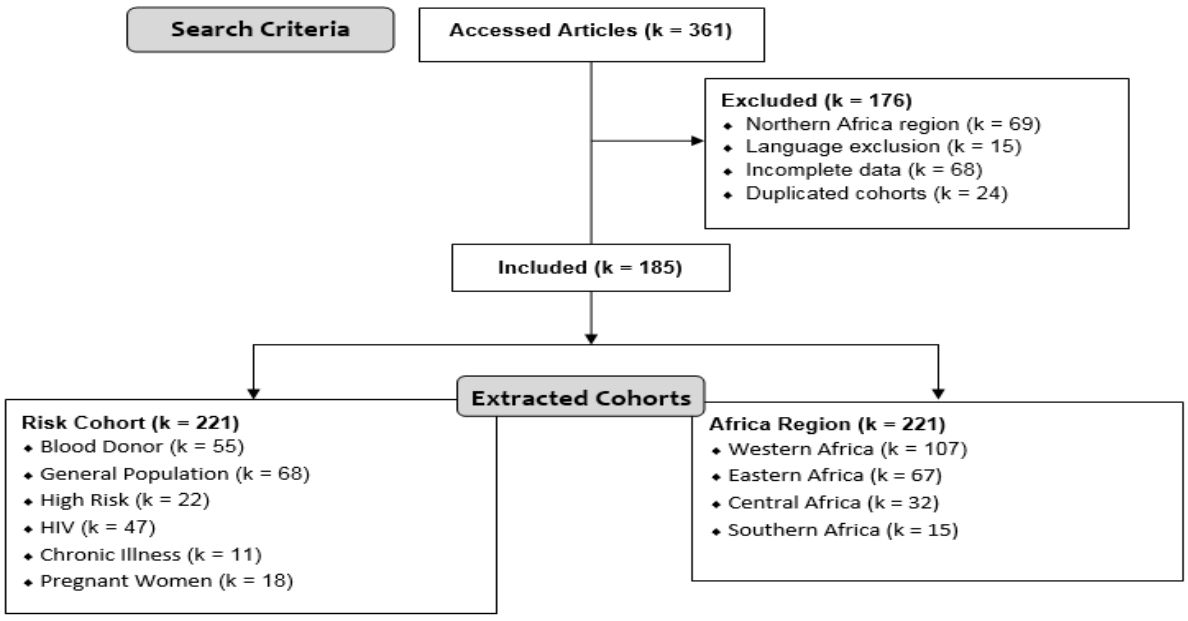

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Figure 1. Article selection and cohort identification

Figure 2 shows that roughly half of articles sampled from Western Africa (*k* = 107 or 48.5%), with another 30% sampling from Eastern Africa (*k* = 67 or 30.3%). Fewer articles sampled from Central Africa (*k* = 32 or 14.4%) and Southern Africa (*k* = 15 or 6.8%).

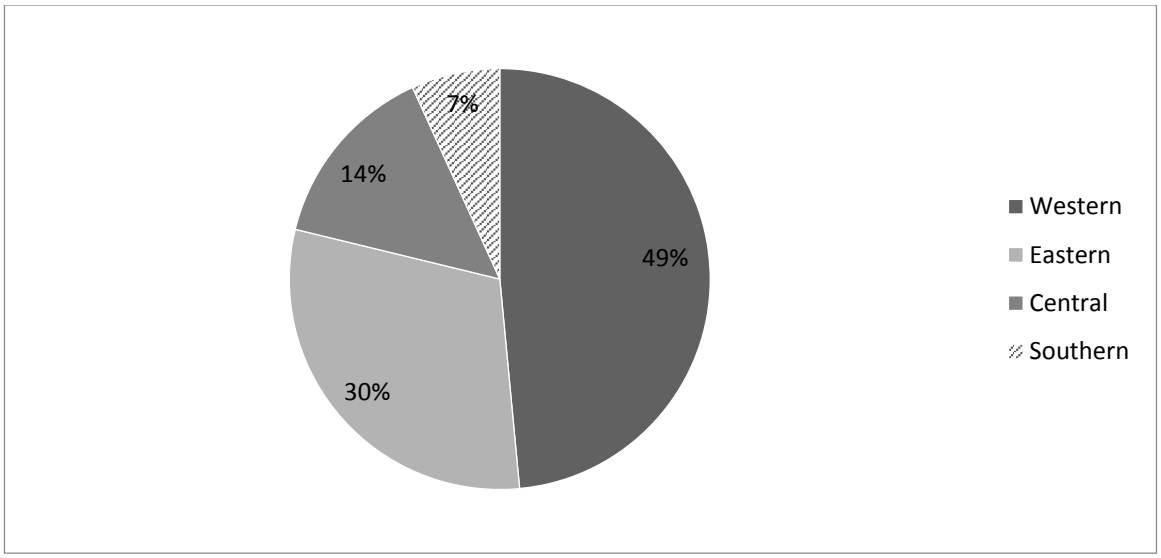

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Figure 2. Proportion of studies included in the meta-analysis by region

Figure 3 shows the distribution of all included studies by cohort and region. For all four regions, the general population and blood donor cohorts represented most of the included studies (at 27.1% each), followed by studies of individuals with comorbid HIV (21.7%). However, within each region, there was considerable variability among the included cohorts (Mora et al., 2016). That is, while most articles in Southern Africa sampled individuals with HIV (64.3%), few articles sampled such individuals in Western Africa (18.3%), Eastern Africa (25.4%), and Central Africa (3.8%).

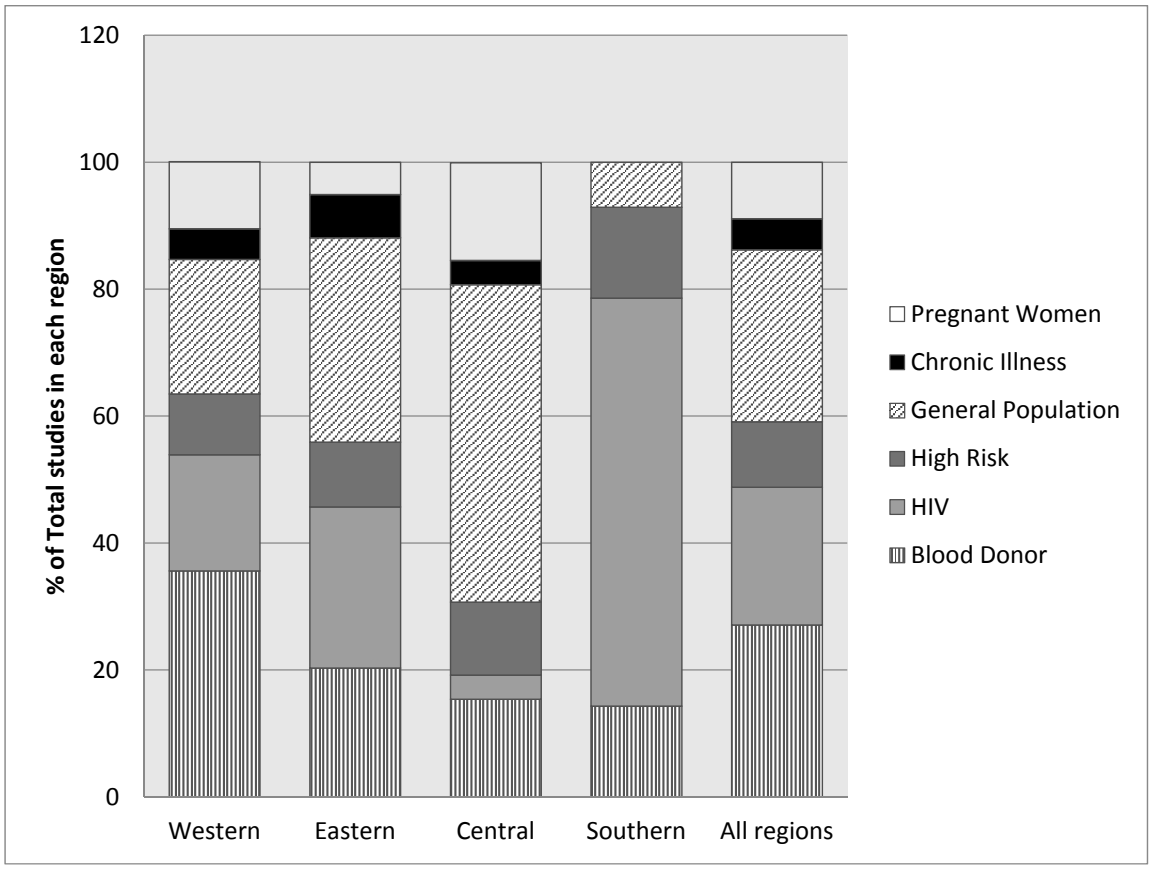

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Figure 3. Proportion of studies included in the meta-analysis by cohort and region

Overall Prevalence Estimates

This section reports the overall prevalence of Hepatitis C in Sub-Saharan Africa. It also compares these pooled estimates when using a double-arcsine transformation, canonical logit transformation, and no transformation as described in Chapter Three.

By far, the logit transformation provided the most conservative (lowest) estimate of HCV seroprevalence in sub-Saharan Africa which was approximately 3.80% (95% CI: 3.20% - 4.50%), while the raw regression approach provided the highest estimate at 5.83% (95% CI:

4.94% - 6.72%). The double-arcsine approach struck a balance between these two approaches yielding an HCV seroprevalence estimate of 4.68% (95% CI: 3.94% - 5.47%) (see Table 2).

Table 2. Overall Prevalence under Competing Transformations

	Average Prevalence	**95% Confidence Interval**		**Precision**	***τ***
		Lower	**Upper**		
Transformation (*k* = 221)					
None	5.83	4.94	6.72	1.78	.070
Logit	3.80	3.20	4.50	1.30	-.150**
Double Arcsine	4.68	3.94	5.47	1.53	.047

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Tau (τ) = Begg and Mazumdar publication bias correlation coefficient. Significance of the tau correlation coefficient is noted as *$p < .05$, **$p < .01$, and ***$p < .001$.

While the logit approach was the most precise among the three competing transformations (CI width = 1.3), it was impugned somewhat by publication bias. Figure 4 shows the asymmetry of the canonical logit approach, and a more formal follow-up assessment for publication bias was conducted using the Begg and Mazumdar (1994) rank correlation test. The test revealed a moderate negative association between the logit transformed study estimates and their sample size ($k = 221$, $\tau = -0.15$, $p = .001$). Under the logit approach, this negative association suggests that studies with small prevalence estimates were missing from the analysis merely because their sample size was insufficient for publication.

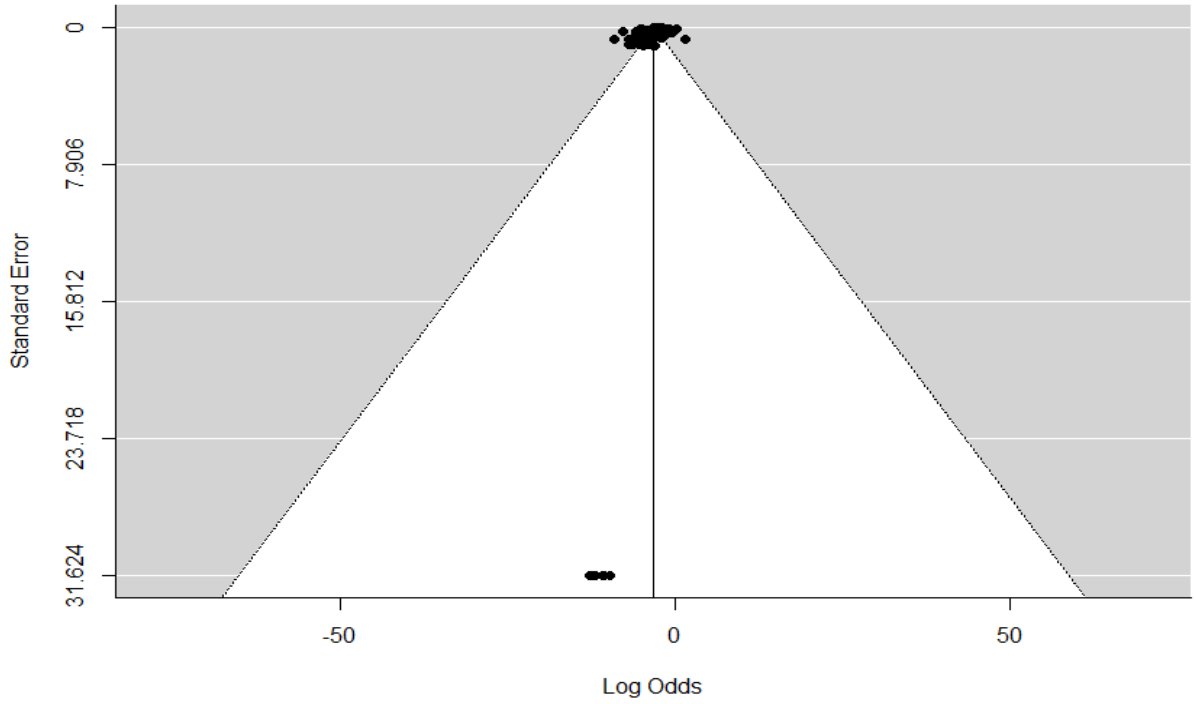

Figure 4. Funnel plot for the overall logit transformed HCV prevalence estimate

Figure 5 shows the asymmetry of the double-arcsine approach. Unlike the logit approach, the double arcsine approach yielded a slightly higher overall prevalence estimate of 4.68% (95% CI: 3.94% - 5.47%) but, by comparison, was more resistant to publication bias in the sense that there was no meaningful association between the double-arcsine transformed study estimates and their sample size as measured using the Begg and Mazumdar (1994) rank correlation test (k = 221, τ = 0.05, p = .30).

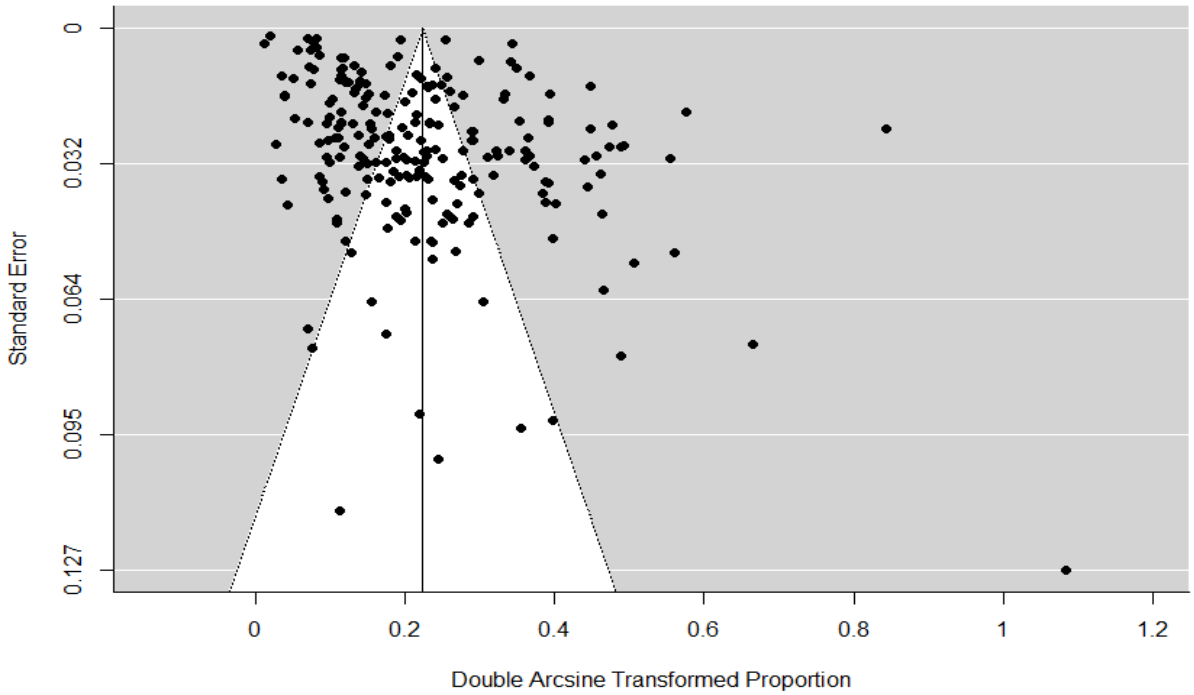

Figure 5. Funnel plot for the overall double-arcsine transformed HCV prevalence estimate

Figure 6 shows the asymmetry of the raw regression approach. Interestingly, the raw regression approach yielded the highest HCV seroprevalence estimate (5.83%, 95% CI: 4.94% - 6.72%) and, by comparison to the logit transformation, was also more resistant to publication bias in the sense that there was no meaningful association between the raw regression study estimates and their sample size as measured by the Begg and Mazumdar (1994) rank correlation test (k = 221, τ = 0.07, p = .12).

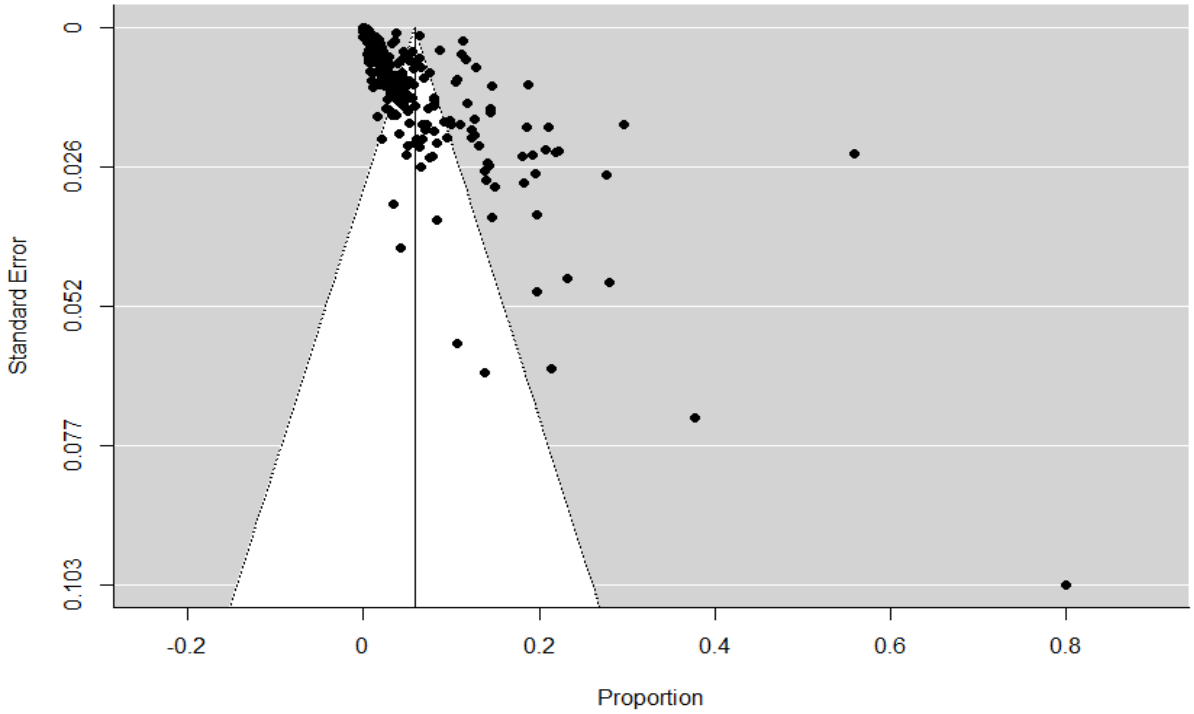

Figure 6. Funnel plot for the overall non-transformed HCV prevalence estimate

Model Fit

Model fit for all three transformations are displayed in Figure 7. In this figure, normal quantile-quantile (QQ) plots assess the normal distribution assumption of the data under each transformation. Recall from Chapter Three, that this plots the quantiles of the observed prevalence distribution (y-axis) against the expected quantiles if the prevalence data is in fact normally distributed (x-axis). When the model fits well, the studies are normally distributed and all fall on a straight line with a slope of 1.00 that goes through the (0,0) point (Wang & Bushman, 1998).

Under each transformation, Figure 7 also shows influential studies that may pull-on the estimated average prevalence. As described in Chapter Three, this figure plots leverage or hat values (x-axis) against studentized residuals (y-axis) where the size of the bubble is proportional to Cook's outlier diagnostic score (Viechtbauer & Cheung, 2010). Studies that are overly influential have large radii and studentized residuals exceeding an absolute value of $z = 3.00$.

When using the double-arcsine transformation, the data were largely normally distributed and only two articles were identified as influential: Diouf et al. (2000) who studied 15 individuals at high-risk for HCV infection in Western Africa had low leverage (h=0.0025) in the model but was clearly an outlier with predicted prevalence more than four standard deviations higher than observed prevalence ($z = 4.83$). Similarly, Pepin et al. (2010) studied 451 individuals from the general population in Central Africa and, by comparison to Diouf et al. (2000), had twice as much leverage (h=0.005) with predicted prevalence more than five standard deviations higher than observed prevalence ($z = 5.02$). Removing these two studies from the model reduced the overall double-arcsine back-transformed prevalence estimate from 4.68% (95% CI: 3.94% – 5.47%) to 4.45% (95% CI: 3.78% - 5.16%).

The data under a canonical logit transformation fit best with nearly all studies normally distributed under the transformation. Using this traditional approach, only two extremely large blood donor studies were considered influential: Fang et al. (2003) who studied 19,709 blood donors in Southern Africa had high leverage ($h = 0.004$) and a predicted prevalence that was more than four standard deviations below observed prevalence ($z = -4.22$). Similarly,

Vermeulen et al. (2009) who studied 73,293 blood donors in Southern Africa also had high leverage (h = 0.005) with predicted prevalence more than three standard deviations below observed prevalence (z = -3.78). Removing these two studies from the model increased the overall canonical-logit back-transformed prevalence estimate from 3.80% (95% CI: 3.20% – 4.50%) to 4.00% (95% CI: 3.41% - 4.69%), which was largely in agreement with the double-arcsine approach.

As expected from the literature review (Chapter Two), the raw regression approach was the most skewed and provided the worst fit as demonstrated by its high number of influential studies: Bowring et al. (2013) who studied 267 high risk individuals in Eastern Africa had high influence (h = 0.004) with a predicted prevalence that was more than three times higher than observed prevalence (z = 3.16). Worse, Diouf et al. (2000), which was also an outlier under the double-arcsine transformation, had similarly low influence under a raw regression approach (h = .001) but was clearly an influential outlier with an estimated prevalence more the *six* times higher than observed prevalence (z = 6.13). Also like the double-arcsine approach, the raw regression model identified Pepin et al. (2010) as an influential study (h = 0.004) with a predicted prevalence estimate more than *eight* times higher than observed prevalence (z = 8.39).

Finally, using the raw regression model Nerreniete et al. (2005) who studied 644 individuals from the general population in Central Africa also had high leverage (h = 0.004) with a predicted prevalence more than three standard deviations above observed prevalence (z =

3.64). Removing these four studies from the model reduced the overall untransformed prevalence estimate from 5.83% (95% CI: 4.94% – 6.72%) to 5.13% (95% CI: 4.45% - 5.81%).

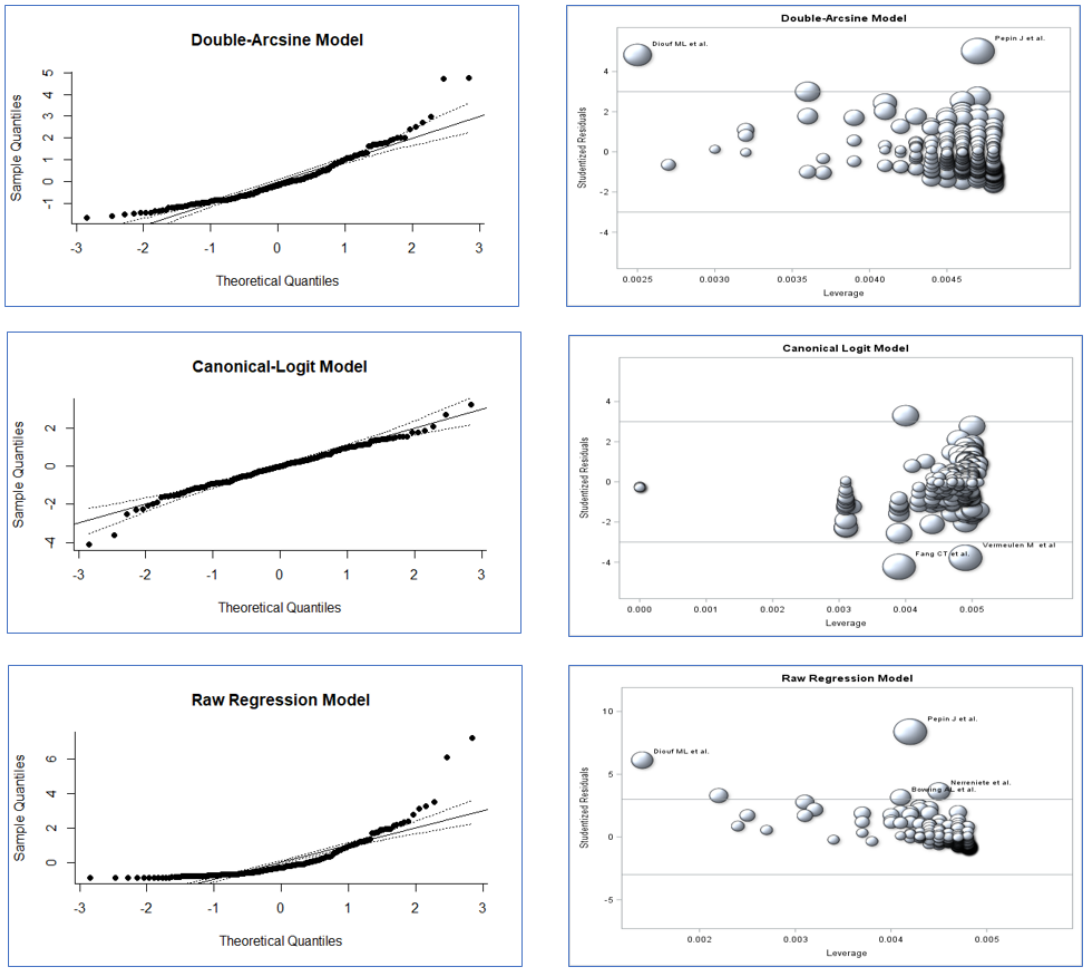

Figure 7. Model fit for the transformed and untransformed estimates

Prevalence by Risk Strata

This section reports the prevalence of Hepatitis C by population risk cohort, including blood donors, those living with human immunodeficiency virus (HIV), individuals from the general population, individuals living with a chronic illness, and those at high-risk for infection.

It also compares these pooled estimates when they are calculated under a double-arcsine transformation, canonical logit transformation, and no transformation. The prevalence estimates for each risk strata are displayed in Table 3.

Regardless of the transformation used, there was significant variability in the prevalence of HCV among all cohorts. This was true when using a double-arcsine approach [overall χ^2 (df=4) = 45.41, $p < .001$], logit transformation [overall χ^2 (df=4) = 47.01, $p < .001$], as well as raw regression approach [χ^2 (df=4) = 37.23, $p < .001$]. Among the competing transformations, the canonical logit approach provided the most conservative (lowest) point estimates for all cohorts, while the raw regression approach provided the highest point estimates for all cohorts.

Prevalence was highest for those at high-risk for HCV infection with estimates of 10.12% (95% CI: 6.42% - 15.60%), 11.25% (95% CI: 8.14% - 14.79%), and 11.97% (95% CI: 9.22% - 14.71%) for the logit, double arcsine, and raw approach, respectively (all $p < .001$). This was followed by those living with a chronic illness who had roughly comparable estimates under a logit transformation (i.e., 7.76%, 95% CI: 3.97 – 14.61%), double arcsine transformation (i.e., 8.40%, 95% CI: 4.72% - 12.98%), and under a raw regression approach (i.e., 8.63%, 95% CI: 4.82% - 12.44%; all $p < .001$).

Table 3. Prevalence Estimates for Each Risk Strata under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision	τ
		Lower	Upper		
Blood Donors (*k* = 55)					
None	2.83	1.20	4.46	3.26	-.184*
Logit	1.79	1.31	2.45	1.14	.003
Double Arcsine	2.13	1.26	3.19	1.93	.144
HIV (*k* = 47)					
None	4.63	2.84	6.41	3.57	.369***
Logit	3.48	2.47	4.89	2.42	-.180
Double Arcsine	3.90	2.61	5.42	2.81	.228*
General Population (*k* = 86)					
None	6.59	5.25	7.93	2.68	.071
Logit	4.63	3.61	5.92	2.31	-.09
Double Arcsine	5.37	4.23	6.63	2.40	.14
Chronic Illness (*k* = 11)					
None	8.63	4.82	12.44	7.62	.491*
Logit	7.76	3.97	14.61	10.64	-.309
Double Arcsine	8.40	4.72	12.98	8.26	-.091
High Risk (*k* = 22)					
None	11.97	9.22	14.71	5.49	.455**
Logit	10.12	6.42	15.60	9.18	-.264
Double Arcsine	11.25	8.14	14.79	6.65	.10

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Tau (τ) = Begg and Mazumdar publication bias correlation coefficient. Significance of the tau correlation coefficient is noted as *$p < .05$, **$p < .01$, and ***$p < .001$.

Conversely, prevalence estimates were much lower for the general population. In this risk strata, prevalence was as low as 4.63 (95% CI: 3.61% - 5.92%) under the logit

transformation. Point estimates for this cohort increased sequentially under a double arcsine transformation at 5.37% (95% CI: 4.23% - 6.63%) and when using a raw regression approach at 6.59% (95% CI: 5.25% - 7.93%; all $p < .001$). This trend continued for those with comorbid HIV where the HCV prevalence was as low as 3.48% (2.47% - 4.89%) when using a logit transformation, 3.90% (95% CI: 2.61% - 5.42%) when using a double arcsine transformation, and 4.63% (95% CI: 2.84% - 6.41%) when applying a raw regression approach (all $p < .001$).

As expected, those donating blood had the lowest prevalence estimates regardless of the transformation method employed. That is, among those donating blood, the prevalence of HCV was 1.79% (95% CI: 1.31% - 2.45%) when using a logit transformation, 2.13 (95% CI: 1.26 – 3.19%) when using a double-arcsine transformation, and 2.83% (95% CI: 1.20 – 4.46%) when using a raw regression approach (all $p < .001$). In fact, post-hoc pairwise comparisons that do not adjusted for inflated type 1 error revealed that blood donors even had a lower prevalence estimate than those in the general population. This was true when using a double-arcsine approach ($z = 4.02$, $p < .001$), canonical logit approach ($z = 4.68$, $p < .001$), and no transformation ($z = 3.50$, $p < .001$).

Regarding model fit, the precision of these estimates was quite variable. Recall that precision represents the spread of the 95% confidence interval for the pooled prevalence statistic (i.e., with the lower end of the interval subtracted from the upper end). As described in Chapter 3, widths closer to zero indicate more precision.

While the raw regression approach resulted in the tightest confidence intervals for the chronic illness (width = 7.62) and high-risk (width = 5.49) cohorts, the canonical logit transformation resulted in the widest precision with widths of 10.64 and 9.18 for these same cohorts, respectively. For all other risk strata, this conclusion flipped: Among blood donors, those in the general population, and those with comorbid HIV, the logit transformation provided the most precise estimates with widths of 1.14, 2.31, and 2.42 for these cohorts, respectively. Conversely, the raw regression results were more uncertain with confidence widths of 2.68, 3.26, and 3.57 for those in the general population, blood donors, and comorbid HIV, respectively.

Publication bias comparisons for each cohort are also displayed in the last column of Table 3. Among blood donor studies, the rank correlation between the prevalence estimates computed under a logit transformation and their standard error was non-significant (k = 55, τ = 0.003, p = .98) suggesting that studies with small prevalence estimates were included in the analysis because they were meaningful (and not solely because they originated from studies with large sample sizes). This conclusion was similar when using the double-arcsine transformation (k = 55, τ = 0.144, p = .12). However, when using a raw regression approach for the blood donor studies, there was noticeable publication bias as measured by the Begg and Mazumdar (1994) rank correlation test (k = 55, τ = -0.184, p = .048). Under a raw regression approach, this significant correlation suggests that the individual studies buttressing the overall prevalence estimate for blood donors were overly dependent on their sample sizes. That is,

blood donor studies with small prevalence estimates may be missing from the analysis merely because their sample sizes were too small.

A similar trend was noticeable among the chronic illness (k = 11) and high-risk (k = 22) cohorts. That is, there was no meaningful association between the study estimates and their sample size for these cohorts under the double arcsine and logit transformations (all $p > .05$). However, it is important to note that Begg and Mazumdar's (1994) correlation test may be underpowered when the number of studies is fewer than 25. Still, despite few articles contributing to the pooled prevalence estimates for the chronic illness and high-risk strata, the raw regression approach remained biased. That is, there was a significant association between the study prevalence estimates and their sample size in this cohort (k = 11, τ = 0.49, p = .04) as well as the high-risk strata (k = 22, τ = 0.46, p = .003).

Among HIV studies, both the raw transformation (k = 47, τ = 0.37, $p < .001$) and double arcsine transformation (k = 47, τ = 0.23, p = .02) methods revealed significant publication bias, while the logit transformation was more resistant to such bias (k = 47, τ = -0.18, p = .08). In the general population, there was no meaningful association between the study estimates and their sample size when using the raw approach (k = 86, τ = 0.07, p = .34), logit approach (k = 86, τ = -0.09, p = .24), or double arcsine approach (k = 86, τ = 0.14, p = .054).

Prevalence by Region

This section reports the prevalence of Hepatitis C by WHO defined regions of Sub-Saharan Africa. It also compares these pooled estimates when they are calculated under a

double-arcsine transformation, canonical logit transformation, and no transformation. The prevalence estimates for each region are displayed in Table 4.

Table 4. Prevalence Estimates for Each African Region under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision	τ
		Lower	Upper		
Central Africa (*k* = 32)					
None	10.69	8.51	12.87	4.36	.305*
Logit	7.74	5.22	11.31	6.09	-.297*
Double Arcsine	9.22	6.85	11.90	5.05	.008
Eastern Africa (*k* = 67)					
None	4.72	3.23	6.22	2.99	.08
Logit	3.04	2.26	4.08	1.82	-.221*
Double Arcsine	3.65	2.57	4.89	2.32	.136
Southern Africa (*k* = 15)					
None	1.48	-1.62	4.58	6.20	.391*
Logit	0.73	0.35	1.52	1.17	.219
Double Arcsine	1.04	0.05	2.89	2.84	-.200
Western Africa (*k* = 107)					
None	5.62	4.41	6.82	2.41	.069
Logit	4.12	3.28	5.16	1.88	-.082
Double Arcsine	4.81	3.81	5.91	2.10	.177*

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Tau (τ) = Begg and Mazumdar publication bias correlation coefficient. Significance of the tau correlation coefficient is noted as *$p < .05$, **$p < .01$, and ***$p < .001$.

Regardless of the transformation used, there was significant variability in the prevalence of HCV among all regions. This was true when using a double-arcsine approach [overall χ^2

(df=3) = 30.29, $p < .001$], logit transformation [overall χ^2 (df=3) = 34.77, $p < .001$], as well as raw regression approach [χ^2 (df=3) = 28.78, $p < .001$]. Among the competing transformations, the canonical logit approach provided the most conservative (lowest) point estimates for all regions, while the raw regression approach provided the highest point estimates for all regions.

Prevalence was highest for those in Central Africa with estimates of 7.74% (95% CI: 5.22% - 11.31%), 9.22% (95% CI: 6.85% - 11.90%), and 10.69% (95% CI: 8.51% - 12.87%) for the logit, double arcsine, and raw approach, respectively (all $p < .001$). This was followed by those living in Western Africa with moderate prevalence estimates under a logit transformation (i.e., 4.12%, 95% CI: 3.28 – 5.16%), double arcsine transformation (i.e., 4.81%, 95% CI: 3.81% - 5.91%), and raw regression approach (i.e., 5.62%, 95% CI: 4.41% - 6.82%; all $p < .001$).

Prevalence rates for those living in Eastern Africa were comparable. It was at 3.04% (95% CI: 2.26% - 4.08%) under a logit transformation, 3.65% (95% CI: 2.57% - 4.89%) under a double-arcsine transformation, and 4.72% (95% CI: 3.23% - 6.22%) when using a raw regression approach. As expected from the literature review, prevalence was lowest in Southern Africa where the estimate was as low as 0.73% (95% CI: 0.35% - 1.52%) under a logit transformation, 1.04% (95% CI: 0.05% - 2.89%) under a double-arcsine transformation, and 1.48% (95% CI: -1.62% - 4.58%) when using a raw regression approach.

Regarding model fit, the precision of these estimates was quite variable. As before, precision represents the spread of the 95% confidence interval for the pooled prevalence

statistic (i.e., with the lower end of the interval subtracted from the upper end). Widths closer to zero indicate more precision.

Except for in Central Africa where the raw regression approach provided the tightest estimate of HCV seroprevalence (width = 4.36) when compared to both the logit (width = 6.09) and double-arcsine approach (width = 5.05), the raw regression approach generally provided the most uncertainty with widths of 2.41, 2.99, and 6.20 for the Western Africa, Eastern Africa, and Southern Africa estimates, respectively. In fact, in Southern Africa the raw regression approach predicted an unacceptable lower confidence bound that was less than 0. Conversely, the canonical logit transformation provided the most precise estimates for these regions with widths of 1.88, 1.82, and 1.17 for the Western, Eastern, and Southern Africa estimates, respectively. Interestingly, this conclusion flipped in Central Africa, where the logit transformation resulted in inferior precision with a width of 6.09 while the raw regression approach provided the tightest confidence with a width of only 4.36.

Publication bias comparisons for each region are also displayed in Table 4. For the logit transformation, there was a large association between the study estimates and their sample size for Central Africa (k = 32, τ = -0.30, p = .02) and Eastern Africa (k = 67, τ = -0.22, p = .01). For the raw regression approach, there was also considerable publication bias for the Central Africa estimate (k = 32, τ = 0.31, p = .01) and, despite few articles, for the Southern Africa estimate (k = 15, τ = 0.39, p = .046). Interestingly, the double-arcsine approach was generally resistant to publication bias as measured by Begg and Mazumdar's (1994) rank correlation test.

This was true except for the Western Africa estimate, where there was a moderate association between the individual study prevalence estimates and their sample size (k = 107, τ = 0.18, p = .01).

Prevalence for Each Cohort Stratified by Region

This section reports the prevalence of Hepatitis C for each population cohort stratified by WHO defined regions of Sub-Saharan Africa. It also compares these pooled estimates when they are calculated under a double-arcsine transformation, canonical logit transformation, and no transformation.

Figure 3 (above) shows the distribution of all included studies by cohort and region. A multivariable mixed-effects model revealed a significant interaction between the cohort and region moderators. This was true when using a double arcsine method [χ^2 (df=19) = 978.02, p < .001], logit transformation method [χ^2 (df=19) = 2106.31, p < .001], as well as when no transformation method was used [χ^2 (df=19) = 314.56, p < .001]. This interaction is shown in Figures 8 and 9.

Essentially, the prevalence estimates for each risk strata *depend* on the African region in which they were sampled and, in addition to Figures 8 and 9, Tables 5 through 8 display these stratified prevalence estimates. Due to too few articles available within the smaller stratified tables, publication bias estimates are not reported (as recommended by Begg & Mazumdar, 1994).

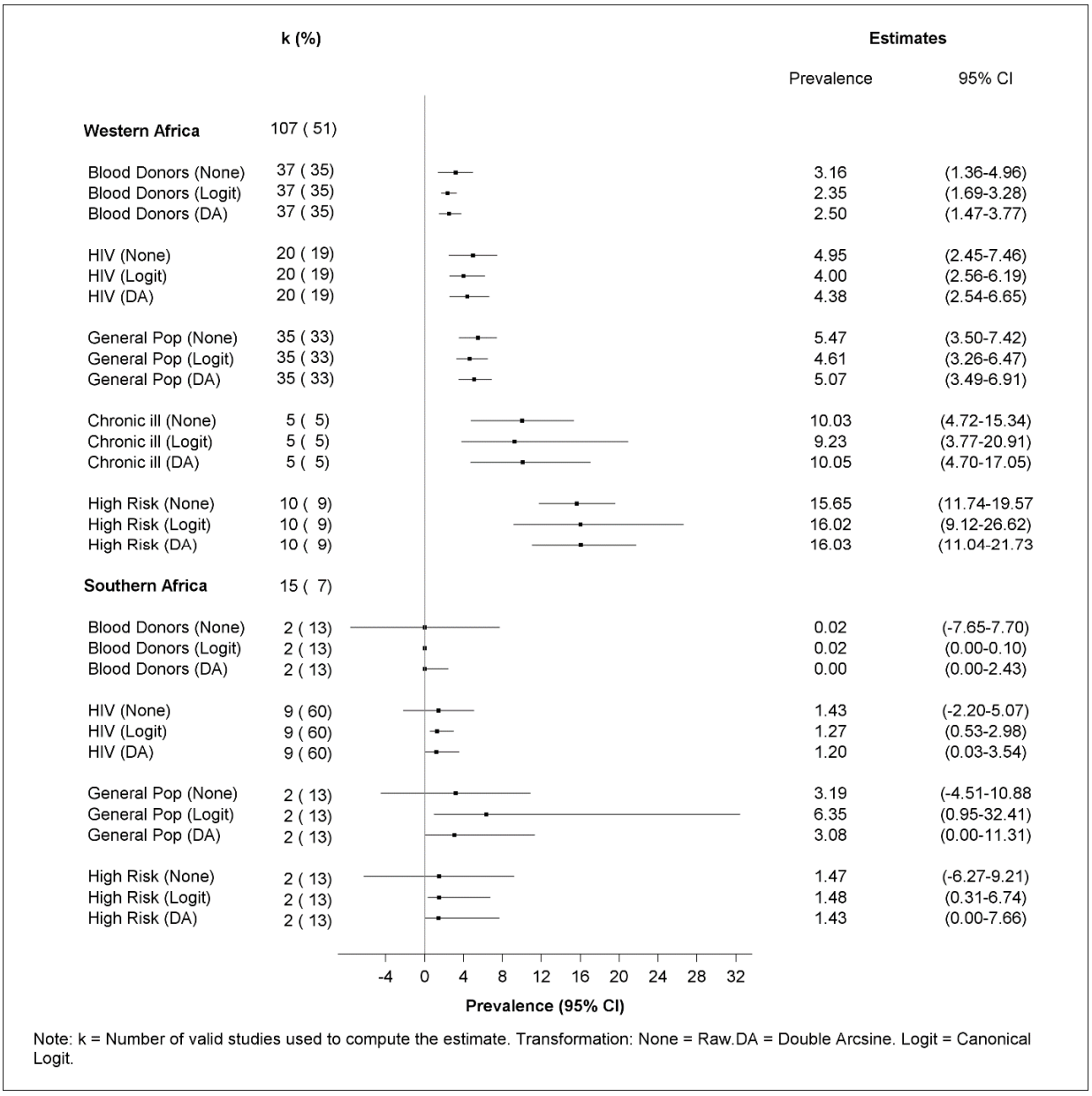

Figure 8. Pooled average prevalence estimates for each cohort in Western and Southern Sub-Saharan Africa

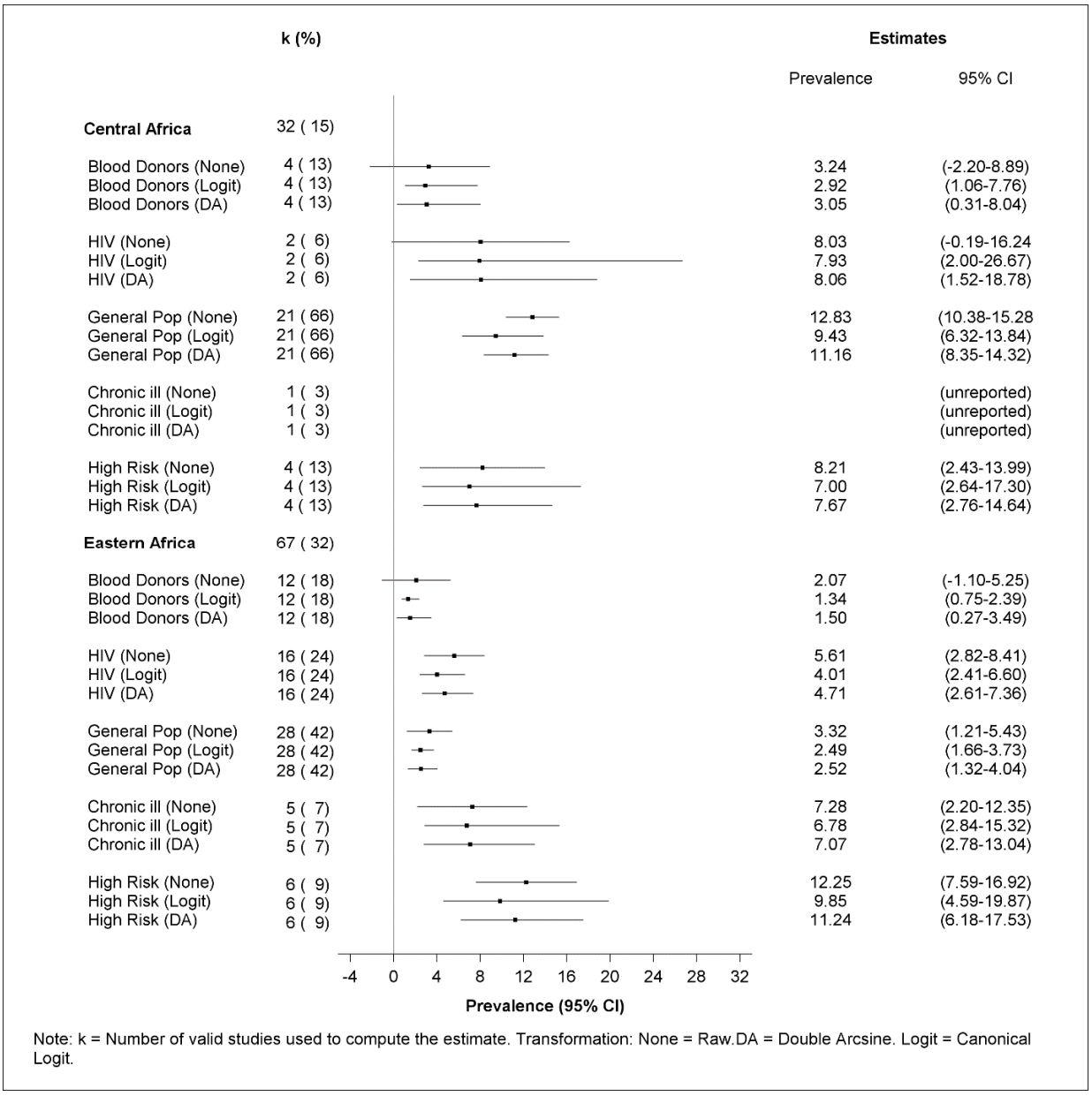

Figure 9. Pooled average prevalence estimates for each cohort in Central and Eastern Sub-Saharan Africa

As expected from the literature review (Chapter Two), the seroprevalence of HCV was alarmingly high in Eastern Africa among those at high-risk for the infection which was estimated at 9.85% (95% CI: 4.59% - 19.87%) when using a logit transformation, 11.24% (95% CI: 6.18% -

17.53%) when using a double arcsine method, and as high as 12.25% (95% CI: 7.59% - 16.92%) when using a raw regression approach (see Table 5). This was followed by those with a chronic illness with estimates of 6.78% (95% CI: 2.84% - 15.32%) when using a logit transformation, 7.07% (95% CI: 2.78% - 13.04%) when using a double arcsine transformation, and 7.28% (95% CI: 2.20% - 12.35%) when using a raw regression approach.

Among those with comorbid HIV in Eastern Africa, the seroprevalence of HCV was comparable when estimated under a logit transformation (i.e., 4.01%, 95% CI: 2.41% - 6.60%) as well as when using a double-arcsine transformation (i.e., 4.71%, 95% CI: 2.61% - 7.36%) but was noticeably (if not significantly) higher when using a raw regression approach (i.e., 5.61%, 95% CI: 2.82% - 8.41%).

Similarly, those in the general population in Eastern Africa had lower prevalence estimates which were also comparable under the three competing transformations: 2.49% (95% CI: 1.66% - 3.73%) for the logit approach, 2.52% (95% CI: 1.32% - 4.04%) for the double-arcsine approach, and 3.32% (95% CI: 1.21% - 5.43%) for the raw regression approach. As expected, blood donors in Eastern Africa had the lowest prevalence estimates which were also comparable under all three competing transformations: 1.34% (95% CI: 0.75% - 2.39%) when using the logit transformation, 1.50% (95% CI: 0.27% - 3.49%) when using the double arcsine transformation, and 2.07% (95% CI: -1.10% - 5.25%) when using a raw regression approach.

Table 5. Prevalence Estimates for Each Cohort in Eastern Africa under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision
		Lower	Upper	
Eastern Africa (*k* = 67)				
Blood Donor (k = 12)				
None	2.07	-1.10	5.25	6.35
Logit	1.34	0.75	2.39	1.64
Double Arcsine	1.50	0.27	3.49	3.22
HIV (k = 16)				
None	5.61	2.82	8.41	5.59
Logit	4.01	2.41	6.60	4.19
Double Arcsine	4.71	2.61	7.36	4.75
General Population (k = 28)				
None	3.32	1.21	5.43	4.22
Logit	2.49	1.66	3.73	2.07
Double Arcsine	2.52	1.32	4.04	2.72
Chronic Illness (k = 5)				
None	7.28	2.20	12.35	10.15
Logit	6.78	2.84	15.32	12.48
Double Arcsine	7.07	2.78	13.04	10.26
High Risk (k = 6)				
None	12.25	7.59	16.92	9.33
Logit	9.85	4.59	19.87	15.28
Double Arcsine	11.24	6.18	17.53	11.35

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval.

These trends were similar in Western Africa, where the prevalence of HCV among those at high-risk for the infection was also alarmingly high yet comparable under the logit (i.e., 16.02%, 95% CI: 9.12% - 26.62%) and double arcsine transformations (i.e., 16.03%, 95% CI: 11.04% - 21.73%) (see Table 6). However, bucking expectation, the raw regression approach predicted a slightly *lower* (if not significantly lower) prevalence estimate for the high-risk cohort in Western Africa at 15.65% (95% CI: 11.74% - 19.57%). As expected from the literature review (Chapter Two), decreasing prevalence was followed by those living with a chronic illness who also had comparable seroprevalence under a logit (i.e., 9.23%, 95% CI: 3.77% - 20.91%), double-arcsine (i.e., 10.05%, 95% CI: 4.70% - 17.05%), and raw regression approach (i.e., 10.03%, 95% CI: 4.72% - 15.34%). In the general population, the prevalence was also noticeably comparable among all three transformation methods: 4.61% (95% CI: 3.26% - 6.47%) for the logit transformation, 5.07% (95% CI: 3.49% - 6.91%) for the double-arcsine transformation, and 5.47% (95% CI: 3.50% - 7.42%) for the raw regression approach (see Table 6).

In Western Africa, the prevalence of HCV among those with comorbid HIV was comparable under all three transformations: 4.00% (95% CI: 2.56% - 6.19%) using a logit transformation, 4.38% (95% CI: 2.54% - 6.65%) using a double-arcsine transformation, and 4.95% (95% CI: 2.45% - 7.46%) using a raw regression approach. As expected, prevalence continued to be lowest among blood donors in this region estimated at 2.35% (95% CI: 1.69% - 3.28%) under a logit transformation, 2.50% (95% CI: 1.47% - 3.77%) under a double arcsine transformation, and 3.16% (95% CI: 1.36% - 4.96%) when using a raw regression approach.

Table 6. Prevalence Estimates for Each Cohort in Western Africa under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision
		Lower	Upper	
Western Africa (k = 107)				
Blood Donor (k = 37)				
None	3.16	1.36	4.96	3.60
Logit	2.35	1.69	3.28	1.59
Double Arcsine	2.50	1.47	3.77	2.30
HIV (k = 20)				
None	4.95	2.45	7.46	5.01
Logit	4.00	2.56	6.19	3.63
Double Arcsine	4.38	2.54	6.65	4.11
General Population (k = 35)				
None	5.47	3.50	7.42	3.92
Logit	4.61	3.26	6.47	3.21
Double Arcsine	5.07	3.49	6.91	3.42
Chronic Illness (k = 5)				
None	10.03	4.72	15.34	10.62
Logit	9.23	3.77	20.91	17.14
Double Arcsine	10.05	4.70	17.05	12.35
High Risk (k = 10)				
None	15.65	11.74	19.57	7.83
Logit	16.02	9.12	26.62	17.50
Double Arcsine	16.03	11.04	21.73	10.69

Note: K = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval.

The effect of the interaction is clearly revealed in the prevalence estimates for Southern Africa (see Table 7) and Central Africa (see Table 8).

Table 7. Prevalence Estimates for Each Cohort in Southern Africa under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision
		Lower	Upper	
Southern Africa (*k* = 15)				
Blood Donor (k = 2)				
None	0.02	-7.65	7.70	15.35
Logit	0.02	0.00	0.10	0.10
Double Arcsine	0.00	0.00	2.43	2.43
HIV (k = 9)				
None	1.43	-2.20	5.07	7.27
Logit	1.27	0.53	2.98	2.45
Double Arcsine	1.20	0.03	3.54	3.51
General Population (k = 2)				
None	3.19	-4.51	10.88	15.39
Logit	6.35	0.95	32.41	31.46
Double Arcsine	3.08	0.00	11.31	11.31
High Risk (k = 2)				
None	1.47	-6.27	9.21	15.48
Logit	1.48	0.31	6.74	6.43
Double Arcsine	1.43	0.00	7.66	7.66

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval.

Unlike general population prevalence estimates in other regions, the general population prevalence estimate in Southern and Central Africa were noticeably higher. Admittedly, there were few articles available for each cohort in Southern Africa (range: 2-9 articles), where the seroprevalence of HCV among those in the general population was estimated to be 3.08% (95% CI: 0.00% - 11.31%) under a double-arcsine transformation, 3.19% (95% CI: -4.51% - 10.88%) under a raw regression approach, and as high as 6.35% (95% CI: 0.95% - 32.41%) under a logit transformation (see Table 7). These wide confidence intervals are the consequence of having access to only two articles for these estimates. Notably, however, only the logit transformation excluded 0% prevalence when the estimate was pooled over the two articles.

In Southern Africa, the seroprevalence of HCV was similar among those with comorbid HIV and those at high-risk for infection. For both cohorts, the HCV prevalence rates were low (see Table 7). Among those with HIV, the HCV prevalence rate was 1.20% (95% CI: 0.03% - 3.54%) when using a double arcsine transformation, 1.27% (95% CI: 0.53% - 2.98%) when using a logit transformation, and 1.43% (95% CI: -2.20% - 5.07%) when using a raw regression approach. Similarly, among those at high-risk for HCV infection, the prevalence rates were comparable under all three transformations: 1.43% (95% CI: 0.00% - 7.66%) when using the double-arcsine approach, 1.48% (95% CI: 0.31% - 6.74%) when using the logit approach, and 1.47% (95% CI: -6.27% - 9.21%) when using a raw regression approach. As before, only the logit approach excluded 0% prevalence from the confidence interval. As expected from the literature review (Chapter Two), blood donors in Southern Africa continued to have the lowest

prevalence estimates which were 0% (95% CI: 0% - 2.43%) when using the double-arcsine transformation, 0.02% (95% CI: 0.00% - 0.10%) when using the logit transformation, and 0.02% (95% CI: -7.65% - 7.70%) when using a raw regression approach.

In Central Africa, the infection rate was also alarmingly high among those in the general population where the number of articles contributing to the estimates was more robust (*k* = 21) (see Table 8).

In this cohort and stratum, the seroprevalence was estimated at 9.43% (95% CI: 6.32% - 13.84%) when using a logit transformation, 11.16% (95% CI: 8.35% - 14.32%) when using a double arcsine transformation, and as high as 12.83% (95% CI: 10.38% - 15.28%) when using a raw regression approach.

Interestingly, in Central Africa the prevalence of HCV was similar among those at high-risk and those with comorbid HIV. For example, in the high-risk cohort prevalence was comparable under the logit transformation (i.e., 7.00%, 95% CI: 2.64% - 17.30%), double arcsine transformation (i.e., 7.67%, 95% CI: 2.76% - 14.64%), and no transformation method (i.e., 8.21%, 95% CI: 2.43% - 13.99%). This was also true among those with comorbid HIV, where the prevalence was 7.93% (95% CI: 2.00% - 26.67%) using a logit transformation, 8.06% (95% CI: 1.52% - 18.78%) when using a double-arcsine transformation, and 8.03% (95% CI: -0.19% - 16.24%) when using a raw regression approach.

Table 8. Prevalence Estimates for Each Cohort in Central Africa under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision
		Lower	Upper	
Central Africa (*k* = 32)				
Blood Donor (k = 4)				
None	3.34	-2.20	8.89	11.09
Logit	2.92	1.06	7.76	6.70
Double Arcsine	3.05	0.31	8.04	7.73
HIV (k = 2)				
None	8.03	-0.19	16.24	16.43
Logit	7.93	2.00	26.67	24.67
Double Arcsine	8.06	1.52	18.78	17.26
General Population (k = 21)				
None	12.83	10.38	15.28	4.90
Logit	9.43	6.32	13.84	7.52
Double Arcsine	11.16	8.35	14.32	5.97
Chronic Illness (k = 1)				
None	--	--	--	--
Logit	--	--	--	--
Double Arcsine	--	--	--	--
High Risk (k = 4)				
None	8.21	2.43	13.99	11.56
Logit	7.00	2.64	17.30	14.66
Double Arcsine	7.67	2.76	14.64	11.88

Note: k = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Estimates are not provided when *k* = 1.

Finally, blood donors continued to have the lowest prevalence of HCV in Central Africa, which was estimated at 2.92% (95% CI: 1.06% - 7.76%) under a logit transformation, 3.05% (95% CI: 0.31% - 8.04%) under a double-arcsine transformation, and 3.34% (95% CI: -2.20% - 8.89%) under a raw regression approach.

Regarding the precision (or width of the confidence intervals) for these interaction estimates, the raw regression approach routinely produced the worst (widest) confidence intervals for the blood donor cohort, HIV cohort, and general population cohort regardless of the African region in which they were estimated. Conversely, the logit transformation produced the most dispersed (or widest) estimates for the chronic illness and high-risk cohorts regardless of the African region in which they were estimated (see Tables 5 through 8).

These trends in precision held true except for four instances: First, in the general population in Southern Africa, the width of the confidence interval was superior under a double arcsine transformation (width = 11.31) than under no transformation (width = 15.39) or logit transformation (width = 31.46). Similarly, for the high-risk cohort in this region, the logit transformation produced the tightest confidence interval (width = 6.43) when compared to the double arcsine transformation (width = 7.66) and no transformation (width = 15.48) methods. Third, in Central Africa the general population estimate was most precise when using a raw regression approach (width = 4.90) compared to the double arcsine approach (width = 5.97) or logit approach (width = 7.52). And, lastly, the raw regression approach produced the tightest CI band for those with comorbid HIV (width = 16.43) when compared to the double arcsine (width

= 17.26) or logit transformation (width = 24.67) methods. However, despite its superior precision, it is important to note that for this later conclusion the raw regression approach still produced an unacceptable lower bound that was less than zero.

Prevalence as a Function of Article Year

This section reports the overall prevalence of Hepatitis C in Sub-Saharan Africa using article year as a surrogate for the temporal time of infection. It also compares these pooled estimates when using a double-arcsine transformation, canonical logit transformation, and no transformation as described in Chapter Three.

Table 9 presents the prevalence estimates by publication year. With overwhelming overlap among all confidence intervals, HCV prevalence did not vary by article year in this study. This was true when using a double-arcsine approach [overall χ^2 (df=2) = 0.07, p = .97], logit transformation [overall χ^2 (df=2) = 0.16, p = .92], as well as raw regression approach [χ^2 (df=2) = 0.24, p = .89].

Point estimates suggest that the logit transformation provided the most conservative (lowest) estimates while the raw regression approach provided the highest prevalence estimates. That is, in 2000-2004, prevalence was lowest when estimated under a logit transformation (i.e., 3.65%, 95% CI: 2.56% - 5.19%) yet higher when estimated under a double arcsine transformation (i.e., 4.52%, 95% CI: 2.56% - 5.19%) as well as when estimated using a raw regression approach (i.e., 5.47%, 95% CI: 3.61% - 7.33%).

Table 9. Prevalence as a Function of Article Year under Competing Transformations

	Average Prevalence	95% Confidence Interval		Precision	τ
		Lower	Upper		
2000 – 2004 (*k* = 52)					
None	5.47	3.61	7.33	3.72	.05
Logit	3.65	2.56	5.19	2.63	-.09
Double Arcsine	4.52	3.08	6.21	3.13	.11
2005 – 2009 (*k* = 95)					
None	5.85	4.50	7.20	2.70	.10
Logit	3.74	2.88	4.83	1.95	-.20**
Double Arcsine	4.67	3.58	5.90	2.32	-.04
2010 – 2013 (*k* = 74)					
None	6.07	4.53	7.61	3.08	.09
Logit	3.98	2.95	5.36	2.41	-.20*
Double Arcsine	4.80	3.54	6.22	2.68	-.01

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Tau (τ) = Begg and Mazumdar publication bias correlation coefficient. Significance of the tau correlation coefficient is noted as *$p < .05$, **$p < .01$, and ***$p < .001$.

This trend was similar among articles published in 2005-2009. That is, under a logit transformation HCV seroprevalence was estimated at 3.74% (95% CI: 2.88% - 4.83%), yet was 4.67% (95% CI: 3.58% - 5.90%) under a double-arcsine transformation and 5.85% (95% CI: 4.50% - 7.20%) when estimated using a raw regression approach. The trend for a more conservative (lower) estimate under a logit transformation than under a double-arcsine transformation or raw regression approach persisted among articles published in 2010-2013. Among these

articles, HCV seroprevalence was as low as 3.98% (95% CI: 2.95% - 5.36%) when using a logit transformation which increased (though not significantly) to 4.80% (95% CI: 3.54% - 6.22%) under a double-arcsine transformation and 6.07% (95% CI: 4.53% - 7.61%) when using a raw regression approach.

Regarding publication bias estimates, there was a moderate association between the logit-transformed study estimates and their sample size among articles published in 2005-2009 (k = 95, τ = -0.20, p = .004) as well as among articles published in 2010-2013 (k = 74, τ = -0.20, p = .01). Otherwise, there was no meaningful publication bias detected when using the double-arcsine approach or raw regression approach as described by Begg and Mazumdar (1994).

Prevalence as a Function of Assay Type

This section reports the overall prevalence of Hepatitis C in Sub-Saharan Africa as a function of the assay type used to detect the virus, including screening assays, second generation assays, third generation assays, and fourth generation assays. It also compares these pooled estimates when using a double-arcsine transformation, canonical logit transformation, and no transformation as described in Chapter Three.

Table 10 presents the prevalence estimates by assay type. In this study, the type of assay used to detect the HCV virus was not a meaningful moderator of HCV seroprevalence. This was true when using a double-arcsine approach [overall χ^2 (df=3) = 1.92, p = .59], logit transformation [overall χ^2 (df=3) = 1.82, p = .61], as well as raw regression approach [χ^2 (df=3) = 1.53, p = .68].

Prevalence was highest among the five articles relying on the second-generation assay which was estimated at 6.07% (95% CI: 2.03% - 16.78%) under a logit transformation, 7.03% (95% CI: 2.13% - 14.31%) when using a double arcsine transformation, and 7.35% (95% CI: 1.11% - 13.58%) when using a raw regression approach. Articles relying on the third-generation assay also reported higher prevalence estimates: 3.88% (95% CI: 3.11% - 4.83%) when using a logit approach, about one percentage point higher (though not significantly higher) at 4.86% (95% CI: 3.90% - 5.91%) when using a double arcsine approach, and much (but not significantly) higher at 6.16% (95% CI: 4.99% - 7.33%) when using a raw regression approach.

HCV seroprevalence was more moderate among articles relying on a screening assay as well as fourth generation assay. As before, the trend continued to show that the logit approach provided a more conservative HCV prevalence estimate, while the raw regression approach provided a much higher HCV prevalence estimate. The double-arcsine method continued to strike a balance between the two other competing transformations. Among the 31 articles using a screening assay, the prevalence of Hepatitis C was estimated at 3.79 (95% CI: 2.38% - 5.98%) when using a logit approach, 4.11 (95% CI: 2.40 – 6.23%) when using a double-arcsine approach, and 4.87% (95% CI: 2.49% - 7.25%) when using a raw regression approach. Results were similar for the fourth-generation assay. That is, HCV seroprevalence was estimated to be 2.86% (95% CI: 1.66% - 4.89%) when using a logit transformation, 3.64% (95% CI: 1.81% - 6.02%) when using a double-arcsine approach, and 4.96% (95% CI: 2.18% - 7.75%) when using a raw regression approach.

Table 10. Prevalence as a function of assay type under competing transformations

	Average Prevalence	95% Confidence Interval		Precision	τ
		Lower	Upper		
Screening (*k* = 31)					
None	4.87	2.49	7.25	4.76	.02
Logit	3.79	2.38	5.98	3.60	-.08
Double Arcsine	4.11	2.40	6.23	3.83	-.05
Second Generation (*k* = 5)					
None	7.35	1.11	13.58	12.47	.80
Logit	6.07	2.03	16.78	14.75	.60
Double Arcsine	7.03	2.13	14.31	12.18	.60
Third Generation (*k* = 131)					
None	6.16	4.99	7.33	2.34	.11
Logit	3.88	3.11	4.83	1.72	-.17**
Double Arcsine	4.86	3.90	5.91	2.01	.08
Fourth Generation (*k* = 23)					
None	4.96	2.18	7.75	5.57	.22
Logit	2.86	1.66	4.89	3.23	.04
Double Arcsine	3.64	1.81	6.02	4.21	.30*

Note: *k* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval. Tau (τ) = Begg and Mazumdar publication bias correlation coefficient. Significance of the tau correlation coefficient is noted as *$p < .05$, **$p < .01$, and ***$p < .001$.

Regarding publication bias among the assays, it is important to point out that the Begg and Mazumdar's (1994) non-parametric rank correlation test was underpowered to detect such bias among articles using the second-generation assay (*k* = 5). However, there was a small

negative association between the logit-transformed study estimates and their sample size among articles using a third-generation assay (k = 131, τ = -0.17, p = .003). Additionally, there was a large positive association between the double-arcsine transformed study estimates and their sample size among articles using a fourth-generation assay (k = 23, τ = 0.30, p = .045). Otherwise, there was no meaningful publication bias detected when using the rank correlation test described by Begg and Mazumdar.

Explained and Unexplained Heterogeneity

Regarding heterogeneity in prevalence estimates across articles, a mixed-effects model comprising the main effects of region, cohort, and a cohort-by-region interaction term had the highest R-square values (see Table 11).

When using no transformation R^2 was equal to 28.48 which did not improve dramatically under a double-arcsine transformation (R^2 = 31.41). However, the amount of explained heterogeneity under a logit transformation was substantially higher by comparison at R^2 = 38.95. As expected from the moderator analysis, the assay type and publication year did not meaningfully contribute to explained heterogeneity as measured by the R-square statistic.

Still, even with moderate R-square values, there remained large variability across studies due to heterogeneity rather than by chance alone. That is, all I^2 values (which express the inconsistency of study results) exceeded 97%, meaning that nearly all total variability in the prevalence estimates used in this dissertation were due to between-article variation (and not sampling error within each article).

Table 11. Estimated Amount of Explained and Unexplained Variability for the Mixed Effects Models

	k	R^2	I^2	95% Confidence Interval for I^2		*p*
				Lower	Upper	
Overall Prevalence	221					
None		--	99.9890	99.9890	99.9931	<.001
Logit		--	98.8077	98.5545	99.0468	<.001
Double Arcsine		--	99.2684	99.1539	99.4409	<.001
Cohort	221					
None		12.98	99.9835	99.9833	99.9895	<.001
Logit		19.49	98.2852	97.9445	98.6649	<.001
Double Arcsine		16.64	99.1007	98.9535	99.3130	<.001
Region	221					
None		13.08	99.9810	99.9815	99.9886	<.001
Logit		13.20	98.5635	98.2365	98.8397	<.001
Double Arcsine		12.36	99.0087	98.8570	99.2522	<.001
Cohort*Region	221					
None		28.48	99.9766	99.9768	99.9859	<.001
Logit		38.95	97.5777	97.0324	98.1096	<.001
Double Arcsine		31.41	98.6812	98.4638	99.0142	<.001
Assay	190					
None		<0.01	99.9893	99.9878	99.9923	<.001
Logit		<0.01	98.8058	98.5232	99.0619	<.001
Double Arcsine		<0.01	99.1811	98.9981	99.3482	<.001
Year	221					
None		<0.01	99.9716	99.9718	99.9822	<.001
Logit		<0.01	98.7450	98.4780	98.9980	<.001
Double Arcsine		<0.01	99.2099	99.0859	99.3970	<.001

Note: *k* = The valid number of studies used to compute the estimates. R^2 = Proportion of variability in the estimated prevalence that is explained by the moderator. I^2 = Proportion of variability across studies that is explained by heterogeneity rather than chance.

Summary

This chapter summarizes the findings for this dissertation. The overall pooled prevalence estimates of HCV in Sub-Saharan Africa ranged between 3.80% to 5.83%, depending on the transformation used. That is, with few exceptions, this dissertation observed

conservative (low) point estimates when using the traditional canonical logit transformation and observed higher point estimates when using no transformation. However, regardless of the transformation approach, there was significant variability among the five population cohorts studied in this analysis. Blood donors had the lowest prevalence rates and, in fact, their HCV prevalence rate was significantly lower than the HCV prevalence estimates for the general population. This was followed by those with comorbid HIV, those from the general population, those living with a chronic illness, and those at high-risk for HCV infection.

Regarding African region, this study found significant variability among the four regions with prevalence being highest in Central and Western Africa and lowest in Eastern and Southern Africa. This was also true regardless of the transformation approach, though the raw regression approach predicted unacceptable estimates that were below 0% prevalence. This study also identified a significant interaction between the population cohorts and the region in which they live. As before, this conclusion was true regardless of the transformation approach employed and highlighted that those in the general population had high prevalence rates in Central and Southern Africa but low prevalence in Eastern and Western Africa. This study also found no meaningful effect for the type of assay used to detect the HCV virus, and that publication year was an unimportant moderator.

Regarding precision, confidence intervals for all prevalence estimates were severely overlapping with few exceptions. This may indicate that the choice of transformation between the double-arcsine and logit methods was inconsequential. Chapter Five will discuss these

findings and place them in context with the literature. It will also discuss new findings and conclude with recommendations for future meta-analyses of HCV in Sub-Saharan Africa.

CHAPTER FIVE

DISCUSSION

A meta-analysis synthesizes effect sizes across many disparate articles, abstracts, conference proceedings, and other evidence with the primary goal of estimating a pooled population effect. In Sub-Saharan Africa (SSA), one population effect of interest is the true prevalence of Hepatitis C (HCV). This is particularly necessary because there are limited population-based study estimates available in the region. Therefore, a meta-analysis that can effectively synthesize individual HCV prevalence estimates offers researchers in SSA a more accurate understanding of the epidemic currently affecting local villages and other communities.

In this study, I estimated the overall prevalence of Hepatitis C in Sub-Saharan Africa as well as the prevalence of HCV among blood donors in the region. I also estimated HCV prevalence rates among those with comorbid HIV, individuals in the general population (e.g., pregnant women, healthy adults, healthy children, etc.), those with a chronic illness, and among individuals at high-risk for the infection (i.e., including prisoners, prison guards, patients with sickle cell disease, hospital workers, sex workers, and intravenous drug users). I stratified these estimates using geographic coordinates described by the World Health Organization (WHO) which were defined as Central, Western, Eastern, and Southern Sub-Saharan Africa, and I varied the methodological approach used for estimating these prevalence rates. That is, when

estimating each prevalence rate, I first transformed the individual study estimates using a traditional canonical logit transformation. Subsequently, I also transformed each study estimate using a double-arcsine transformation as well as no transformation. I compared these three approaches to better understand the impact of such methodologies on our conclusions about the HCV prevalence rate in sub-Saharan Africa.

As previously discussed in Mora et al. (2016), the distribution of available studies for this meta-analysis was imbalanced across the four main regions of SSA (as shown in Chapter Four, Figure 2). That is, nearly half of the original studies estimating the prevalence of HCV in Sub-Saharan Africa took place in Western Africa while another 30% occurred in Eastern Africa. These findings agree with earlier meta-analyses of Hepatitis C in Sub-Saharan Africa (Rao et al., 2015). I also report that this meta-analysis over-sampled large blood donor studies as well as individuals from the general population (as shown in Chapter Four, Figure 3); this finding was also in agreement with earlier meta-analyses of HCV in sub-Saharan Africa (Rao et al., 2015).

Regardless of the transformation method, I found that blood donors had the lowest prevalence rate (as shown in Chapter Four, Table 3) and that this was true in all African regions (as shown in Chapter Four, Figures 8 and 9 as well as Tables 5 through 8). These findings agree with earlier reports by Rao et al. (2015) as well as Mora et al. (2016). One reason for this finding is due to the rigorous screening policies used for selecting blood donors, which tends to skew the sample towards younger and healthier individuals (Baha et al., 2013; Chilundo & Sahay, 2005; Cunha et al., 2007).

Indeed, an important finding in this study was that, regardless of the transformation method, blood donors had significantly lower prevalence estimates when compared to those in the general population. This finding contrasts with those reported in Rao et al. (2015) who ultimately combined the blood donor and general population cohorts when estimating an overall low-risk prevalence rate. I argue in this study that the low prevalence rate among blood donors makes them distinct from the general population, and that this is true regardless of the methodological approach used to estimate the pooled prevalence estimate.

Moreover, blood donors accounted for 25% of the included studies in this meta-analysis and contributed the largest sample sizes (k = 55; Mdn = 1,081, IQR: 258 – 3,316; Range: 100 – 73,293). As described in Barendregt et al. (2013), this means their weight towards an overall pooled SSA prevalence estimate was substantial and, for this reason, an overall estimate that includes these individuals may be misleading. Further, because high-sample size studies contribute more weight to an aggregate analysis than low-sample size studies, this effect would be true regardless of whether one uses a transformation proposed in this study or no transformation at all. The consequence is that the inclusion of large blood donor studies with low prevalence suppresses (or pulls down) the overall pooled prevalence rate of Hepatitis C in sub-Saharan Africa.

Regarding the competing transformations used to estimate prevalence among the five population cohorts who are at-risk for HCV infection, another key finding in this study was that all confidence intervals were severely overlapping meaning the choice of transformation was

largely superfluous (as shown in Chapter Four, Table 3). This was true for all comparisons *except* the general population, which carried an unacceptably high prevalence rate when no transformation of the raw effect sizes is used. Indeed, with blood donors removed from the general population, I find little to no overlap between the logit and raw approaches, meaning the choice between using a logit transformation or no transformation may result in conflicting conclusions about the prevalence of HCV among the general population in sub-Saharan Africa. In fact, the difference in point estimates between the logit and raw approaches for the general population was approaching 2%. On sensitivity analysis, this was clearly the consequence of attenuated variances for the Nerreniete et al. (2005) and Pepin et al. (2010) studies (see Table 12).

As described by Barendregt et al. (2013) and Trikalinomous, Trow, and Schmid (2013), these two studies experienced severely diminished variance estimates and were consequently heavily weighted in the meta-analysis when no transformation was used. This effect was lasting. In fact, residual analyses identified that the observed prevalence estimates in Nerreniete et al. (2005) and Pepin et al. (2010) were more than three standard deviations higher than that the estimates predicted by the raw regression models (z = 8.39 and 3.64, respectively). Interestingly, when these two studies were suppressed, the overlap between the logit and raw approaches for the general population widened indicating there was no longer any meaningful difference between the two methodological approaches.

Table 12. Influential Studies

	Cohort	Transformation	*N*	*n*	*p*	*v*	*z*
Western Africa							
Diouf ML et al.	High Risk	Double Arcsine	15	12	0.800	0.016	4.83
Diouf ML et al.	High Risk	None	15	12	0.800	0.011	6.13
Central Africa							
Pepin J et al.	General Population	Double Arcsine	451	252	0.559	0.0006	5.02
Pepin J et al.	General Population	None	451	252	0.559	0.0005	8.39
Nerreniete et al.	General Population	None	644	191	0.297	0.0003	3.64
Southern Africa							
Fang CT et al.	Blood Donors	Logit	19,709	2	0.0001	0.507	-4.22
Vermeulen M et al.	Blood Donors	Logit	73,293	27	0.0004	0.037	-3.78
Eastern Africa							
Bowring Al et al.	High Risk	None	267	74	0.277	0.0008	3.16

Note: *N* = Total sample, *n* = number positive, *p* = back-transformed prevalence estimate, *v* = estimated study variance, *z* = standardized residual for observed versus expected prevalence estimate.

Regarding publication bias, I also identified that the double arcsine and logit transformations were generally resistant to publication bias among the five population cohorts (as shown in Chapter Four, Table 3). However, when the analysis pooled individual study estimates without using a transformation, the HIV, chronic illness, and high-risk cohorts clearly suffered from publication bias as measured by Begg and Mazumdar's (1994) rank correlation test. That is, these cohorts experienced significantly large positive correlation coefficients meaning that, for these cohorts, the raw regression models anticipated a larger number of high

sample studies with low prevalence; such studies are not anticipated in the HIV, chronic illness, or high-risk cohorts (Layden et al., 2014; Mora et al., 2016; Rao et al., 2015).

One explanation for this finding is that Begg and Mazumdar's (1994) correlation coefficient is essentially a non-parametric association between each study's adjusted prevalence estimate (x-axis) and its adjusted standard error (y-axis). This is analogous to a correlation between each study's effect size and sample size. In their seminal paper, Begg and Mazumdar describe a negative correlation as one where the meta-analysis oversamples studies with high prevalence estimates carrying *high* standard errors. Conversely, they describe a positive correlation as one where the meta-analysis oversamples studies with high prevalence estimates that carry *low* standard errors. In this dissertation, these positive publication bias coefficients make sense: Among studies of those living with HIV, those with a chronic illness, and those at high-risk for infection, we anticipate high prevalence rates and, when no transformation is used, we anticipate low standard errors due to the attenuated variances engendered by the raw regression approach (Barendregt et al., 2013; Trikalinomous et al., 2013).

Regarding model-fit diagnostics, this study used normality, linearity, and influential outlier plots to show that the data under a raw regression model was unacceptably skewed and had the highest number of influential studies pulling on the overall prevalence rate (as shown in Figure 7). Conversely, the data under a canonical logit transformation was normally distributed and, under this transformation, only two large blood donor studies (each sampling 73,293 and

19,709 individuals, respectively) were considered influential or pulling down on the overall average pooled prevalence of Hepatitis C in sub-Saharan Africa (as shown in Figure 7).

Admittedly, it may be inappropriate to use regression diagnostics to determine whether a study should be removed from a meta-analysis, particularly because it is difficult to distinguish studies with large sampling error from true outliers (Schmidt & Hunter, 2014). However, on sensitivity analysis, removing these two large blood donor studies from the logit transformed model nominally increased the overall prevalence estimate from 3.80% (95% CI: 3.20% - 4.50%) to 4.00% (95% CI: 3.41% - 4.69%) which was in agreement with the double-arcsine estimate (see Supplemental Table 2). This conclusion is supported by Viechtbauer and Cheung (2010) who argue that large hat-values (or large leverage statistics) are engendered by studies with extremely large sample sizes. While this revised estimate contrasts with the 2.98% (95% CI: 2.86% - 3.10%) prevalence rate reported by Rao et al. (2015), it nonetheless may be a more accurate representation of the disease burden in SSA when these two large blood donor studies are excluded from the model.

Table 13. Sensitivity Analysis for Overall Prevalence

	K	**Average Prevalence**	**95% Confidence Interval**		**Precision**
			Lower	**Upper**	
Excluding Influential Studies					
None	217	5.13	4.45	5.81	1.36
Logit	219	4.00	3.41	4.69	1.28
Double Arcsine	219	4.45	3.78	5.16	1.38

Note: *K* = The valid number of studies used to compute the estimates. Precision = Width of the confidence interval.

Regarding African region, this study found significant variability among studies in Central Africa, Western Africa, Eastern Africa, and Southern Africa. Like Rao et al. (2015), we found that prevalence was highest in Central and Western Africa and lowest in Eastern and Southern Africa. This was true regardless of the transformation method used for the analysis. Further, the confidence intervals for all four regions were severely overlapping among the competing transformations used to compute these estimates. This means that, as before, the choice of transformation for region estimates was largely unimportant (as shown in Chapter Four, Table 4). However, in at least one instance the raw approach predicted an unacceptable lower bound well below 0% prevalence - a problem unique to the raw regression approach which agrees with findings by Agresti (2002), Barendregt et al. (2013), and Trikalinomous et al. (2013).

Importantly, regardless of the transformation method, there was a profound interaction between African region and the population cohorts (as shown in Chapter Four, Figures 8 and 9 as well as Tables 5 through 8). This essentially means it is difficult to directly interpret the main effect of each region without considering the cohorts that live within those regions (Mora et al., 2016). For example, while the prevalence of HCV in Central Africa was somewhere between 7.74% to 10.69% depending on the transformation used, 21 (65%) of these studies were from the general population cohort and had a high prevalence estimate in the region ranging between 9.43% and 12.83% (as shown in Chapter Four, Figure 3 and Table 8). Conversely, in Eastern Africa, where the prevalence of HCV was somewhere between 3.04% to 4.72% depending on the transformation method used, 28 (42%) of these studies were from the

general population cohort and had a much lower prevalence estimate in the region ranging between 2.49% and 3.32% (as shown in Chapter Four, Figure 3 and Table 5).

Clearly, the populations living in each region affect regional prevalence estimates. As discussed in Mora et al. (2016), if one knew the proportion of each cohort living in each demarcated region using census data, it would be possible to calculate the number of affected individuals for each cohort-by-region stratum. However, there is no census data available at the cohort level. At best, we can only estimate the number of individuals affected in each African region using the United Nations census data (https://esa.un.org/unpd/wpp/Publications/Files/Key_Findings_WPP_2015.pdf). These estimates are provided in Table 14.

Using the point prevalence estimates from Chapter Four, Table 4, as well as the census data provided by the UN, I conclude that the choice of transformation matters. That is, if a researcher uses no transformation of the raw prevalence estimates, the number of individuals affected in sub-Saharan Africa is expected to be about 5,320,313 - 9,337,157 cases higher than if one uses one of the proposed transformations recommended in this dissertation.

Interestingly, the choice of transformation does not affect the order of prevalence. That is, regardless of the transformation method used, the number of individuals affected by HCV was remains highest in Western Africa (range: 8.1 - 11.1 million) and Eastern Africa (range: 6.7 - 10.5 million), followed by Central Africa (range: 6.1 - 8.5 million). As anticipated from the literature review, the number of individuals affected by the virus was always lowest in Southern Africa regardless of the transformation method used (range: 308K - 626K).

Table 14. Estimated Number of Individuals Affected by HCV by Region

African Region	Census *N*	Census Proportion	Estimated HCV Prevalence per Region	Estimated number affected
Double Arcsine				
Central	79,280,089.00	0.15	9.22	7,309,624
Western	197,082,039.60	0.36	4.81	9,479,646
Eastern	221,715,242.20	0.41	3.65	8,092,606
Southern	42,312,928.13	0.08	1.04	440,054
Total	540,390,298.93			25,321,930
Logit				
Central	79,280,089.00	0.15	7.74	6,136,279
Western	197,082,039.60	0.36	4.12	8,119,780
Eastern	221,715,242.20	0.41	3.04	6,740,143
Southern	42,312,928.13	0.08	0.73	308,884
Total	540,390,298.93			21,305,086
Raw				
Central	79,280,089.00	0.15	10.69	8,475,042
Western	197,082,039.60	0.36	5.62	11,076,011
Eastern	221,715,242.20	0.41	4.72	10,464,959
Southern	42,312,928.13	0.08	1.48	626,231
Total	540,390,298.93			30,642,243

Note: Estimated HCV prevalence per region was taken from the double-arcsine estimates in Table 3. The 2015 census data was taken from https://esa.un.org/unpd/wpp/Publications/Files/Key_Findings_WPP_2015.pdf

All studies are limited, and this dissertation is no different. Certainly, the literature search for this study failed to balance the number of articles per region with the number of cohorts sampled. This means that, in some regions, there were as few studies representing individuals donating blood, those living with comorbid HIV, those living with a chronic illness, or those otherwise at high-risk for HCV infection. I also did not detect any differences in HCV prevalence by assay type (regardless of the transformation method employed). This conflicts with previous findings by Candotti et al. (2001), Scheiblauer et al. (2006), Seremba et al. (2010),

Mullis et al. (2013), and Layden et al. (2014). However, 10% of the assay data was missing or not reported in the original research articles used for this dissertation. Further, among articles that did report assay information, it was overwhelming constant with 70% of the included studies using a third-generation assay. Finally, the uncertainty in the pooled prevalence estimates was quite profound. In this dissertation, the inconsistency index (I^2) for each moderator was between 97-99%, meaning nearly all variability in the individual HCV prevalence estimates was attributable to between-study variation (as shown in Chapter 4, Table 7).

Summary of Implications and Conclusions

The *primary* goal of this dissertation was to estimate the prevalence of HCV in Sub-Saharan Africa. A secondary goal was to compare these estimates when no transformation was used, when a traditional logit transformation was used, and when a double-arcsine transformation was used.

In this study, I confirmed that an overall pooled prevalence estimate of HCV in Sub-Saharan Africa is largely inappropriate, particularly because of the large number of high-sample blood donor studies that suppress the overall prevalence rate. We also confirmed that blood donors have such low prevalence that they tend to be distinct from the general population. Future meta-analyses may want to avoid combining these two cohorts without first checking for differences in their prevalence estimates.

Regarding the choice of transformation, this study did not identify any meaningful differences between the logit and double-arcsine transformations. That is, they were generally

comparable in precision and had severely overlapping confidence intervals for all moderator analyses. It should be noted that, by comparison to the double-arcsine transformation, the data under a logit transformation was more normally distributed and had fewer influential studies. For these reason, I recommend using the logit transformation proposed in this dissertation for the meta-analysis of HCV in Sub-Saharan Africa. Conversely, I caution future analysts considering a raw regression approach. Not only is this method severely impugned in the literature (Agresti, 2002), this study confirmed it is specifically inferior for modeling the prevalence of HCV in Sub-Saharan Africa. In this study, when no transformation was used, the prevalence estimates were inflated as measured by standardized residuals, individual study variances were severely attenuated, publication bias estimates were quite severe and, in some instances, I predicted HCV prevalence estimates well below zero.

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Note an asterisk indicates an article contributing to the meta-analysis estimates.

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VITA

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