STIs AS A CAUSE OF INFERTILITY

Final Presentation

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PROJECT OVERVIEW

PROJECT OBJECTIVES

Understand the extent to which STIs contribute to infertility in LMIC settings

Assist in building the case for increased resource allocation to STI prevention, diagnostics, and treatment

PROJECT BACKGROUND

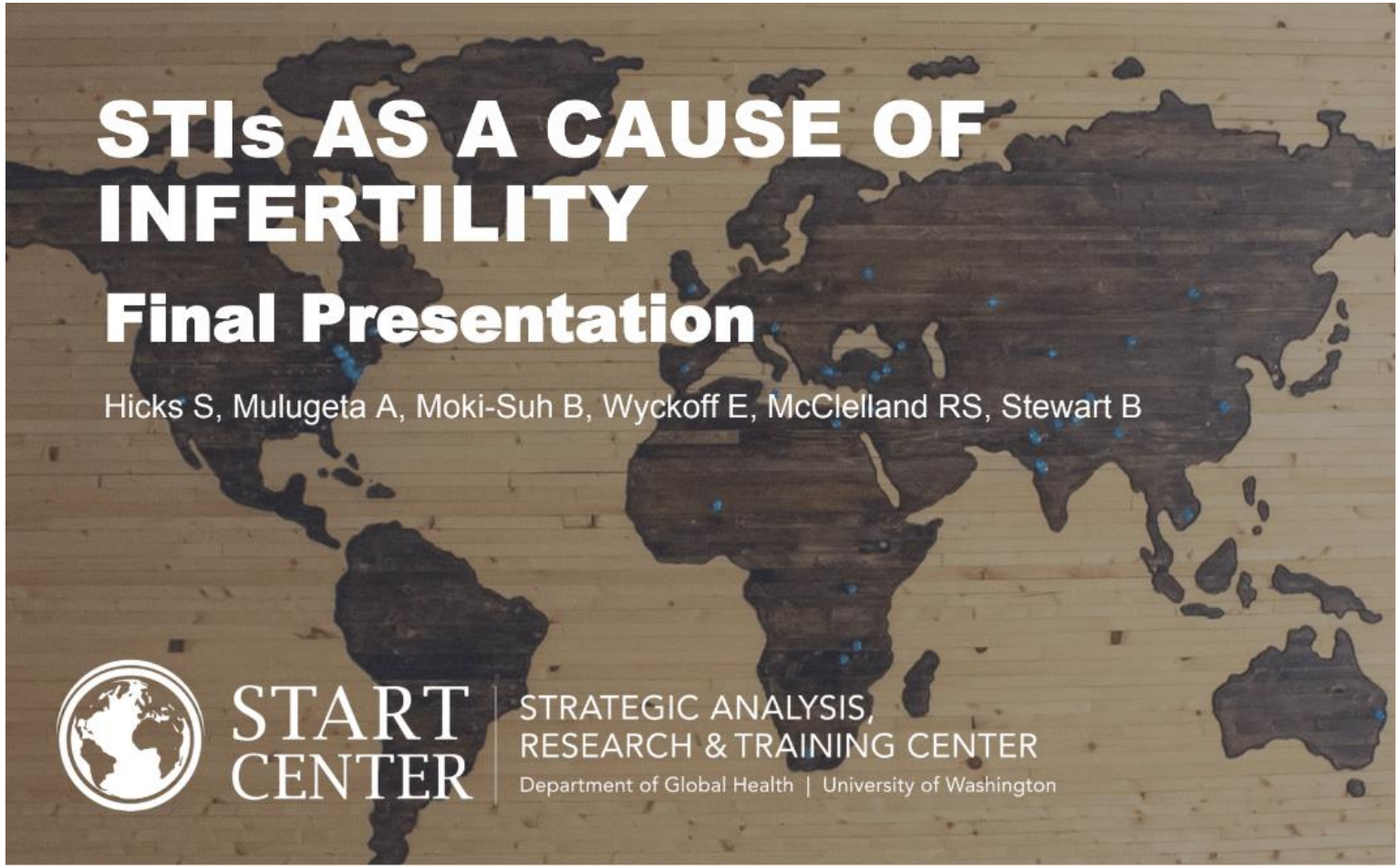
PROBLEM STATEMENT

- Female infertility is a global public health concern
- There is limited evidence of how STIs contribute to infertility in LMIC settings due to:
  - Limited surveillance and screening of STIs
  - Complications of diagnosing infertility in resource-limited settings
  - Asymptomatic STIs

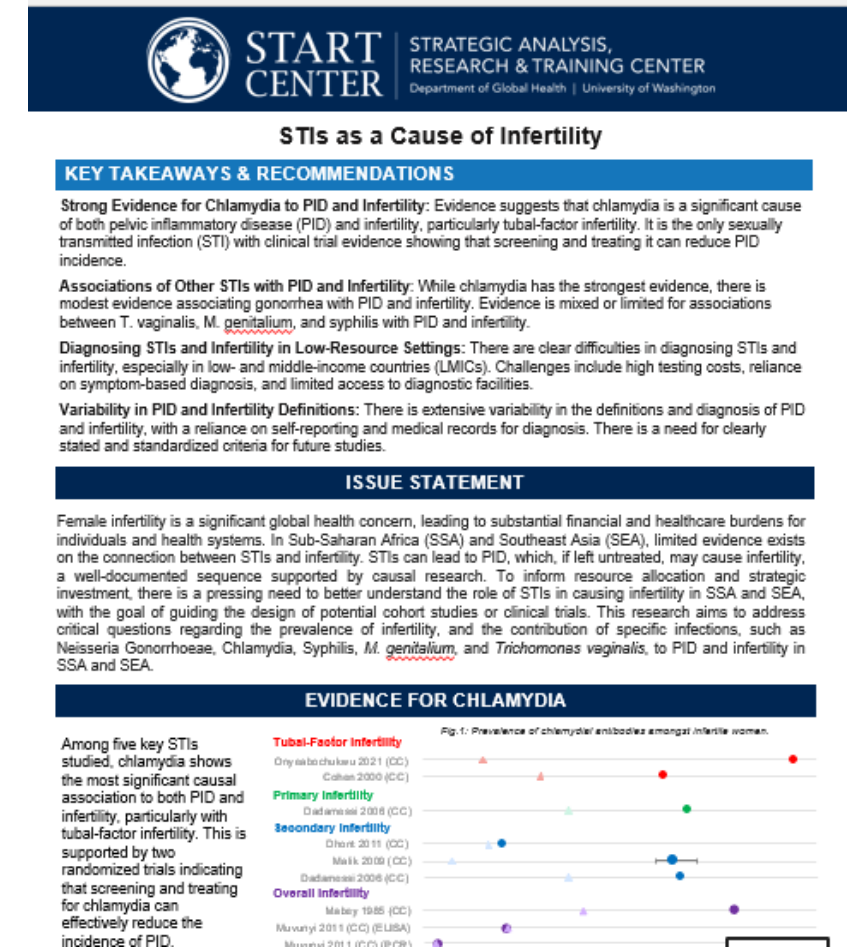
PROJECT GOAL

- Project findings and recommendations will inform future investments in STI prevention, treatment, and diagnostics to target female infertility attributable to STIs

DELIVERABLES



Presentation to the Women's Health Innovation team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STIs as a Cause of Infertility

KEY TAKEAWAYS & RECOMMENDATIONS

Strong Evidence for Chlamydia to PID and Infertility: Evidence suggests that chlamydia is a significant cause of both pelvic inflammatory disease (PID) and infertility, particularly tubal-factor infertility. It is the only sexually transmitted infection (STI) with clinical trial evidence showing that screening and treating it can reduce PID incidence.

Associations of Other STIs with PID and Infertility: While chlamydia has the strongest evidence, there is modest evidence associating gonorrhea with PID and infertility. Evidence is mixed or limited for associations between T. vaginalis, M. genitalium, and syphilis with PID and infertility.

Diagnosing STIs and Infertility in Low-Resource Settings: There are clear difficulties in diagnosing STIs and infertility, especially in low- and middle-income countries (LMICs). Challenges include high testing costs, reliance on symptom-based diagnosis, and limited access to diagnostic facilities.

Variability in PID and Infertility Definitions: There is extensive variability in the definitions and diagnosis of PID and infertility, with a reliance on self-reporting and medical records for diagnosis. There is a need for clearly stated and standardized criteria for future studies.

ISSUE STATEMENT

Female infertility is a significant global health concern, leading to substantial financial and healthcare burdens for individuals and health systems. In Sub-Saharan Africa (SSA) and Southeast Asia (SEA), limited evidence exists on the connection between STIs and infertility. STIs can lead to PID, which, if left untreated, may cause infertility, a well-documented sequence supported by causal research. To inform resource allocation and strategic investment, there is a pressing need to better understand the role of STIs in causing infertility in SSA and SEA, with the goal of guiding the design of potential cohort studies or clinical trials. This research aims to address critical questions regarding the prevalence of infertility, and the contribution of specific infections, such as Neisseria Gonorrhoeae, Chlamydia, Syphilis, *M. genitalium*, and *Trichomonas vaginalis*, to PID and infertility in SSA and SEA.

EVIDENCE FOR CHLAMYDIA

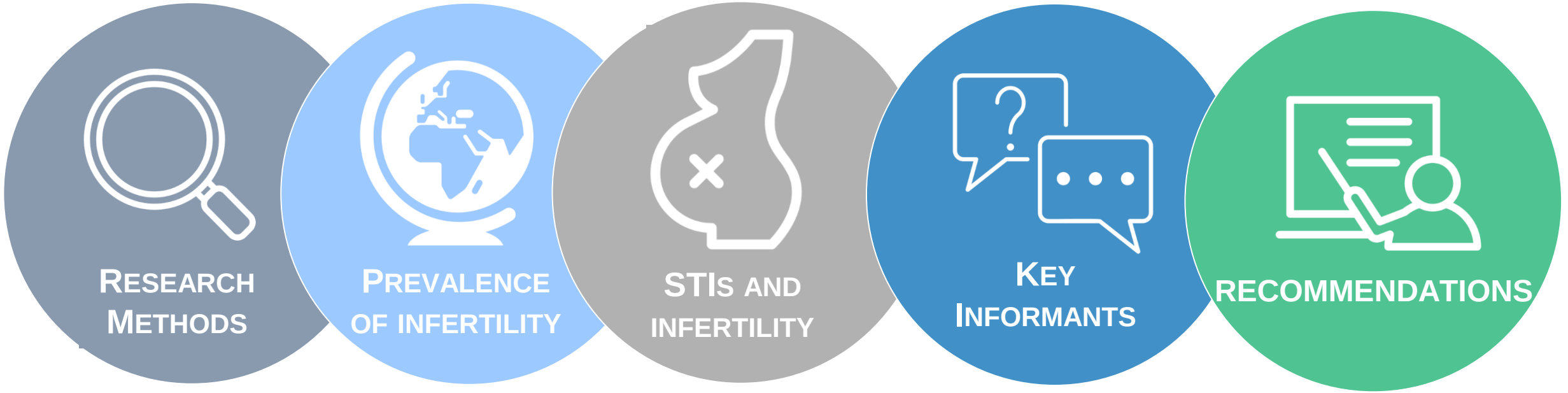
Among five key STIs studied, chlamydia shows the most significant causal association to both PID and infertility, particularly with tubal-factor infertility. This is supported by two randomized trials indicating that screening and treating for chlamydia can effectively reduce the incidence of PID.

Fig.1: Prevalence of chlamydial antibodies amongst infertile women.

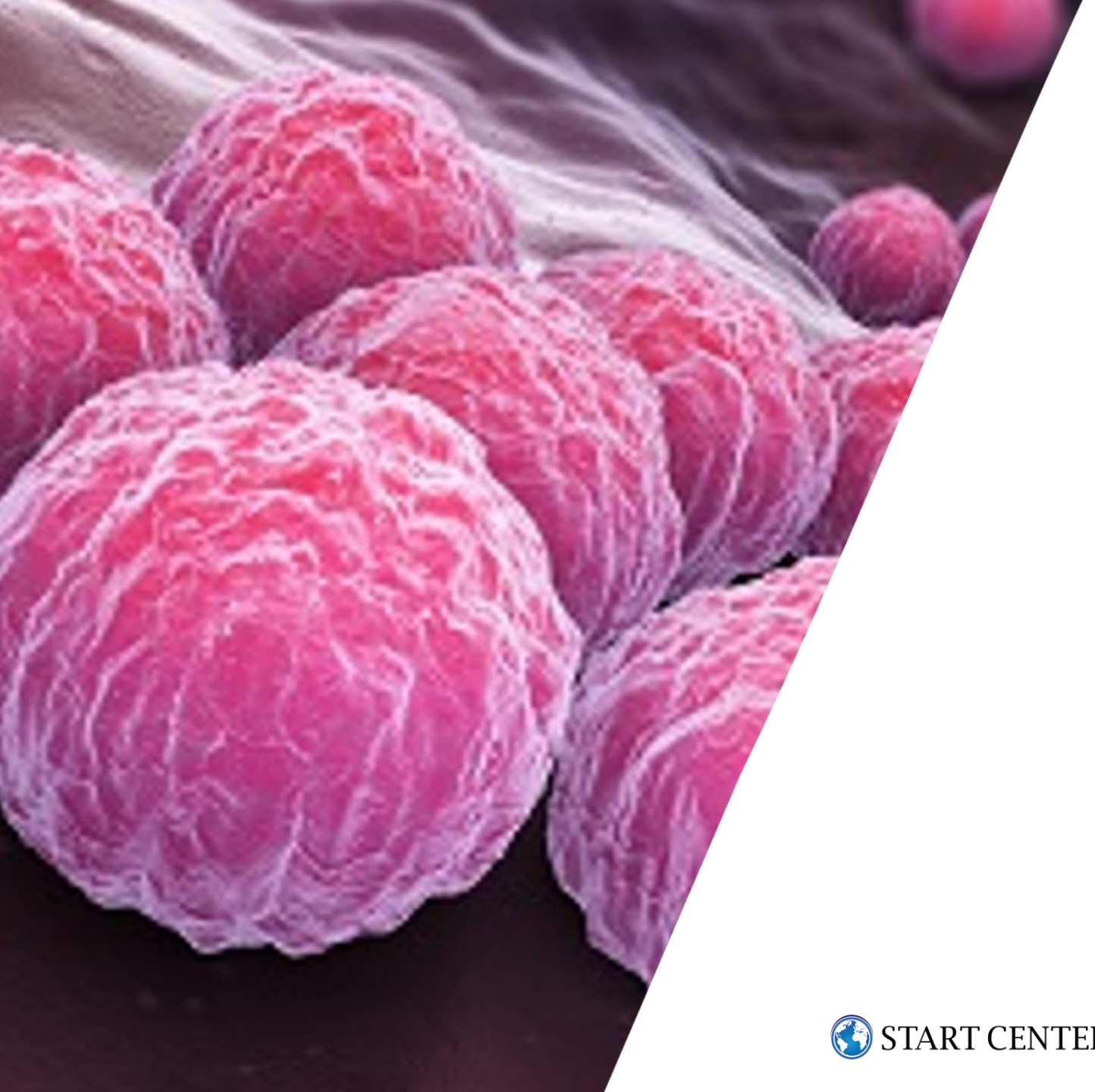
Executive summary of findings

PRESENTATION OVERVIEW

OBJECTIVE: HIGHLIGHT KEY FINDINGS AND RECOMMENDATIONS FOR FUTURE INVESTMENT PATHWAYS



RESEARCH METHODS



KEY SEXUALLY TRANSMITTED INFECTIONS

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Treponema pallidum*
- *Trichomonas vaginalis*
- *Mycoplasma genitalium*

METHODS OVERVIEW

Completed seven literature searches on the causal pathway between each key STI and infertility (Appendix A; focused on literature from sub-Saharan Africa and Southeast Asia)

Summarized findings along each step of the causal pathway

Conducted key informant interviews to supplement and inform literature review findings

PREVALENCE & CAUSES OF INFERTILITY

INFERTILITY PREVALENCE ESTIMATES

Unadjusted, age-standardized infertility prevalence; women aged 20-49 (DHS 2021)*

	Primary Infertility	Secondary Infertility
Sub- Saharan Africa	• Range: 0.7%- 3.9% • Regional average:1.5%	• Range: 3.3%- 20.0% • Regional average: 10.7%
Southeast Asia	• Range: 2.4%- 3.6% • Regional average: 2.9%	• Range: 12.8%- 24.9% • Regional average: 19.3%
Global	• Overall: 1.7%	• Overall: 18.4%

**Data available for 11 countries in sub- Saharan Africa and 4 countries in Southeast Asia. Global estimates pulled from all available DHS 2021 data.*

INFERTILITY PREVALENCE ESTIMATES

Pooled prevalence estimates of infertility; individuals of reproductive age (WHO 2023)*

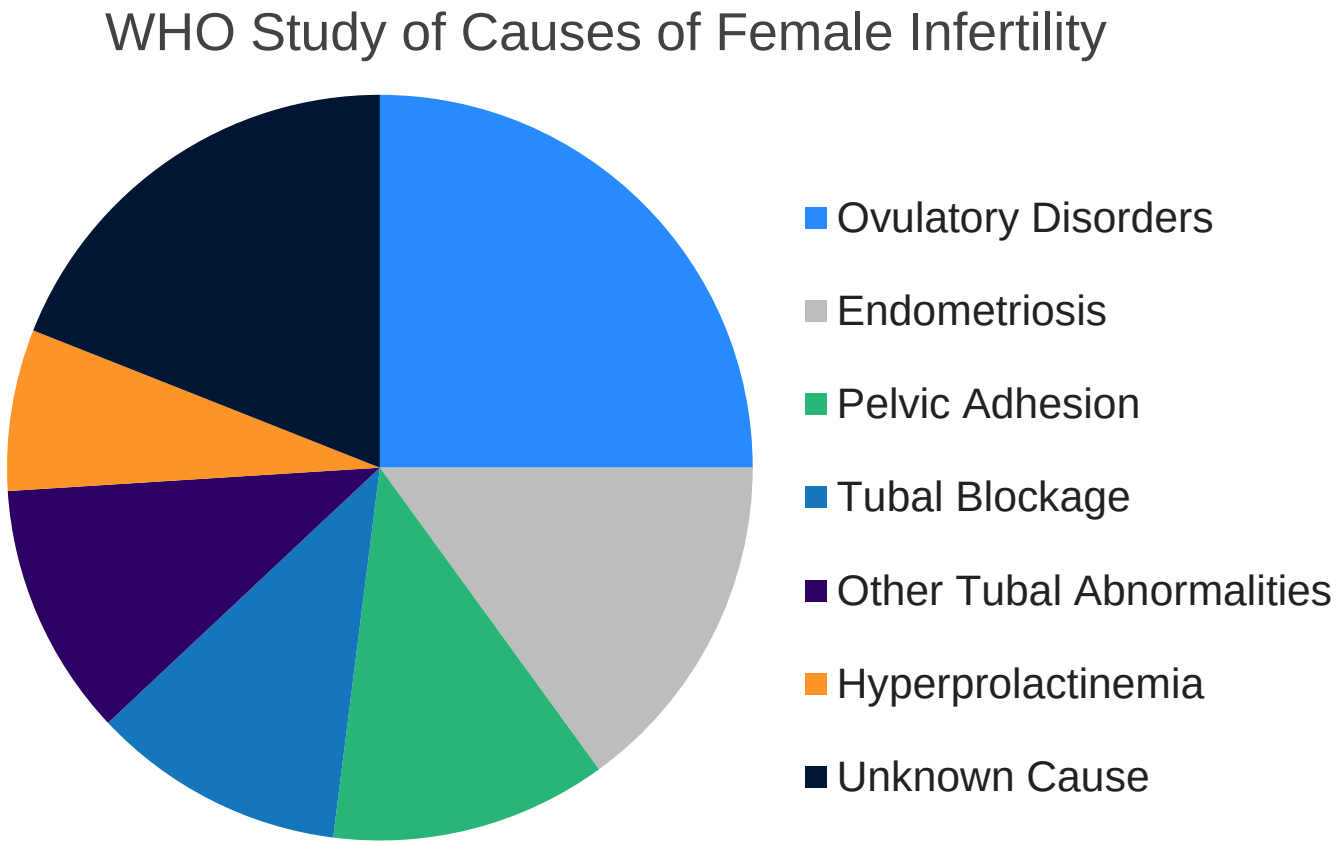
	Primary Infertility	Secondary Infertility	Overall Infertility
Lifetime Prevalence	• 9.6% (95% CI: 6.3-14.3)	• 6.5% (95% CI: 3.9-10.7)	• Global: 18% (95% CI: 15-20) • African Region: 13% (95% CI: 9-19)
12-Month Period Prevalence	• 9.0% (95% CI: 6.6-12.2)	• 4.9% (95% CI: 2.7-8.8%)	• Global: 13% (95% CI: 11-15) • African Region: 16% (95% CI: 10-26)

**Pooled infertility prevalence estimates are provided for all studies, including respondents of both male and female genders*

OTHER CAUSES OF INFERTILITY

WHO-facilitated study examining most common causes of female infertility among 8500 couples:

- Ovulatory Disorders (25%)
- Endometriosis (15%)
- **Tubal Blockage** (11%)
- Other Tubal abnormalities (11%)
- Hyperprolactinemia (7%)
- Unknown Cause (19%)



OTHER CAUSES OF INFERTILITY

Ovulatory Disorders

- Infrequent or absent ovulation
- Often due to aging, hormonal imbalance or other disorders

Endometriosis

- Can cause pelvic adhesion & damage to ovarian tissue
- Disrupts fertilization

Tubal Abnormalities

- Bilateral or Partial Occlusion leads to **Tubal Factor Infertility**
- Pelvic Adhesions

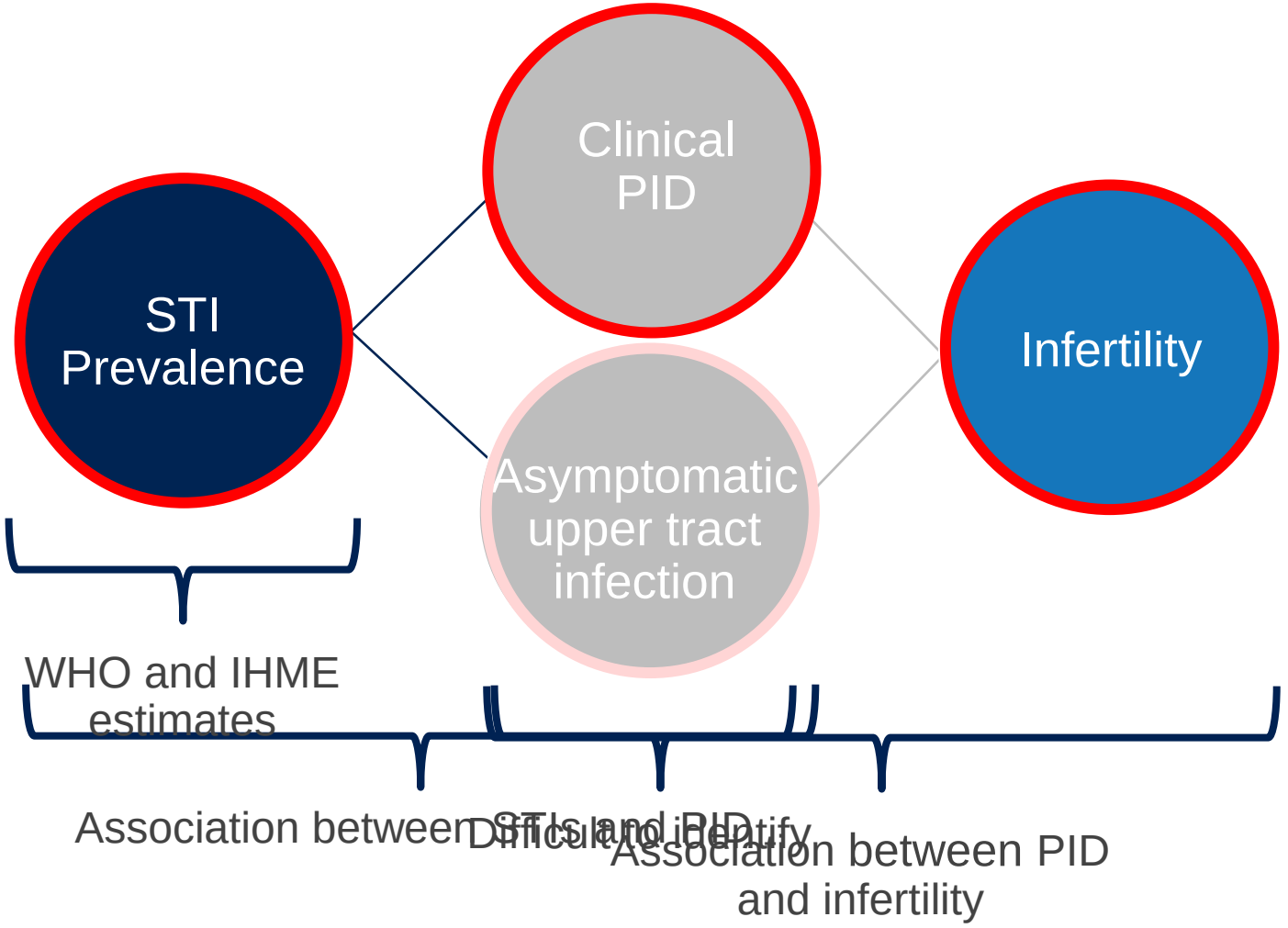
Uterine Abnormalities

- Uterine Fibroids
- Uterine anomalies or adhesions

RELATIONSHIP BETWEEN STIs AND INFERTILITY

ESTIMATING ASSOCIATIONS

Pathway between STIs and Tubal-Factor Infertility



KEY CONSIDERATIONS

Study participants

Relevant exposure-outcome intervals

Variability in PID definitions

Variability in infertility definitions

Overall approach to recommendations

STUDY PARTICIPANTS

Demographic Considerations

- Wide sample size range from 40 participants to a general population of women (516,720).
- Studies included women across a broad age range (16 – 49 years), post-menopausal women (mean age 58 ± 8.5 years) and women aged ≤ 35 years
- Women admitted for treatment of PID and/or gynecological problems.
- Women consulting/presenting with infertility or managed in the gynecological department for up to 5 years

EXPOSURE-OUTCOME INTERVALS

Methodological Challenges

- Cross-sectional – limited ability to establish causality
- Prospective cohort – etiologically relevant time period after STI diagnosis is unclear
    - Time of PID/infertility diagnosis is not necessarily indicative of when the condition first developed
    - Treatment required following diagnosis
- Case-control – prevalence of current STI does not inform the association with the outcome
    - Reliance on accurate medical records necessary to identify historical STI infections within etiologically relevant window

PID DEFINITIONS

PID DIAGNOSTIC	NUMBER OF ARTICLES (32)
Self-report: abdominal pain, pelvic tenderness, vaginal discharge etc.	20
Hysterosalpingography	2
Laparoscopy and "syndromic diagnosis"	1
Varied diagnostic methods (systematic review and Meta analyses)	1
Microscopy	3
Detection of pelvic peritonitis or a pelvic mass	3
Not specified	2

- PID definitions and diagnosis are variable across studies
- Reliance on participant self-reporting of symptoms for PID diagnosis
- PID is primarily a clinical diagnosis; difficult to parameterize for research studies
- Need for clearly stated diagnostic criteria for future studies

INFERTILITY DEFINITIONS

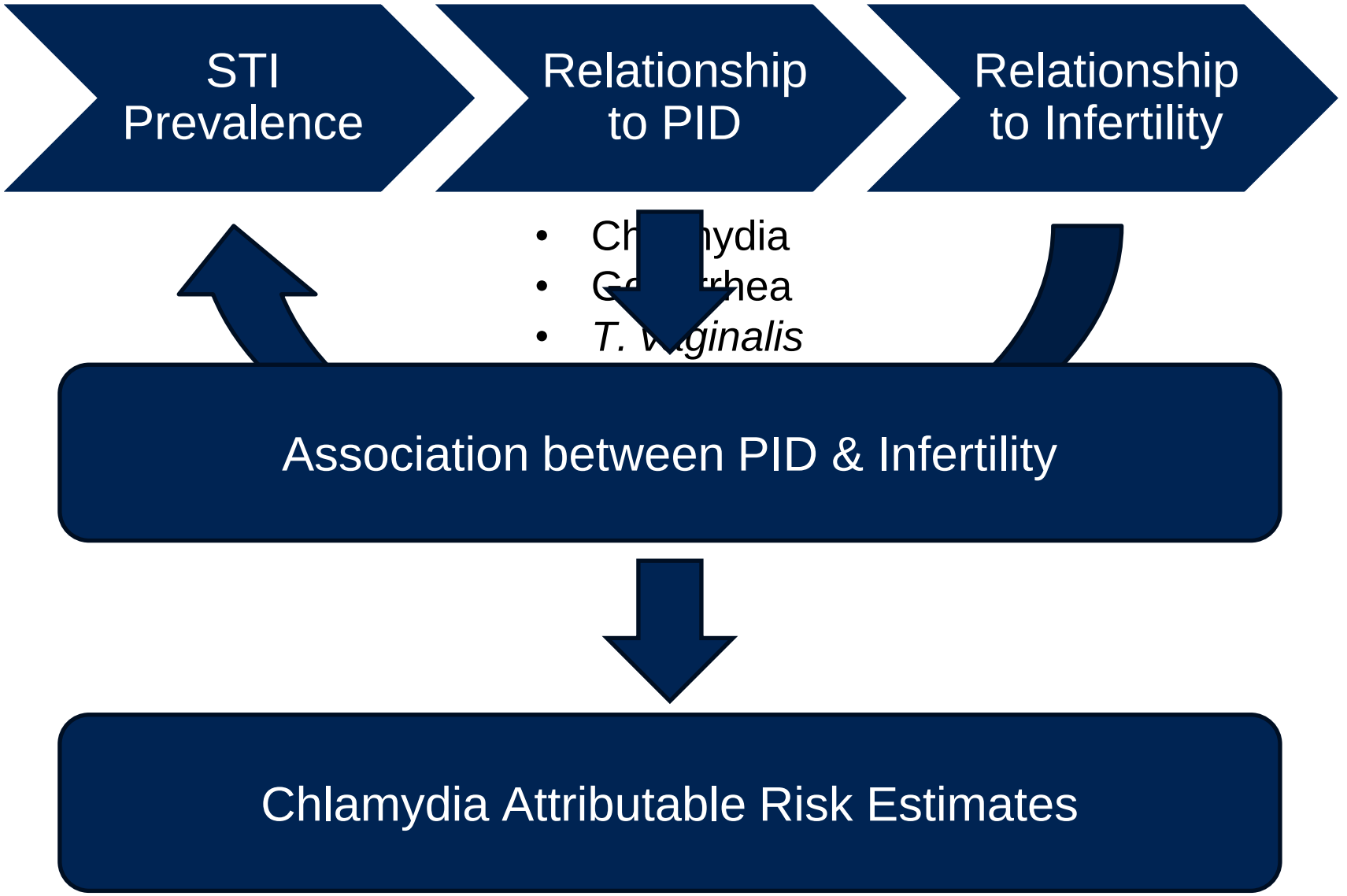
INFERTILITY DIAGNOSTIC		NUMBER OF ARTICLES
Not explicitly stated		21
Hysterosalpingography		16
Self-report	No time limit stated	16
	>2 years	3
	1 year	1
Laparoscopy		6
Determination by on OB/GYN		3
Pelvic echography		1
Tubal insufflation		1

- Only two prospective studies included
- Reliance on medical records or clinician assessment in cross-sectional visits
- Need for standardized definitions in future studies

APPROACH TO RECOMMENDATIONS

- Broad data summaries including the relative quality of the different studies used
- Varying data quality and Intrinsic limitations across studies; conclusions drawn were weighted on data with the stronger quality.
- Overall, confident overarching recommendations made with comprehensive links to all studies in appendix

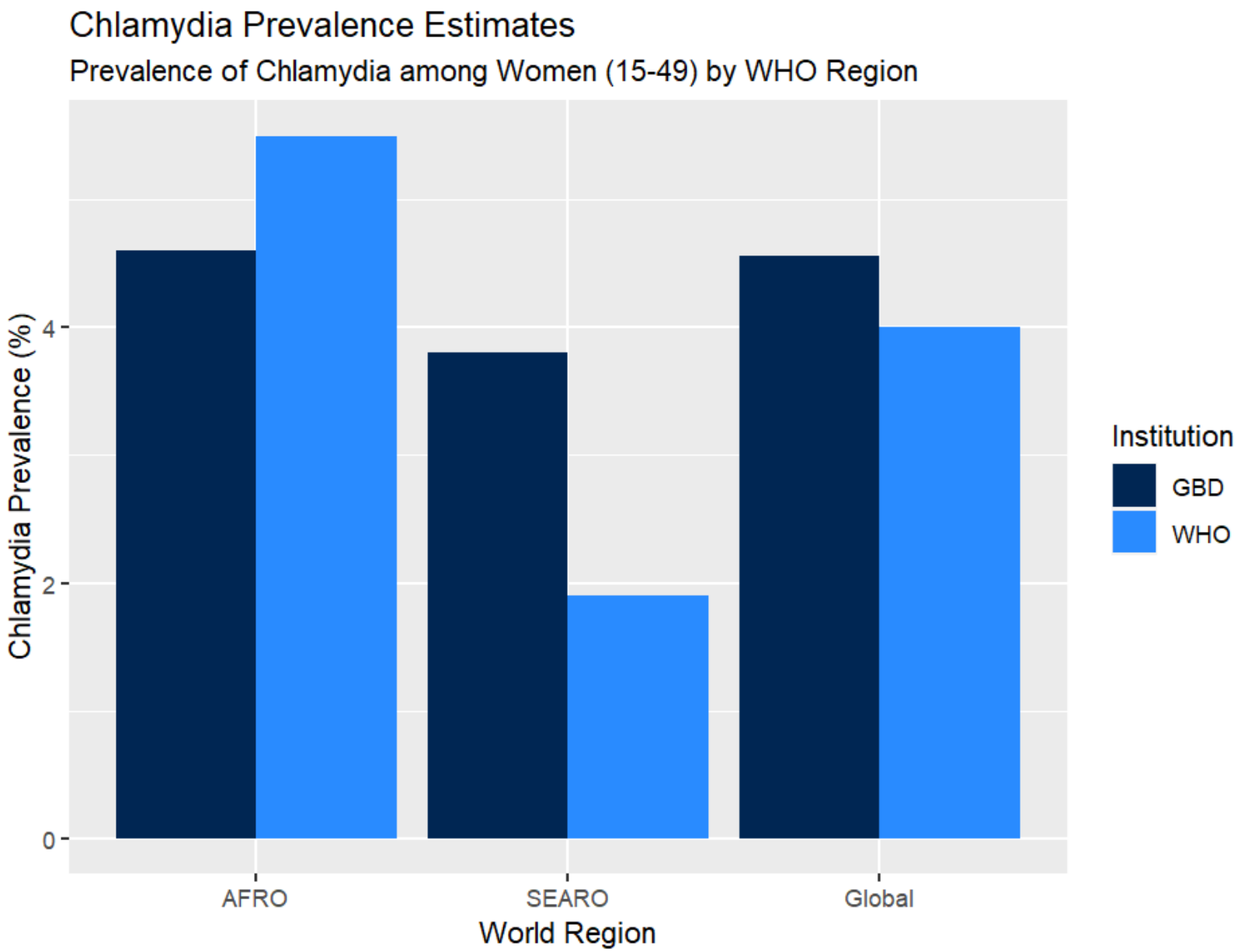
DATA ROADMAP



CHLAMYDIA

- Strong evidence for chlamydia as a cause of both PID and infertility
- Strongest associations between chlamydia and tubal-factor infertility
- Only STI with clinical trial evidence
    - Screening and treating chlamydia reduces incidence of PID

PREVALENCE OF CHLAMYDIA



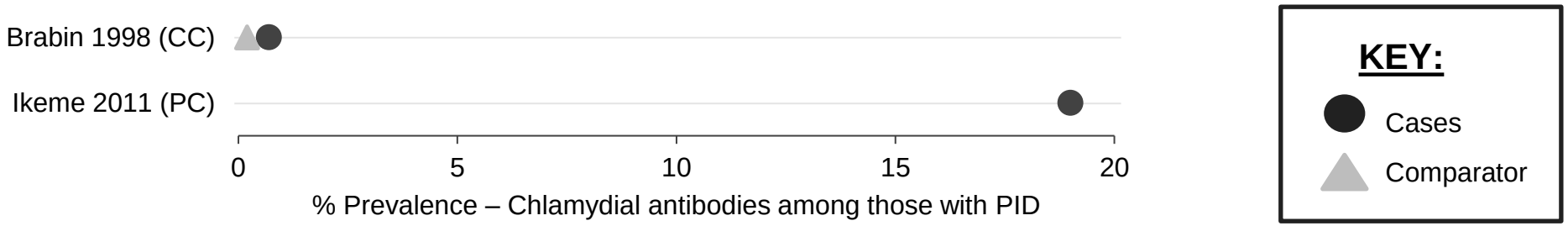
AVAILABLE STUDY DESIGNS

Chlamydia & PID

	Study Type	# Studies	Measure of Association
Chlamydia & PID	RCT	2	Relative risk
	Prospective Cohort	3	Prevalence of chlamydia
			Prevalence of chlamydial antibodies
			Odds ratio
	Retrospective Cohort	1	Hazard ratio
	Case-Control	1	Prevalence
	Cross-Sectional	8	Prevalence of chlamydia (n=1)
			Prevalence of chlamydial antibodies (n=6)
			Proportion of co-infection with PID (n=1)
	Scoping Review	1	Prevalence of chlamydia
	Modeling Study	1	Correlation coefficient between chlamydial antibodies and PID

CHLAMYDIA AND PID

Prevalence - Chlamydial antibodies among those with PID



Prevalence – PID among those with history of chlamydial antibodies

Study, Year	Study Design	Population	Outcome	Prevalence
Peeling 1997	PC	Commercial sex workers (Kenya)	Prevalence of PID among those with history of chlamydial antibodies who acquired subsequent chlamydia infection	48.2%

PC = prospective cohort
CC = case-control

CHLAMYDIA AND PID

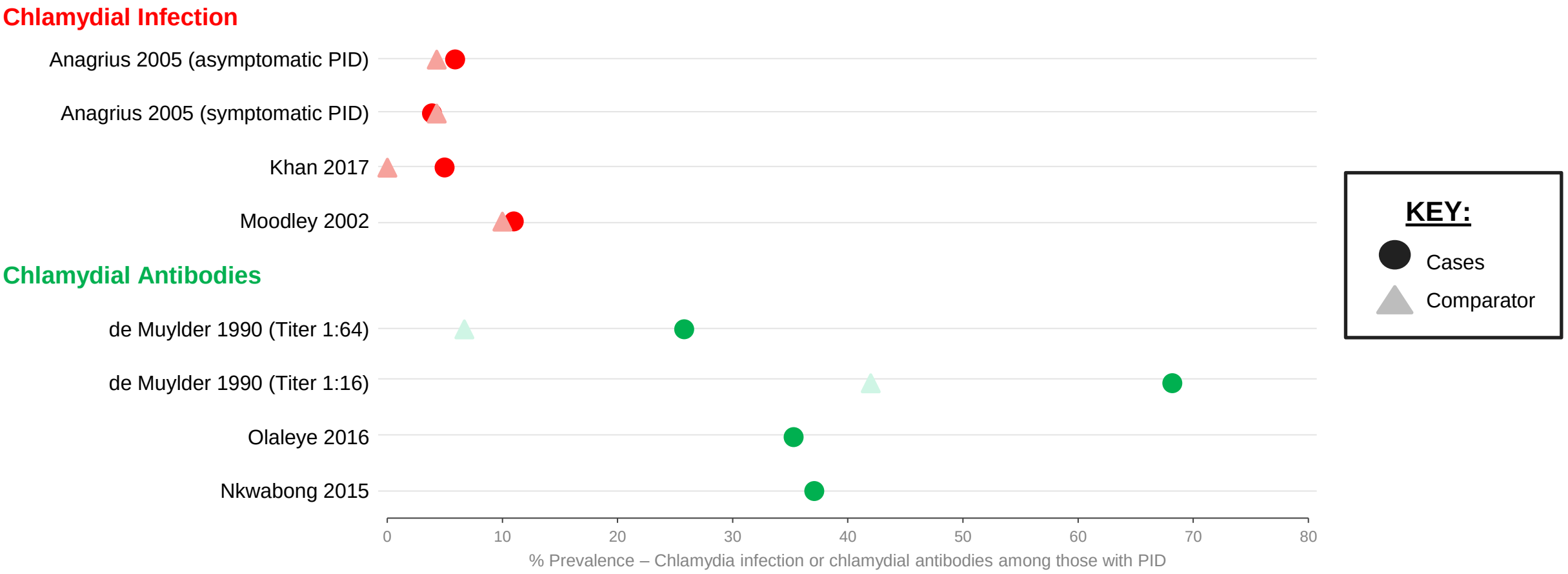
Measures of Association

Study, Year	Study Design	Population	Outcome	Measure	95% CI
Davies 2016	RC	General population; age 15-44 (Denmark)	Hazard ratio; positive chlamydial antibody test	HR = 1.5	1.43-1.57
Davies 2016	RC	General population; age 15-44 (Denmark)	Hazard ratio; 2+ positive chlamydial antibody tests compared to 1 positive test	HR = 1.2	1.11-1.31
Kimani 1996	PC	Commercial sex workers (Kenya)	Odds ratio; PID among those with history of chlamydia infections (antibody testing)	OR = 1.8	1.30-2.40
Peeling 1997	PC	Commercial sex workers (Kenya)	Odds ratio; PID during subsequent chlamydia infections (antibody testing) among women with prior chlamydia infection	OR = 2.6	1.10-6.20
Oakeshott 2010	RCT	Sexually active female students (UK)	Relative risk; PID among those screened for chlamydia	RR = 0.65	0.34-1.22
Scholes 1996	RCT	Women enrolled in an HMO; age 18-34 (USA)	Relative risk; PID among those screened for chlamydia	RR = 0.44	0.20-0.90

RC = retrospective cohort
PC = prospective cohort
RCT = randomized controlled trial

CHLAMYDIA AND PID

Prevalence – Chlamydial Infection OR Chlamydial Antibodies among those with PID*



*All studies are cross-sectional

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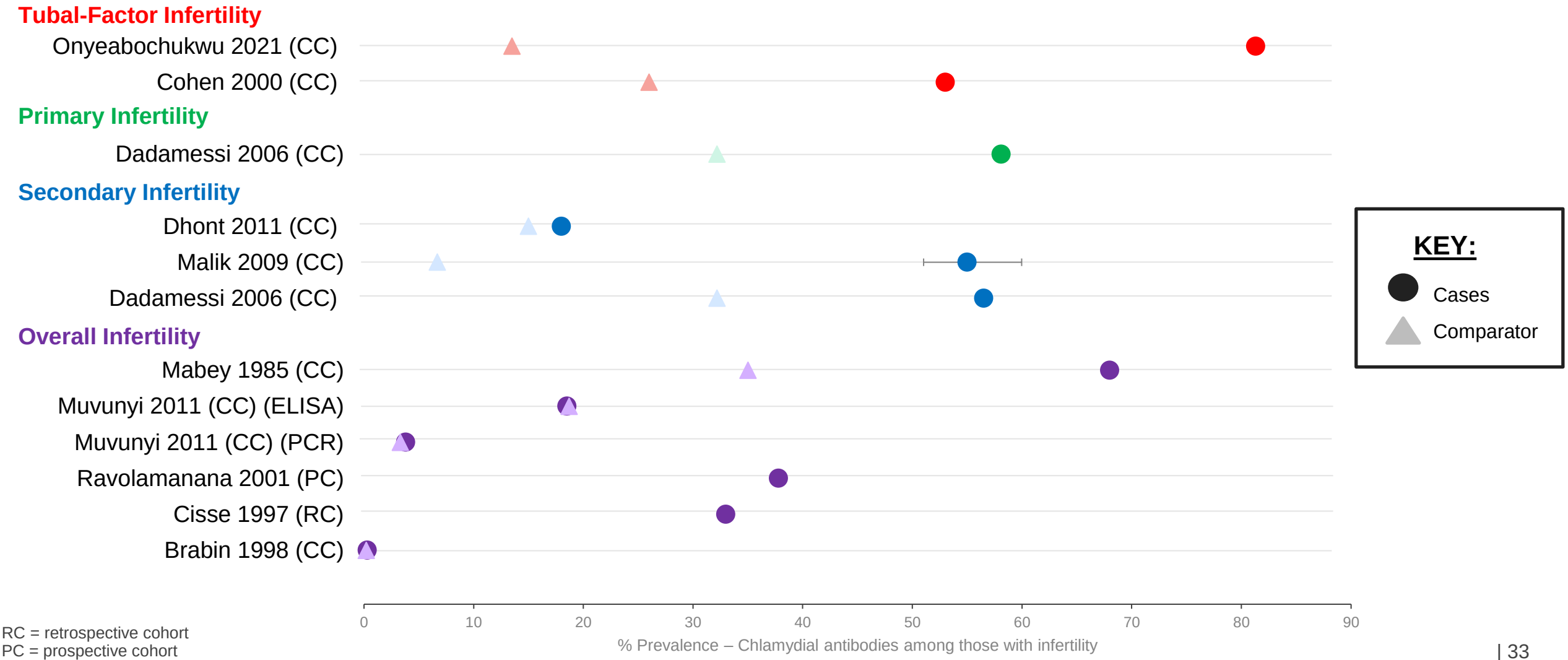
AVAILABLE STUDY DESIGNS

Chlamydia & Infertility

	Study Type	# Studies	Measure of Association
Chlamydia & Infertility	Prospective Cohort	2	Prevalence of infertility (n=1)
			Prevalence of chlamydial antibodies (n=1)
	Retrospective Cohort	1	Prevalence of chlamydial antibodies (n=6)
	Case-Control	16	Odds ratio (n=7)
			Prevalence of chlamydia (n=5)
			Prevalence of chlamydial antibodies (n=7)
			Prevalence of infertility (n=2)
	Cross-Sectional	15	Prevalence of chlamydia (n=4)
			Prevalence of chlamydial antibodies (n=10)
			Odds ratio (n=1)
			Prevalence of infertility (n=1)
	Scoping Review	1	Prevalence of chlamydia
	Literature Review	2	Prevalence of chlamydia
			Prevalence of chlamydial antibodies
	Modeling Study	1	Prevalence of chlamydia

CHLAMYDIA AND INFERTILITY

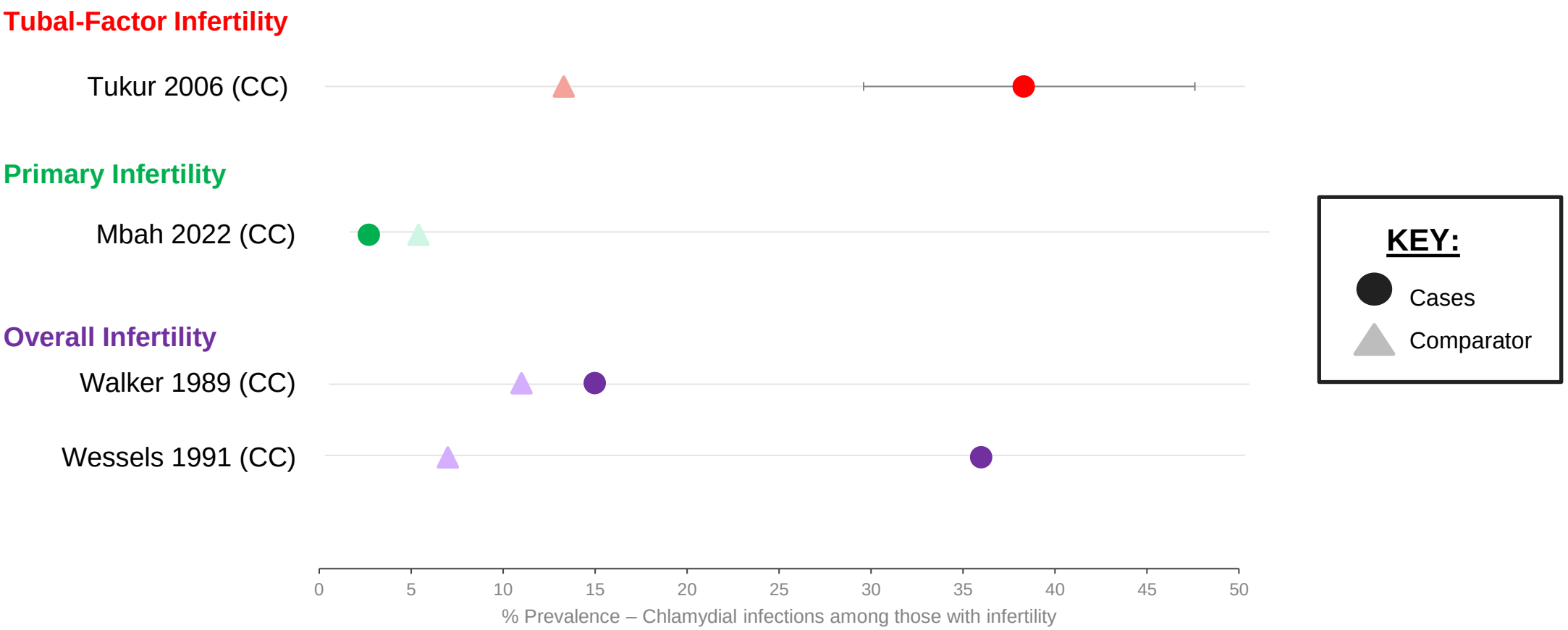
Prevalence - Chlamydial Antibodies among those with Infertility



RC = retrospective cohort
PC = prospective cohort
CC = case-control

CHLAMYDIA AND INFERTILITY

Prevalence - Chlamydia Infections among those with Infertility



CC = case-control

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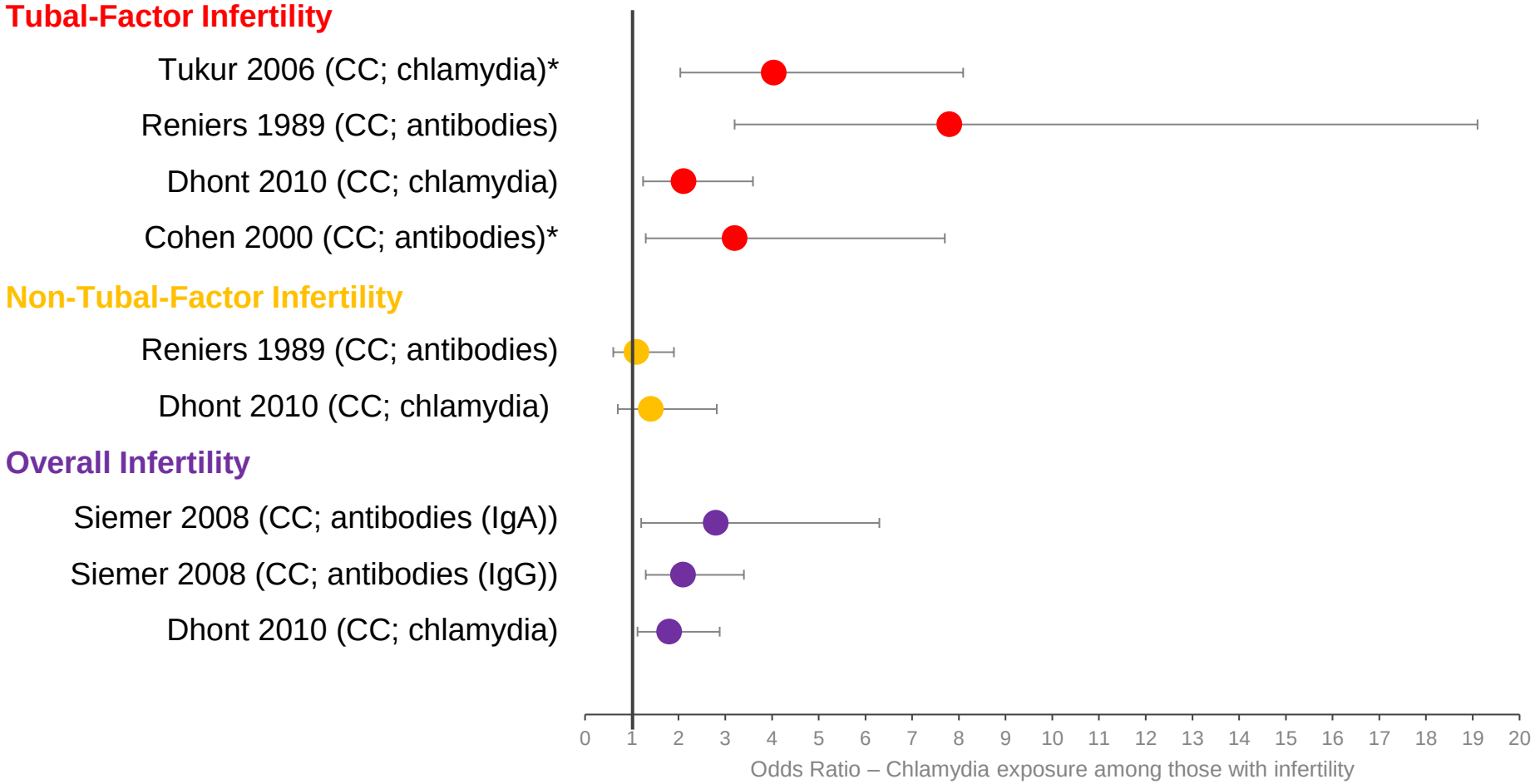
CHLAMYDIA AND INFERTILITY

Prevalence – Infertility among those with Chlamydial Antibodies

Study, Year	Study Design	Population	Outcome	Prevalence
Ikeme 2011	PC	Women age 20-34 attending fertility clinic (Nigeria)	Prevalence of infertility among those with chlamydial antibodies (IgG)	2.4%

CHLAMYDIA AND INFERTILITY

Odds Ratios – Chlamydia Exposure among those with Infertility



CC = case-control
*OR is not adjusted

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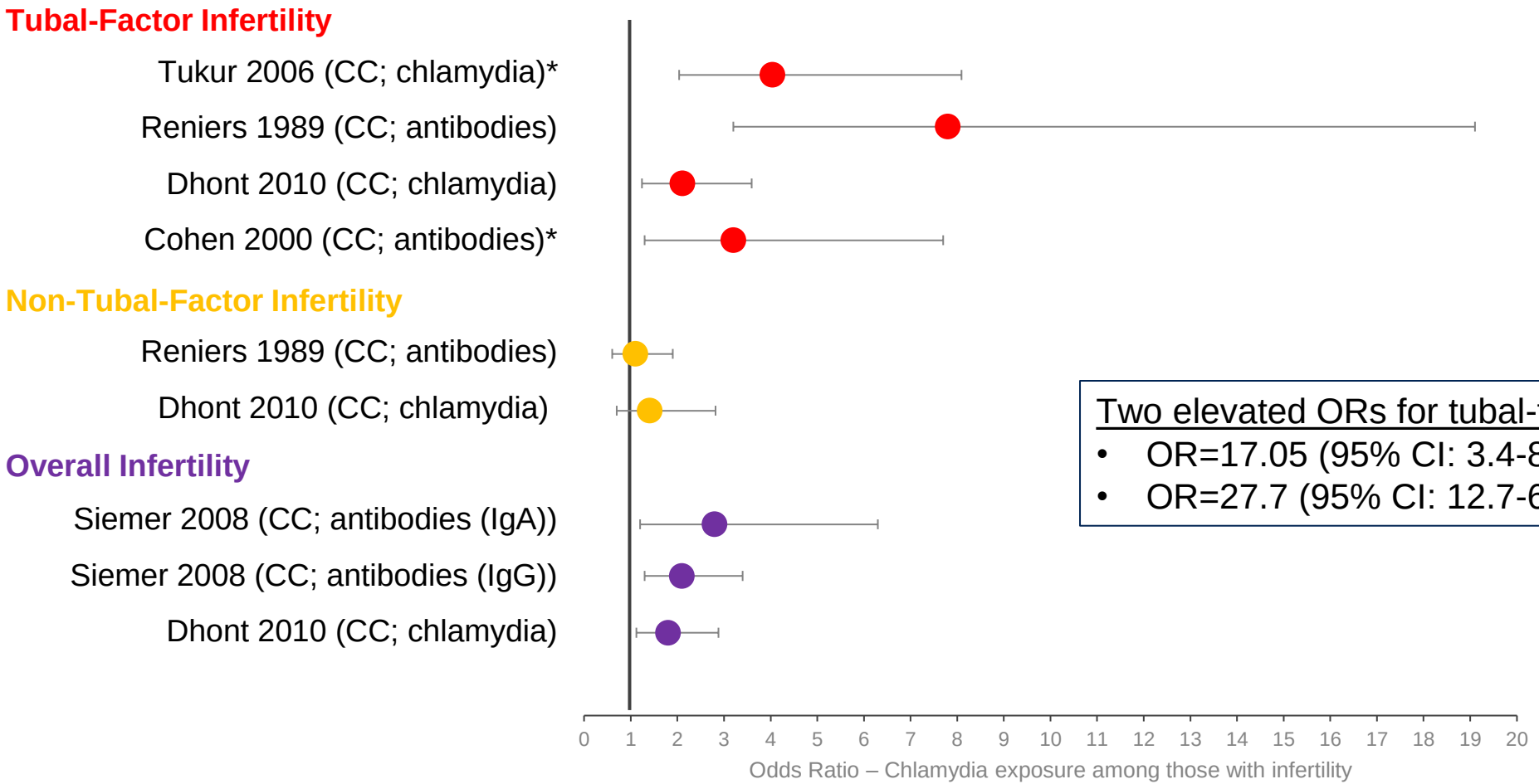
CHLAMYDIA AND INFERTILITY

Odds Ratios – Chlamydia Exposure among those with Infertility



Two elevated ORs for tubal-factor infertility:

- OR=17.05 (95% CI: 3.4-85.5) – self report
- OR=27.7 (95% CI: 12.7-67.2) – antibodies*

CC = case-control
*OR is not adjusted

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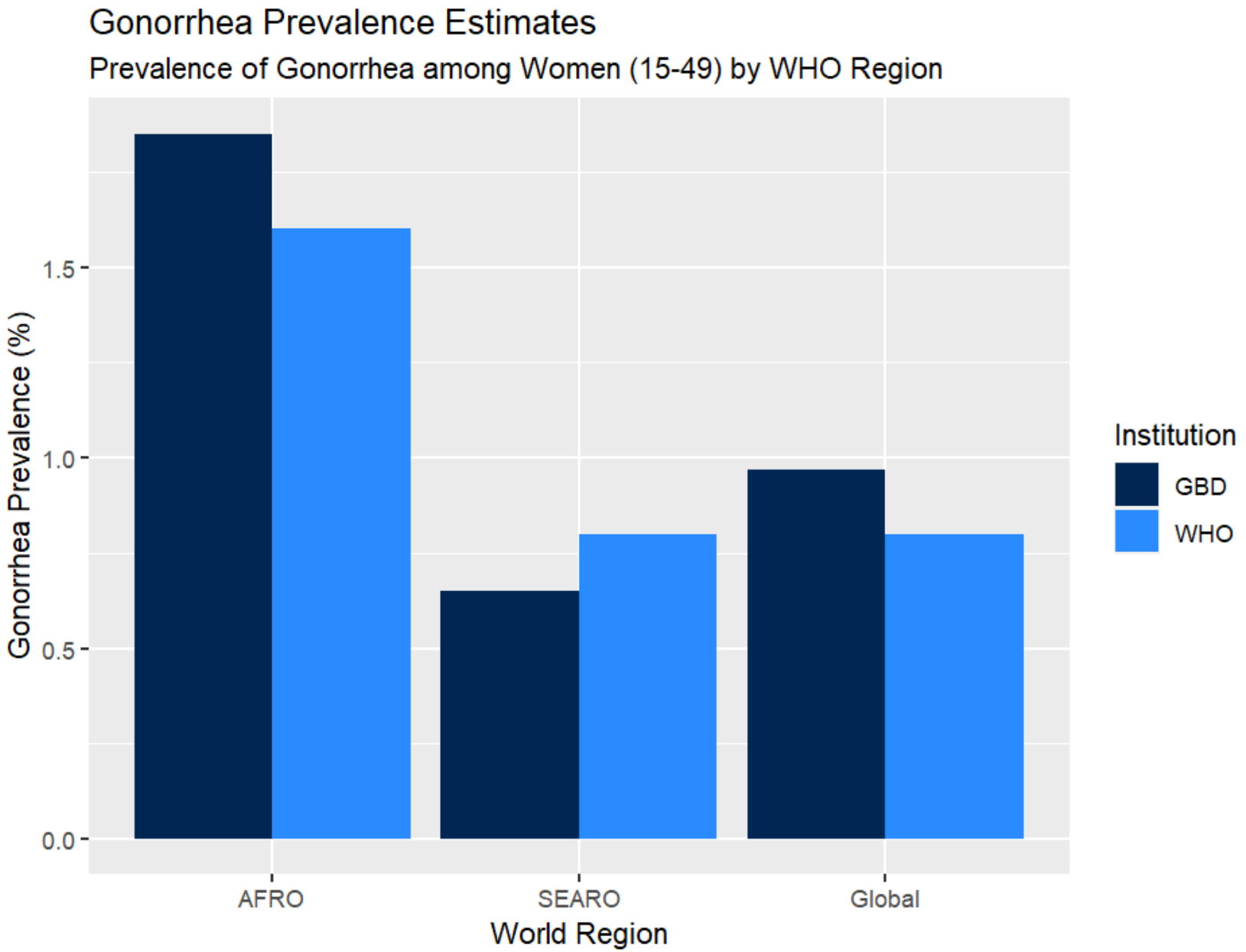
GONORRHEA

- Modest evidence of an association between gonorrhea and PID, but less evidence than for chlamydia
- Mixed evidence of an association between gonorrhea and infertility

PREVALENCE OF GONORRHEA



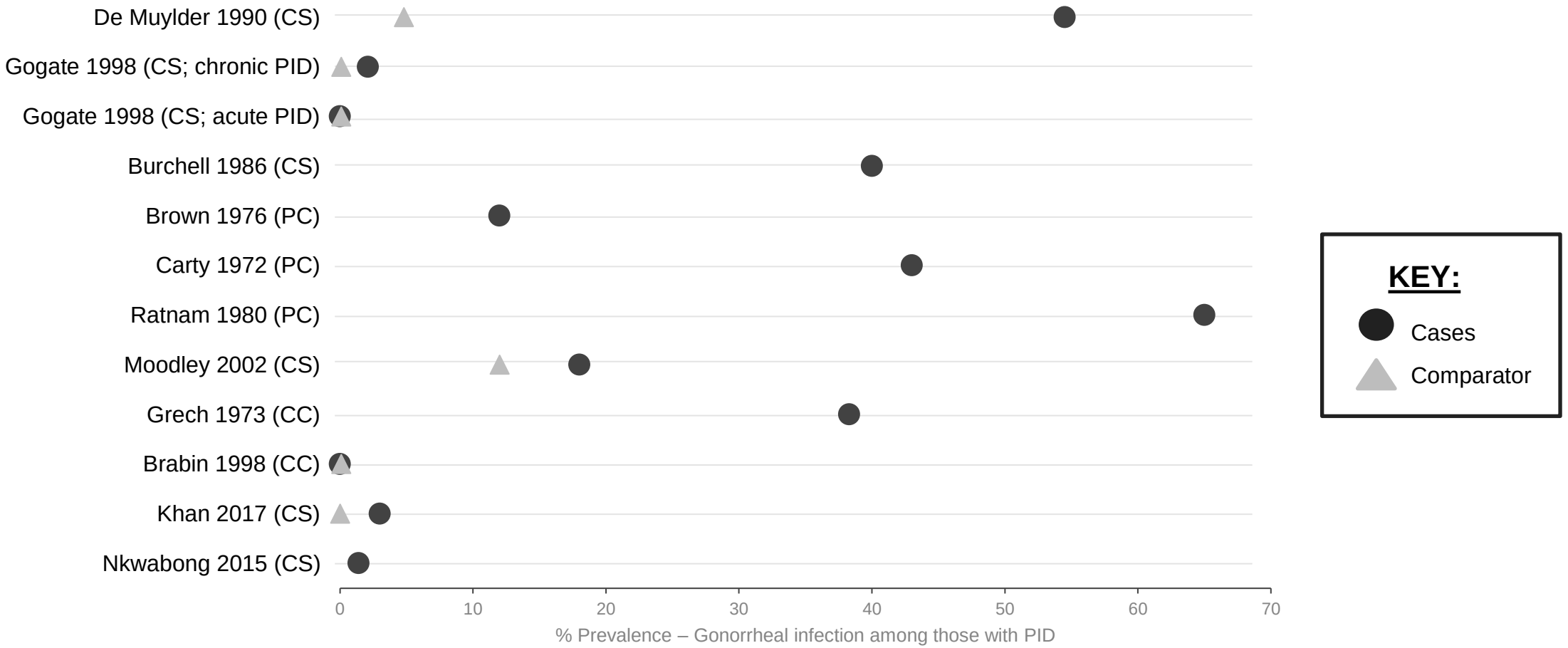
AVAILABLE STUDY DESIGNS

Gonorrhea & PID

	Study Type	# Studies	Measure of Association
Gonorrhea & PID	Cross-Sectional	5	Prevalence of gonorrhea among those with PID (n=4)
			Relative risk (n=1)
	Scoping Review	2	Prevalence of PID among women with gonorrhea
	Case Control	3	Prevalence of gonorrhea among those with PID (n=2)
			Prevalence of gonorrhea among those with PID and Salpingitis (n=1)
	Prospective Cohort	6	Prevalence of gonorrhea among those with PID
	Retrospective Cohort	2	Prevalence of PID among those with gonococcal infection

GONORRHEA AND PID

Prevalence – Gonorrheal Infection among those with PID



CC = case-control
PC = prospective cohort
CS = cross-sectional

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GONORRHEA AND PID

Measures of Association

Study, Year	Study Design	Population	Outcome	Measure	95% CI
Moodley 2002	CS	Postmenopausal women (mean age 58); South Africa	Relative risk of PID comparing those with gonococcal infection to those without gonococcal infection	RR = 1.5	1.0-2.3
Moodley 2002	CS	Postmenopausal women living with HIV; South Africa	Relative risk of PID comparing those with gonococcal infection to those without gonococcal infection	RR = 1.4	0.9-2.3
De Muylder 1990	CS	Women hospitalized with PID; Zimbabwe	Odds ratio; gonococcal infection among those with PID compared to without PID	OR = 23.8	8.0-76.2
Peeling 1997	PC	Commercial sex workers; Kenya	Odds ratio; gonococcal-only-PID among those with no chlamydial antibodies compared to those with chlamydial antibodies	OR = 1.04	0.53-2.06

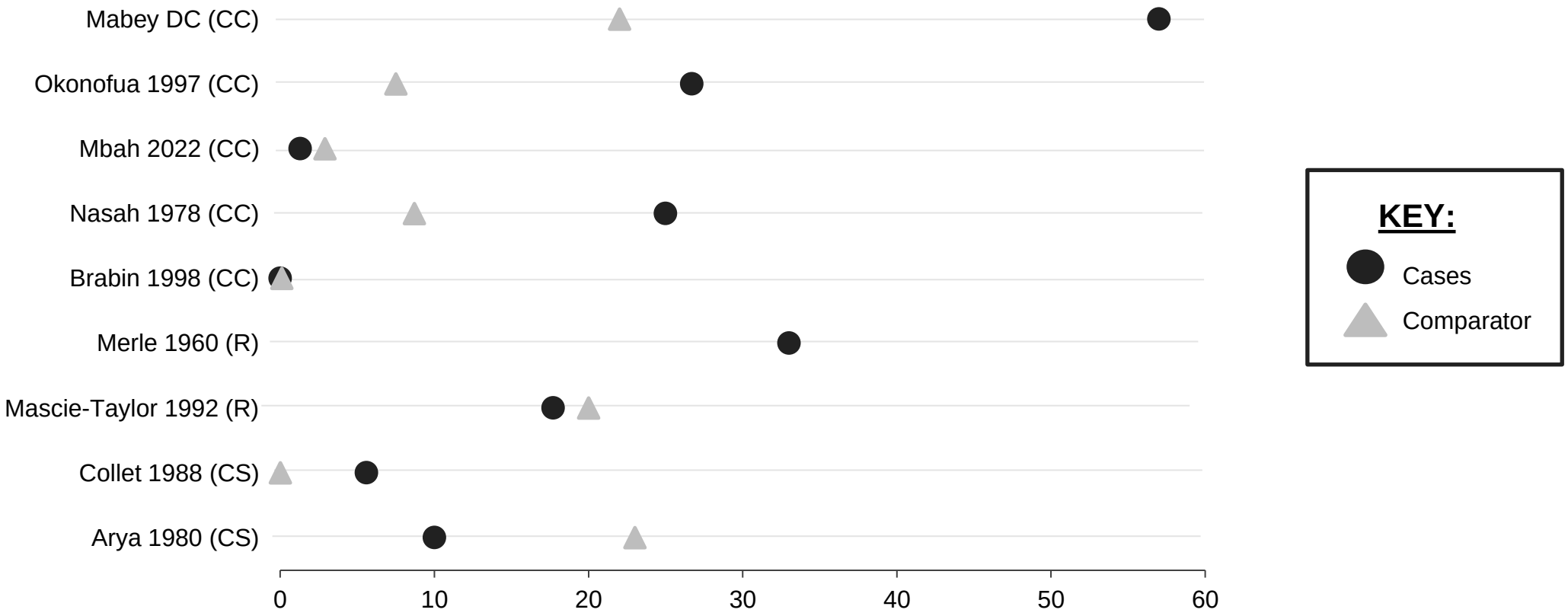
AVAILABLE STUDY DESIGNS

Gonorrhea & Infertility

	Study Type	# Studies	Measure of Association
Gonorrhea & Infertility	Cross-Sectional	5	Prevalence of gonorrhea (n=4)
			Prevalence of history of gonorrheal infection (n=1)
	Scoping Review	2	Prevalence of gonorrhea
	Case Control	7	Prevalence of gonorrhea (n=5)
			Prevalence of gonorrhea amongst those with secondary infertility (n=1)
			Prevalence of gonorrheal antibodies (n=1)
	Modeling Study	1	Impact of prevalence on population growth rate

GONORRHEA AND INFERTILITY

Prevalence – Gonorrhea among those with Infertility



CC = case-control
PC = prospective cohort
CS = cross-sectional
R = literature review

GONORRHEA AND INFERTILITY

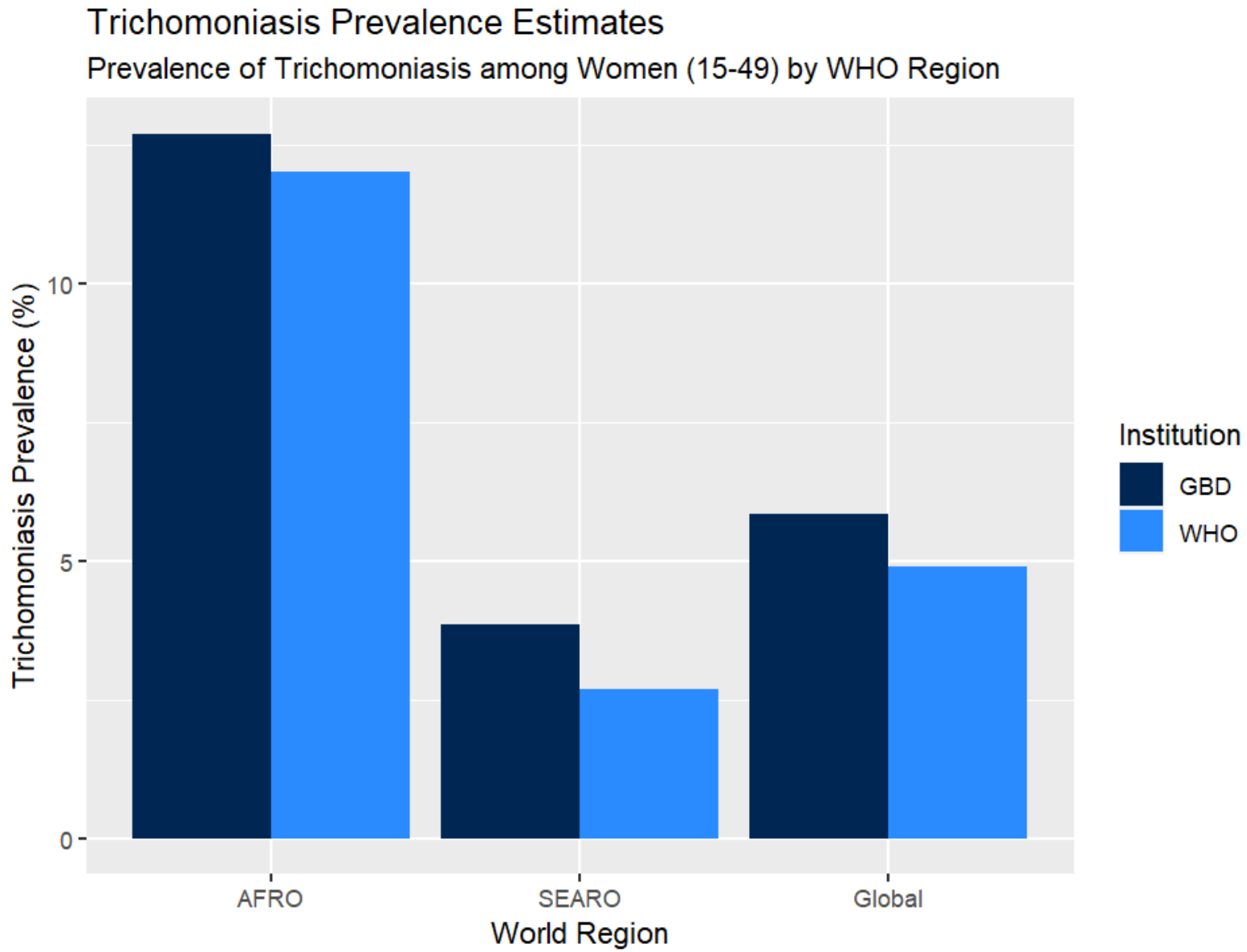
Measures of Association

Study, Year	Study Design	Population	Outcome	Measure	95% CI
Okonofua 1997	CC	Community-based sample of women; Nigeria	Odds ratio; gonorrheal antibody prevalence comparing cases of infertility to controls	OR = 4.5	Not reported

T. vaginalis

- Preliminary evidence of an association between *T. vaginalis* and PID
- Mixed evidence of an association between *T. vaginalis* and infertility
- Mixed evidence of an association between *T. vaginalis* and infertility

PREVALENCE OF TRICHOMONIASIS



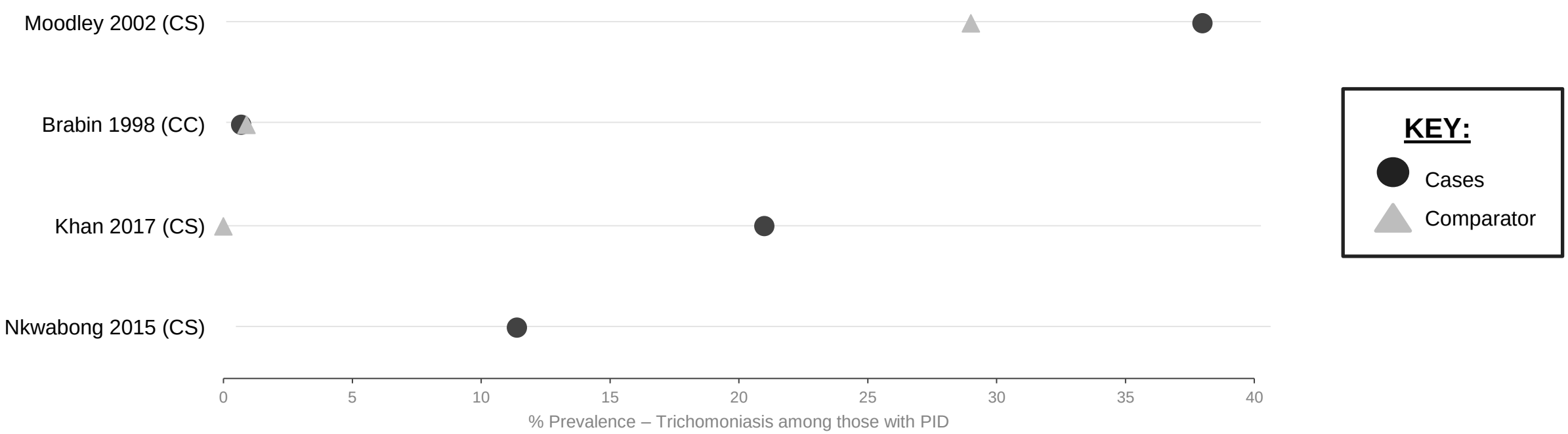
AVAILABLE STUDY DESIGNS

Trichomoniasis & PID

	Study Type	# Studies	Measure of Association
Trichomoniasis & PID	Case Control	2	Prevalence of trichomoniasis
			Adjusted odds ratio
	Cross-Sectional	4	Prevalence of trichomoniasis (n=2)
			Relative risk (n=1)
			Proportion of women with Trichomoniasis and PID (n=1)

TRICHOMONIASIS AND PID

Prevalence – Trichomoniasis among those with PID



CS = cross-sectional
CC = case-control

TRICHOMONIASIS AND PID

Measures of Association

Study, Year	Design	Population	Outcome	Measure	95% CI
Moodley 2002	CS	Women attending rural STI clinic (South africa	Relative Risk; Trich among those with PID	RR = 1.5	1.1-2.1
Paisarntaniwong 1995	CC	Women enrolled in an HMO; age 18-34 (USA)	Adjusted OR: Trich in women with PID, adjusted for age and douching	OR = 4.72	0.96-29.1

CS = cross-sectional
CC = case control

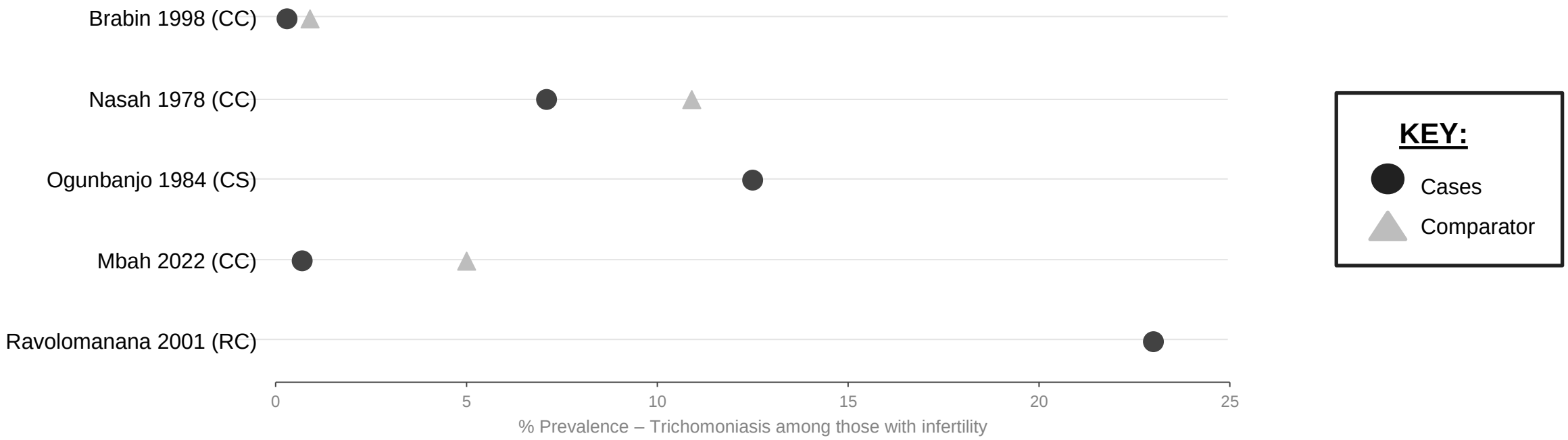
AVAILABLE STUDY DESIGNS

Trichomoniasis & Infertility

	Study Type	# Studies	Measure of Association
Trichomoniasis & Infertility	Case Control	3	Prevalence of *T. vaginalis* in women with infertility
	Prospective Cohort	1	Prevalence of *T. vaginalis* in women with infertility
	Cross-Sectional	2	Prevalence of *T. vaginalis* in women with infertility (n=1)
			Adjusted odds ratio (n=1)

TRICHOMONIASIS AND INFERTILITY

Prevalence – Trichomoniasis among those with infertility



CS = cross-sectional
CC = case-control
RC = retrospective cohort

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TRICHOMONIASIS AND INFERTILITY

Measures of Association

Study, Year	Design	Population	Outcome	Measure	95% CI
Klinger 2006	CS	Women aged 20-44 who were part of sampled households (Tanzania)	Adjusted odds ratio of having Trichomoniasis among those reporting infertility problems	OR = 2.67	1.50-4.77

CS = cross-sectional

M. genitalium

- Mixed evidence of an association between *M. genitalium* and PID
- Modest evidence of an association between *M. genitalium* and infertility

PREVALENCE OF *M. genitalium*

- *M. genitalium* prevalence is not systematically collected by IHME or the WHO

- Prevalence of *M. genitalium* is thought to be slightly lower than that of chlamydia

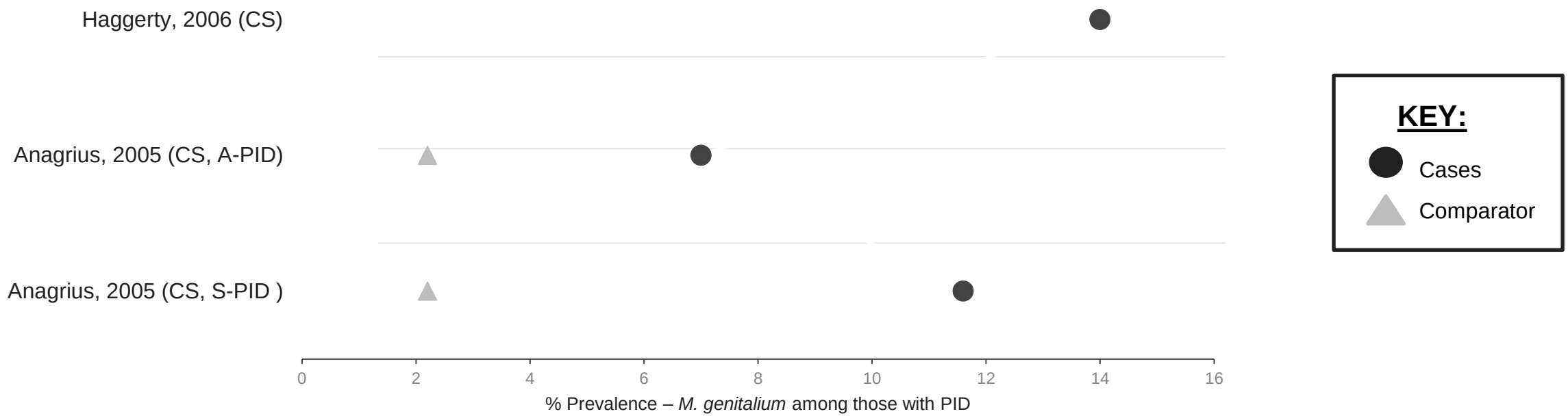
AVAILABLE STUDY DESIGNS

M. genitalium & PID

	Study Type	# Studies	Measure of Association
***M. genitalium* & PID**	Systematic Review and Meta-analysis	1	Pooled odds ratio
	Prospective Cohort	1	Incidence rate of PID
	Cross sectional	2	Prevalence of M. genitalium

M. genitalium AND PID

Prevalence – *M. genitalium* among those with PID



CS = cross sectional
A-PID = Asymptomatic PID
S-PID = Symptomatic PID

M. genitalium AND PID

Measures of Association

Study, Year	Study Design	Population	Outcome	Measure	95% CI
Lis 2015	Systematic Review and Meta-Analysis	10 studies; women of reproductive age (Global)	Pooled odds ratio; M. gen infection associated with significantly increased risk of PID	OR = 2.14	1.31 - 3.49
Oakeshott 2010	PC	Sexually active female students; age 16-27 (UK)	Relative risk; PID among women with and without M. gen	RR = 2.3	0.74 - 7.46

PC = prospective cohort

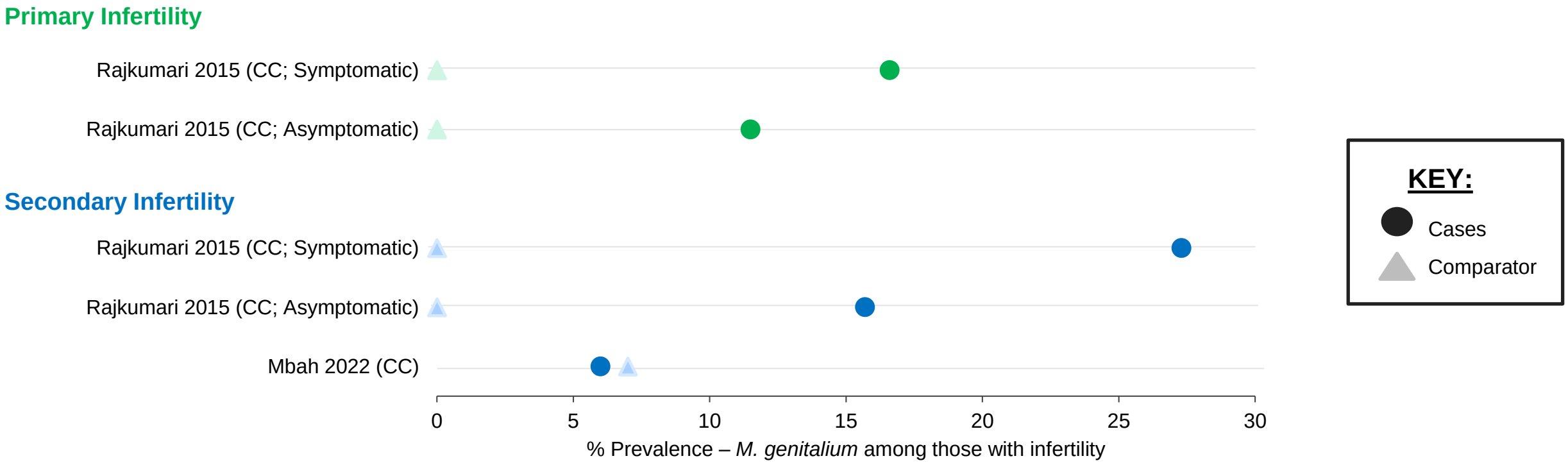
AVAILABLE STUDY DESIGNS

M. genitalium & Infertility

	Study Type	# Studies	Measure of Association
***M. genitalium* & Infertility**	Systematic Review and Meta-analysis	1	Pooled odds ratio
	Prospective Cohort	1	Adjusted fecundity rate for M. genitalium
	Case-Control	3	Prevalence of M. genitalium (n= 2)
			Adjusted odds ratio (n=1)

M. genitalium AND INFERTILITY

Prevalence – *M. genitalium* among those with Infertility



CC = Case control

M. genitalium AND INFERTILITY

Measures of Association

Study, Year	Study Design	Population	Outcome	Measure	95% CI
Egbe 2020	CC	Women presenting with infertility; fertile controls (Cameroon)	Adjusted odds ratio of having *M. genitalium* among those with tubal-factor infertility	AOR = 5.13	1.19 – 22.02
Lis 2015	Sys-Met	5 studies; women of reproductive age (Global)	Pooled odds ratio of having *M. genitalium* among those with infertility	Pooled OR = 2.43	0.93 – 6.34
Lokken 2023	PC	Non-pregnant women trying to conceive (Kenya)	Adjusted fecundability ratio; association between *M. genitalium* and fecundability	Adjusted fecundability ratio = 0.73%	0.44 – 1.23

CC = Case control
Sys-Met = systematic review and meta analysis
PC = prospective cohort

PID & INFERTILITY

- Elevated prevalence of PID among women with infertility
- Large associations observed between PID and infertility

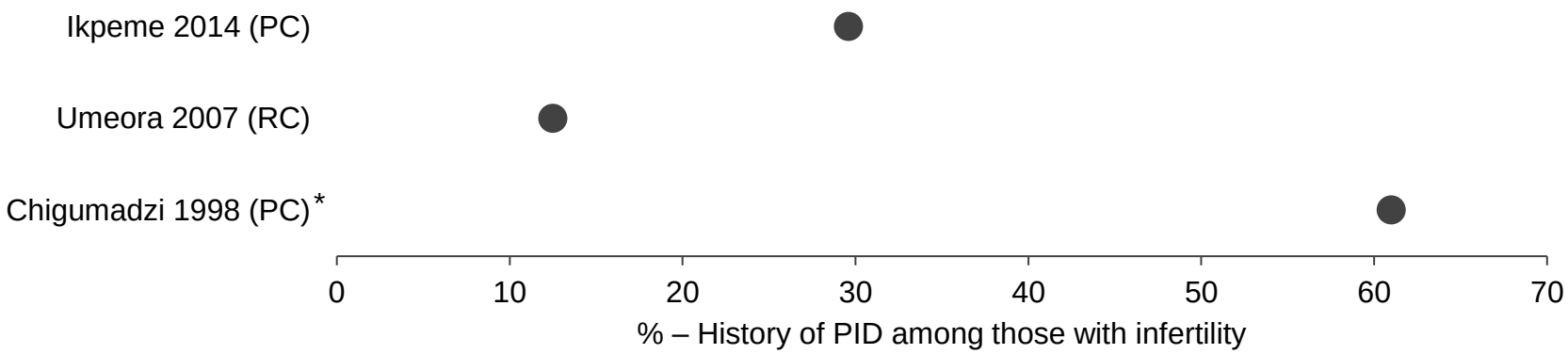
AVAILABLE STUDY DESIGNS

PID & Infertility

	Study Type	# Studies	Measure of Association
PID & Infertility	Prospective Cohort	2	Prevalence of PID among those with infertility
	Retrospective Cohort	1	Prevalence of PID among those with infertility
	Case-Control	3	Odds ratio (n=2)
			Prevalence of infertility among those with PID (n=1)
	Case-Cohort	1	Prevalence of tubal occlusion among those with PID
	Scoping Review	1	Attributable risk of infertility due to PID
	Cross-Sectional	7	Prevalence of PID among those with infertility (n=4)
			Prevalence of infertility among those with PID (n=3)

PID AND INFERTILITY

History of (suggested) PID among those with Infertility



Prevalence – Infertility among those with PID

Study, Year	Study Design	Population	Outcome	Prevalence
Grech 1973	CC	Women diagnosed with acute PID (Uganda)	Prevalence of infertility among cases of PID	25.6%

RC = retrospective cohort
PC = prospective cohort
CC = case-control
*History of suggested PID

PID AND INFERTILITY

Measures of Association

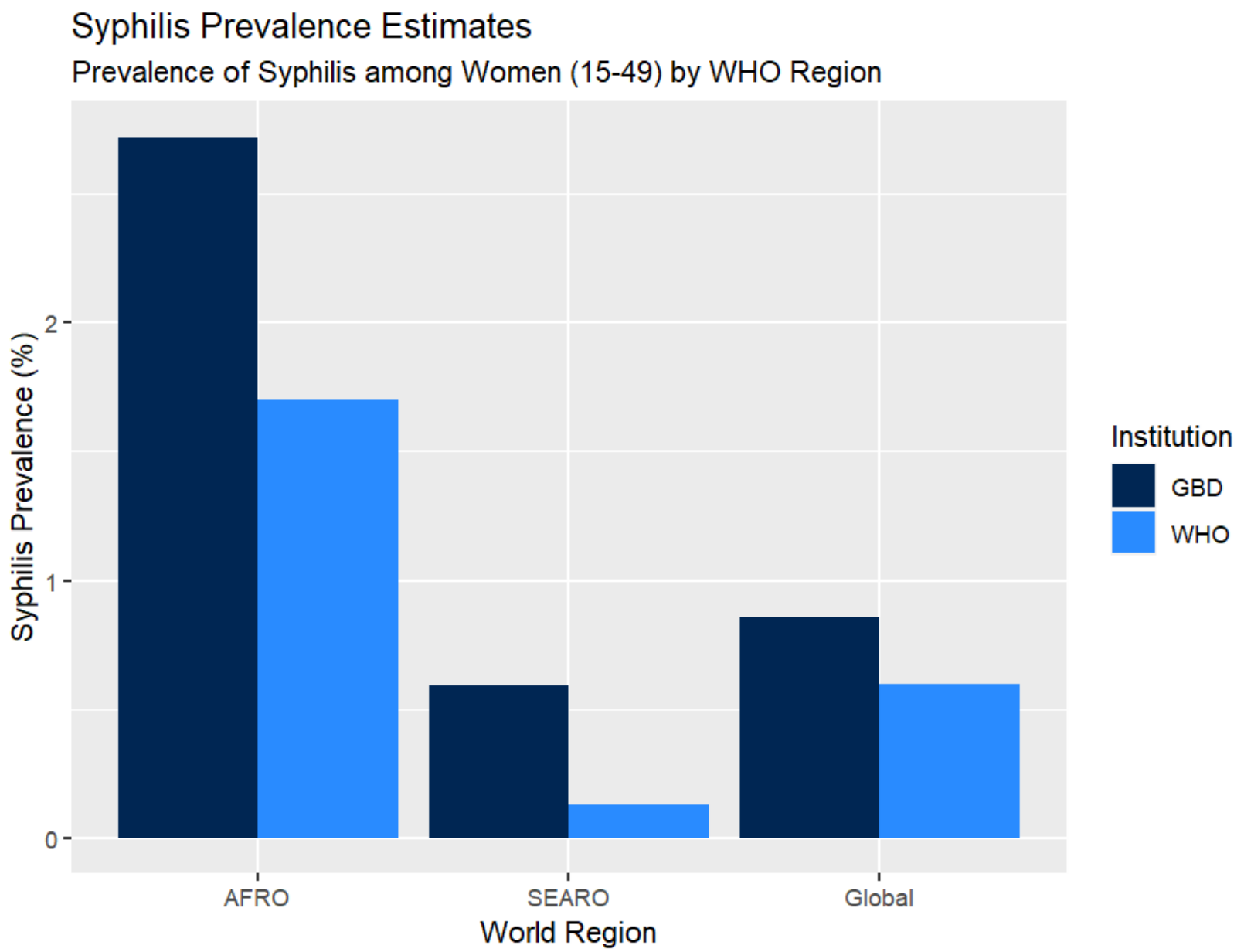
Study, Year	Study Design	Population	Outcome	Measure	95% CI
Okonofua 1995	CC	Infertile women and pregnant controls (Nigeria)	Odds ratio of PID among infertile women compared to pregnant controls	OR = 8.7	1.8-56.4
Cohen 2000	CC	Women with tubal infertility and fertile controls (Kenya)	Odds ratio of PID among women with tubal infertility compared to fertile controls	OR = 16	5.5-47

RC = retrospective cohort
PC = prospective cohort
CC = case-control

SYPHILIS

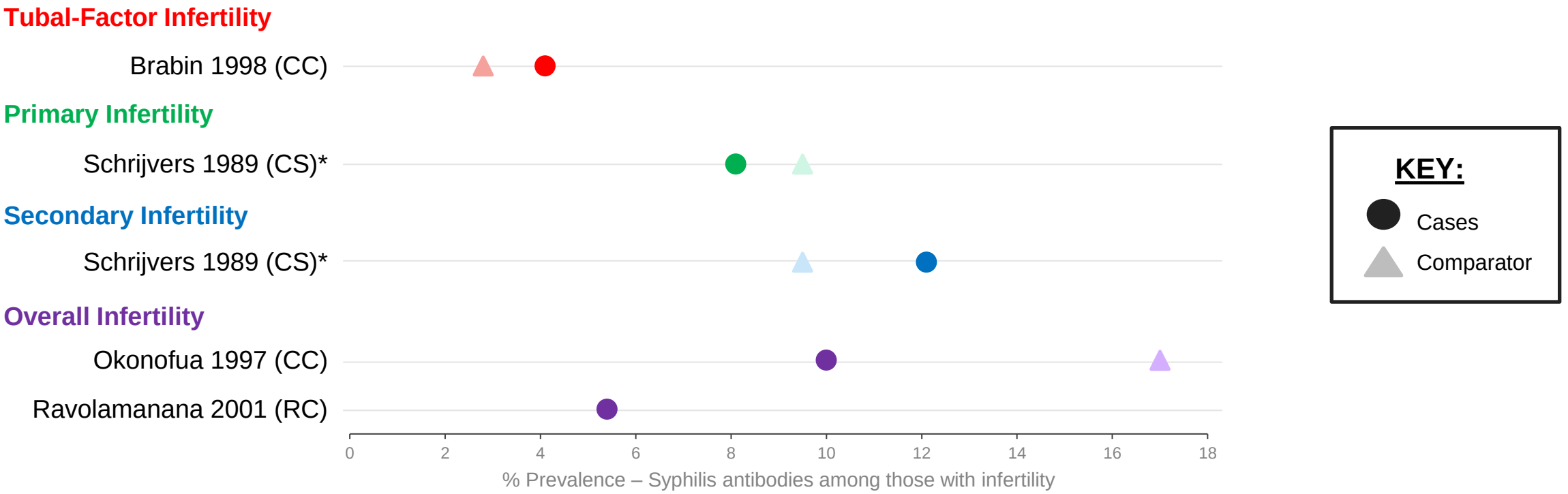
- No evidence of an association between syphilis and PID
- Limited evidence of an association between syphilis and infertility

PREVALENCE OF SYPHILIS



SYPHILIS AND INFERTILITY

Prevalence - Syphilis Antibodies among those with Infertility



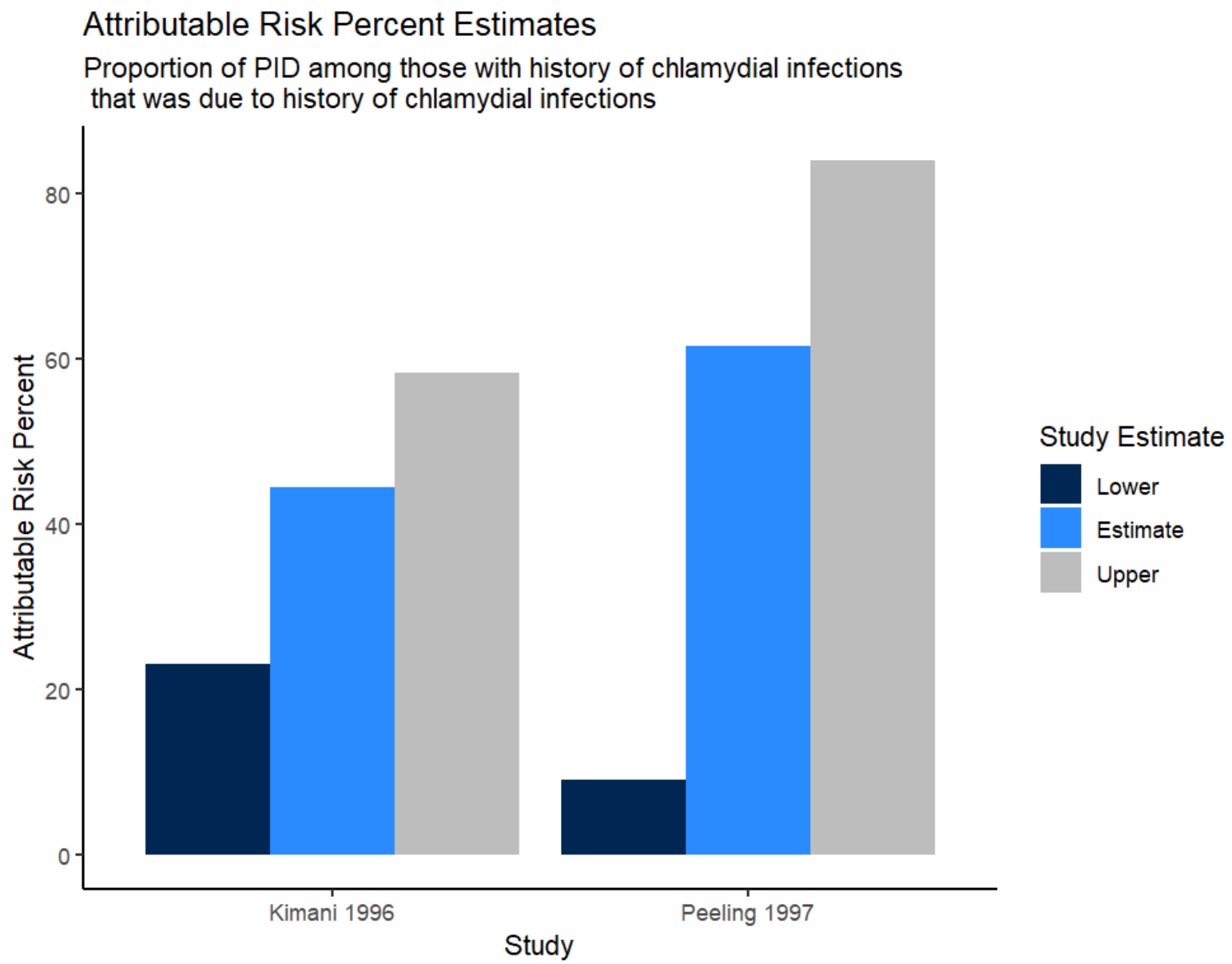
Study, Year	Study Design	Population	Outcome	Prevalence Measure
Lagarde 2003	CS	Population-based sample of women (Senegal)	Prevalence of infertility among women >40 years with TPHA+ test	62.5%
			Prevalence of infertility among women >40 with TPHA+ test and RPR+ test	50%

RC = retrospective cohort
CS = cross-sectional
CC = case-control
*age-adjusted prevalence

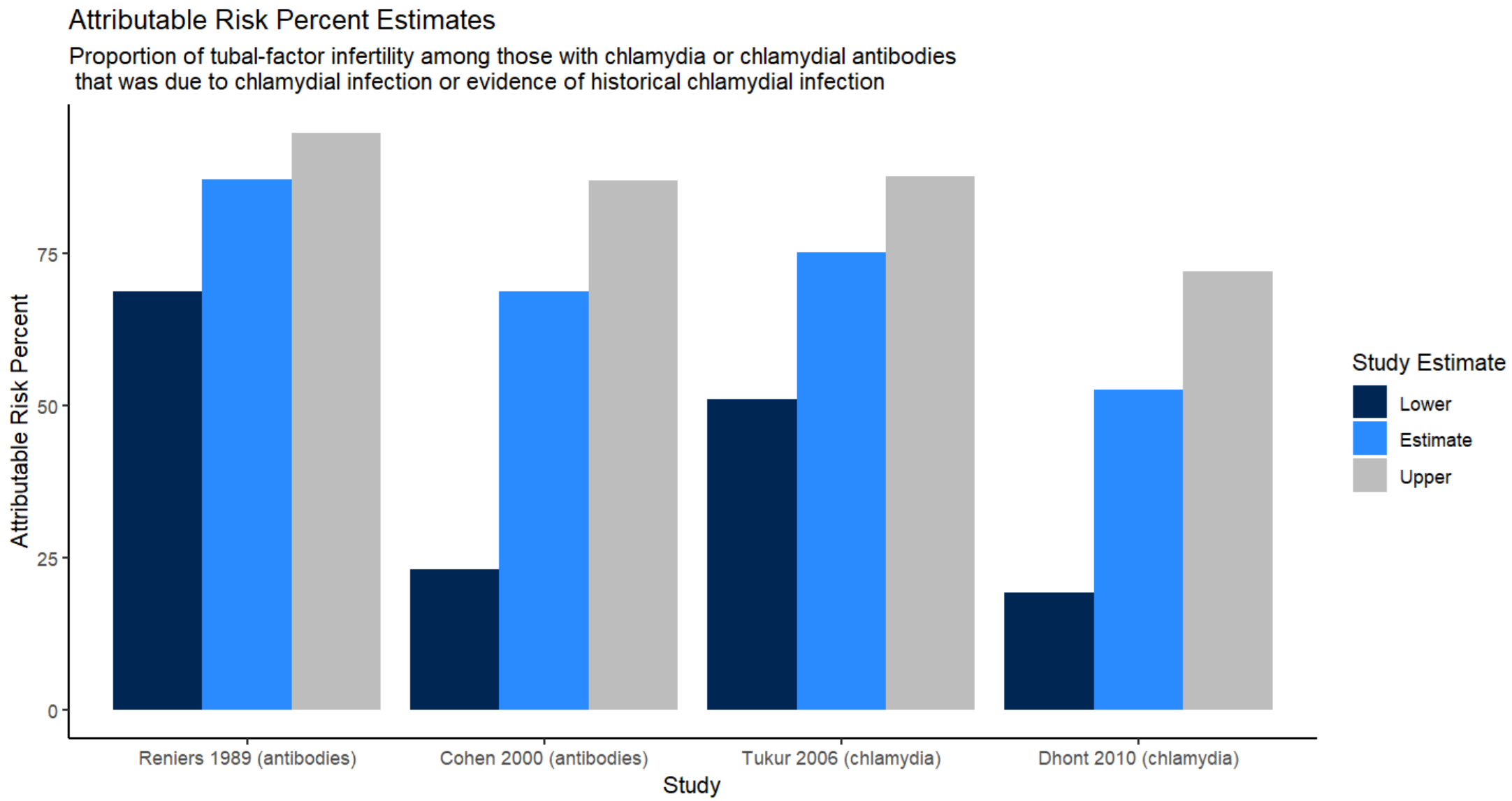
CHLAMYDIA ATTRIBUTABLE RISK ESTIMATES

START CENTER

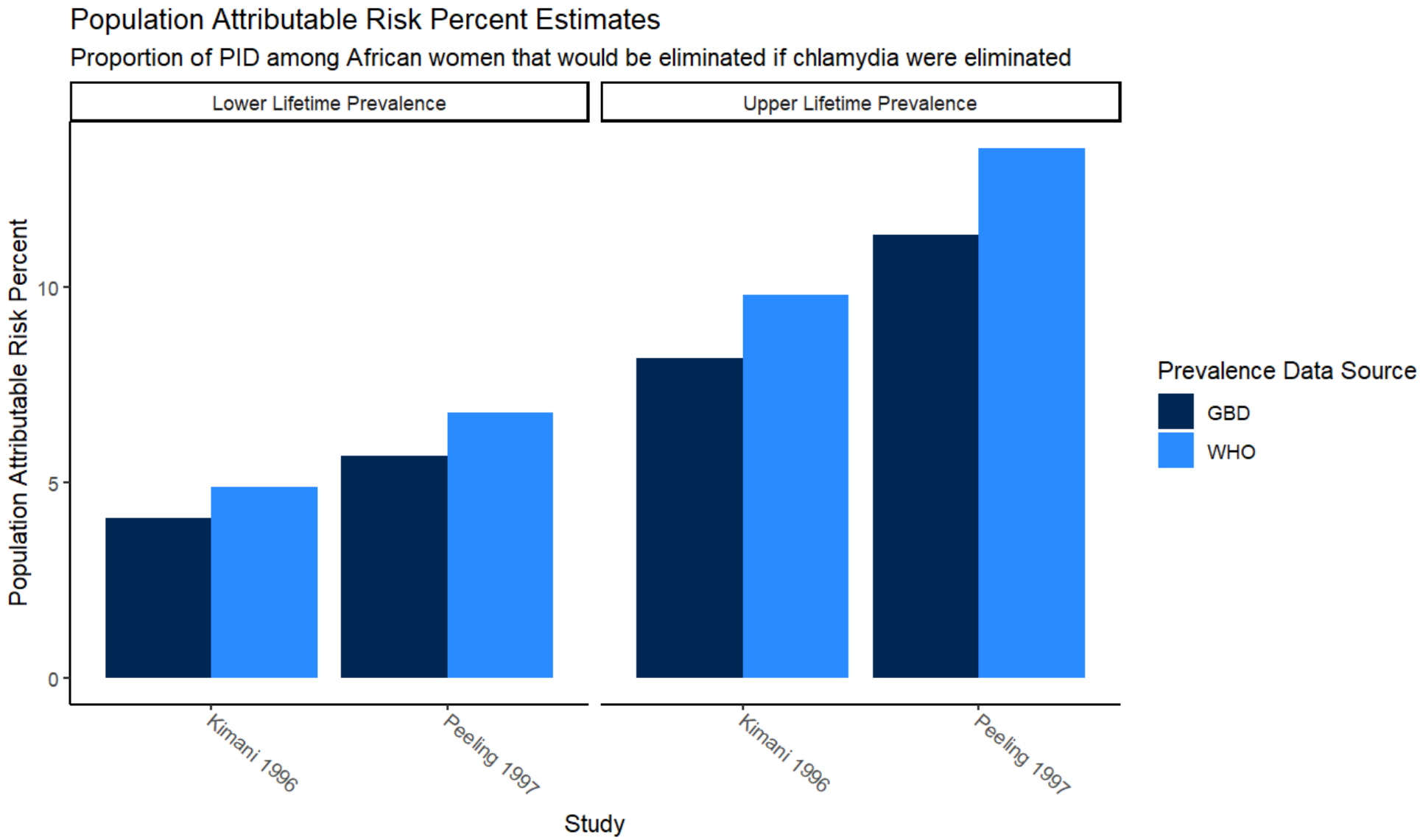
ATTRIBUTABLE RISK PERCENT - PID



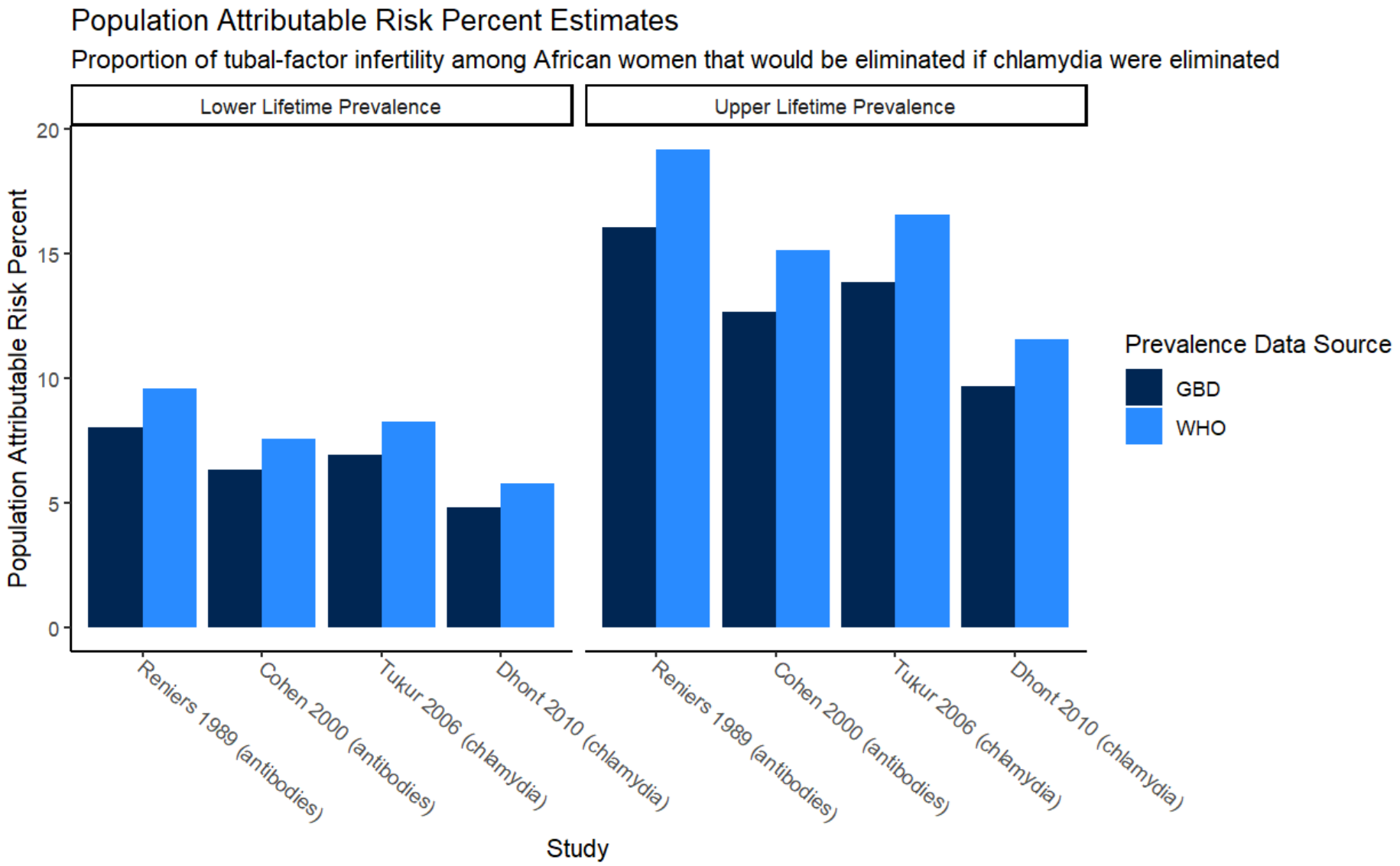
ATTRIBUTABLE RISK PERCENT - INFERTILITY



POPULATION ATTRIBUTABLE RISK PERCENT - PID



POPULATION ATTRIBUTABLE RISK PERCENT - INFERTILITY



KEY INFORMANTS

KEY INFORMANTS

University of Washington Faculty

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Assistant Professor; Health Metrics Sciences & Family Medicine

- Global Burden of Disease Lead on Reproductive, Genitourinary and Digestive Disease estimation

Elizabeth Bukusi, MM, MPH, PhD

Research Professor; Global Health & Obstetrics and Gynecology

- Chief Research Officer at Kenya Medical Research Institute
- Research foci include STIs and reproductive health

KEY TAKEAWAYS FROM KIIs

01

The IHME primarily uses systematic reviews and data from country partners to estimate STI incidence.

02

Infertility prevalence is collected through surveys like DHS and MICS, but they may not match clinical definitions. Critical data gaps persist around measuring infertility in sub- Saharan Africa.

03

Challenges in measuring STI prevalence include data from pregnant populations, which may not reflect the general population, and limited access to point-of-care tests, often resulting in symptom-based diagnosis.

04

In LMICs, PID diagnosis relies on broad symptom-based approaches. Prevalence is determined using facility-level data, which may underestimate cases due to limited access to healthcare.

OVERALL FINDINGS

Overarching Themes from KIIs

Chlamydia and gonorrhea are the primary STIs linked to infertility in clinical practice, with an emphasis on tubal factor infertility. In LMIC settings, this is particularly difficult to diagnose as STI infections are often sub-clinical

Challenges in diagnosing STIs and infertility in low-resource settings include high testing costs, reliance on symptom-based diagnosis, and limited access to diagnostic facilities.

Consistency in definitions is essential when diagnosing infertility in sub-Saharan Africa to ensure accurate and comparable data across regions and populations.

SUMMARY OF EVIDENCE

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Chlamydia	• Overall evidence suggests that chlamydia is an important cause of PID • Two randomized trials provide evidence that screening and treatment may reduce PID • Need additional clinical trials to evaluate effects of screening and treating on incidence of chronic pelvic pain and infertility

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Existing Clinical Trials – Screening for Chlamydia to Reduce PID Incidence

1. Scholes 1996

- RR = 0.44 (95% CI: 0.20-0.90)
- Incidence of PID among women screened = 8 per 10,000 woman-months
- Incidence of PID among controls = 18 per 10,000 woman-months

2. Oakeshott 2010

- RR = 0.65 (95% CI: 0.34-1.22)
- Incidence of PID among women screened = 1.3%
- Incidence of PID among controls = 1.9%

SUMMARY OF EVIDENCE

Chlamydia	• Overall evidence suggests that chlamydia is an important cause of PID • Two randomized trials provide evidence that screening and treatment may reduce PID • Need additional clinical trials to evaluate effects of screening and treating on incidence of chronic pelvic pain and infertility
Gonorrhea	• Evidence of an association between gonorrhea and PID, but less compared to chlamydia • Limited ability to determine impact of historical infections due to lack of gonorrhea antibody tests • No clinical trials to date evaluating gonorrhea prevention strategies to reduce incidence of PID

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M. genitalium	• Moderate evidence of an association between *M. genitalitum* and infertility • Mixed evidence of an association between *M. genitalium* and PID • Need initial clinical trials to examine effect screening and treating on PID and related outcomes

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T. vaginalis	• Low quality epidemiological studies in literature review • Potential for high impact given elevated prevalence of *T. vaginalis* in SSA and SEA

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Chlamydia	• Overall evidence suggests that chlamydia is an important cause of PID • Two randomized trials provide evidence that screening and treatment may reduce PID • Need additional clinical trials to evaluate effects of screening and treating on incidence of chronic pelvic pain and infertility
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T. vaginalis	• Low quality epidemiological studies in literature review • Potential for high impact given elevated prevalence of *T. vaginalis* in SSA and SEA
Syphilis	• No demonstrated association between syphilis and PID • Limited evidence of association between syphilis and infertility with low quality evidence

CONCLUSIONS

Strong evidence to support focusing investments on chlamydia

- Strongest evidence for association with PID and with infertility
- Only randomized trial evidence among five key STIs

Modest evidence for gonorrhea as cause of PID

- Mixed evidence for gonorrhea as cause of infertility
- Lower prevalence and concentration among key populations may position gonorrhea as a lower priority for investment

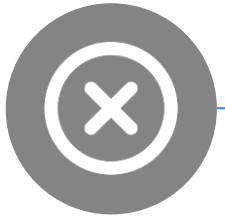
M. genitalium may be an important emerging priority for research

- Prevalence close to that of chlamydia
- Unique opportunity to compare screen & treat vs. SOC approach for multiple outcomes as screen & treat is not currently recommended

CONCLUSIONS

Need to clarify association between *T. vaginalis* and PID/infertility

- Potential for large impact given elevated prevalence of *T. vaginalis* in sub-Saharan Africa and Southeast Asia



Limited evidence for associations between syphilis and PID/infertility

- Remains an important cause of long-term health consequences for women and infants (e.g. congenital syphilis)

THANK YOU!

Questions?

START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

APPENDICES

APPENDICES

A Literature Searches & Included Articles

B References

C Country-Specific Data on Infertility and STI Prevalence

D Methodological Challenges by Study Design

APPENDIX A

Literature Searches & Included Articles

Topic	Search String	Number Returned Articles	Number Included
Chlamydia & PID	("Chlamydia*"[MeSH Terms] OR "Chlamydia trachomatis"[MeSH Terms] OR "Chlamydiaceae"[MeSH Terms] OR "Chlamydiales"[MeSH Terms]) AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR (Pelvic inflammatory disease* [Title/Abstract]) OR (endometritis [Title/Abstract]) OR (oophoritis [Title/Abstract]) OR (salpingitis [Title/Abstract]) OR (parametritis [Title/Abstract]) OR (Adnexitis [Title/Abstract]) OR Upper Genital Tract Infection [Title/Abstract] OR Adnexitis [Title/Abstract] OR Asymptomatic Upper Genital Infection [Title/Abstract] OR Asymptomatic PID [Title/Abstract] OR Asymptomatic Pelvic Inflammatory [Title/Abstract]) OR (asymptomatic upper genital tract infection [Title/Abstract]) AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR BURKINA FASO[Title/Abstract] OR CABO VERDE[Title/Abstract] OR CAMEROON[Title/Abstract] OR CENTRAL AFRICAN REPUBLIC[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR COTE D'IVOIRE[Title/Abstract] OR DEMOCRATIC REPUBLIC OF THE CONGO[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR EQUATORIAL GUINEA[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR SAO TOME[Title/Abstract] AND PRINCIPE[Title/Abstract] OR SENEGAL[Title/Abstract] OR SIERRA LEONE[Title/Abstract] OR SOMALIA[Title/Abstract] OR SOUTH AFRICA[Title/Abstract] OR SOUTH SUDAN[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	362	17

APPENDIX A (CONTINUED)

Literature Searches & Included Articles

Topic	Search String	Number Returned Articles	Number Included
Gonorrhea & PID	("Gonorrhea"[Mesh] OR "Neisseria gonorrhoeae"[Mesh] OR gonorrhoea* OR gonorrhea* OR "N. gonorrhea" OR "N. gonorrhoeae" OR "Neisseria gonorrhea" OR "Neisseria gonorrhoeae") AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR "Pelvic inflammatory disease*" OR endometritis OR oophoritis OR salpingitis OR parametritis OR Adnexitis OR "Upper Genital Tract Infection" OR Adnexitis OR "asymptomatic upper genital tract infection" OR "Asymptomatic PID" OR "Asymptomatic Pelvic Inflammatory" OR "asymptomatic upper genital tract infection") AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR "BURKINA FASO"[Title/Abstract] OR "CABO VERDE"[Title/Abstract] OR CAMEROON[Title/Abstract] OR "CENTRAL AFRICAN REPUBLIC"[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR "COTE D'IVOIRE"[Title/Abstract] OR "DEMOCRATIC REPUBLIC OF THE CONGO"[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR "EQUATORIAL GUINEA"[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR "SAO TOME AND PRINCIPE"[Title/Abstract] OR SENEGAL[Title/Abstract] OR "SIERRA LEONE"[Title/Abstract] OR SOMALIA[Title/Abstract] OR "SOUTH AFRICA"[Title/Abstract] OR "SOUTH SUDAN"[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	77	16
Syphilis & PID	("syphili*" or "Treponema pallidum" or "T. pallidum" or "Treponem*" OR "Syphilis, Latent"[Mesh] OR "Syphilis"[Mesh] OR "Syphilis, primary" [Supplementary Concept] OR "Syphilis, secondary" [Supplementary Concept] OR "Syphilis tertiary" [Supplementary Concept] OR "Treponema pallidum"[Mesh]) AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR "Pelvic inflammatory disease*" OR endometritis OR oophoritis OR salpingitis OR parametritis OR Adnexitis OR "Upper Genital Tract Infection" OR Adnexitis OR "asymptomatic upper genital tract infection" OR "Asymptomatic PID" OR "Asymptomatic Pelvic Inflammatory" OR "asymptomatic upper genital tract infection") AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR "BURKINA FASO"[Title/Abstract] OR "CABO VERDE"[Title/Abstract] OR CAMEROON[Title/Abstract] OR "CENTRAL AFRICAN REPUBLIC"[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR "COTE D'IVOIRE"[Title/Abstract] OR "DEMOCRATIC REPUBLIC OF THE CONGO"[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR "EQUATORIAL GUINEA"[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR "SAO TOME AND PRINCIPE"[Title/Abstract] OR SENEGAL[Title/Abstract] OR "SIERRA LEONE"[Title/Abstract] OR SOMALIA[Title/Abstract] OR "SOUTH AFRICA"[Title/Abstract] OR "SOUTH SUDAN"[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	31	0

APPENDIX A (CONTINUED)

Literature Searches & Included Articles

Topic	Search String	Number Returned Articles	Number Included
T. vaginalis & PID	("Trichomonas vaginalis"[Mesh] OR “Trichomonas vaginalis” OR “T. vaginalis” OR trichomoniasis OR trich*) AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR “Pelvic inflammatory disease*” OR endometritis OR oophoritis OR salpingitis OR parametritis OR Adnexitis OR “Upper Genital Tract Infection” OR Adnexitis OR “asymptomatic upper genital tract infection” OR “Asymptomatic PID” OR “Asymptomatic Pelvic Inflammatory” OR “asymptomatic upper genital tract infection”) AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR “BURKINA FASO”[Title/Abstract] OR “CABO VERDE”[Title/Abstract] OR CAMEROON[Title/Abstract] OR “CENTRAL AFRICAN REPUBLIC”[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR “COTE D'IVOIRE”[Title/Abstract] OR “DEMOCRATIC REPUBLIC OF THE CONGO”[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR “EQUATORIAL GUINEA”[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR “SAO TOME AND PRINCIPE”[Title/Abstract] OR SENEGAL[Title/Abstract] OR “SIERRA LEONE”[Title/Abstract] OR SOMALIA[Title/Abstract] OR “SOUTH AFRICA”[Title/Abstract] OR “SOUTH SUDAN”[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	36	6
M. genitalium & PID	("Mycoplasma genitalium"[Mesh] OR "M. genitalium" OR "Mycoplasma genital*" OR "Mycoplasma Infections"[Mesh] OR Mycoplasma OR Mycoplasm*) AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR "Pelvic inflammatory disease*" OR endometritis OR oophoritis OR salpingitis OR parametritis OR Adnexitis OR "Upper Genital Tract Infection" OR Adnexitis OR "asymptomatic upper genital tract infection" OR "Asymptomatic PID" OR "Asymptomatic Pelvic Inflammatory" OR "asymptomatic upper genital tract infection") AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR "BURKINA FASO"[Title/Abstract] OR "CABO VERDE"[Title/Abstract] OR CAMEROON[Title/Abstract] OR "CENTRAL AFRICAN REPUBLIC"[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR "COTE D'IVOIRE"[Title/Abstract] OR "DEMOCRATIC REPUBLIC OF THE CONGO"[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR "EQUATORIAL GUINEA"[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR "SAO TOME AND PRINCIPE"[Title/Abstract] OR SENEGAL[Title/Abstract] OR "SIERRA LEONE"[Title/Abstract] OR SOMALIA[Title/Abstract] OR "SOUTH AFRICA"[Title/Abstract] OR "SOUTH SUDAN"[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	16	4

APPENDIX A (CONTINUED)

Literature Searches & Included Articles

Topic	Search String	Number Returned Articles	Number Included
PID & Infertility	(("infertility"[MeSH Terms] OR "infertility"[Title/Abstract] OR "sterility"[Title/Abstract] OR "fertility"[Title/Abstract] OR "fertility"[MeSH Terms) AND ("Pelvic inflammatory disease"[MeSH Terms] OR "Endometritis"[MeSH Terms] OR "Oophoritis"[MeSH Terms] OR "Salpingitis"[MeSH Terms] OR "Parametritis "[MeSH Terms] OR (Pelvic inflammatory disease* [Title/Abstract]) OR (endometritis [Title/Abstract]) OR (oophoritis [Title/Abstract]) OR (salpingitis [Title/Abstract]) OR (parametritis [Title/Abstract]) OR (Adnexitis [Title/Abstract]) OR Upper Genital Infection [Title/Abstract] OR Adnexitis [Title/Abstract] OR Asymptomatic Upper Genital Infection [Title/Abstract] OR Asymptomatic PID [Title/Abstract] OR Asymptomatic Pelvic Inflammatory [Title/Abstract] OR asymptomatic upper genital tract infection [Title/Abstract]) AND (ANGOLA[Title/Abstract] OR BENIN[Title/Abstract] OR BOTSWANA[Title/Abstract] OR BURKINA FASO[Title/Abstract] OR CABO VERDE[Title/Abstract] OR CAMEROON[Title/Abstract] OR CENTRAL AFRICAN REPUBLIC[Title/Abstract] OR CHAD[Title/Abstract] OR CONGO[Title/Abstract] OR COTE D'IVOIRE[Title/Abstract] OR DEMOCRATIC REPUBLIC OF THE CONGO[Title/Abstract] OR DJIBOUTI[Title/Abstract] OR EQUATORIAL GUINEA[Title/Abstract] OR ERITREA[Title/Abstract] OR ESWATINI[Title/Abstract] OR ETHIOPIA[Title/Abstract] OR GABON[Title/Abstract] OR GAMBIA[Title/Abstract] OR GHANA[Title/Abstract] OR GUINEA[Title/Abstract] OR GUINEA-BISSAU[Title/Abstract] OR KENYA[Title/Abstract] OR LESOTHO[Title/Abstract] OR LIBERIA[Title/Abstract] OR MALAWI[Title/Abstract] OR MALI[Title/Abstract] OR MAURITANIA[Title/Abstract] OR MOZAMBIQUE[Title/Abstract] OR NAMIBIA[Title/Abstract] OR NIGER[Title/Abstract] OR NIGERIA[Title/Abstract] OR RWANDA[Title/Abstract] OR SAO TOME[Title/Abstract] AND PRINCIPE[Title/Abstract] OR SENEGAL[Title/Abstract] OR SIERRA LEONE[Title/Abstract] OR SOMALIA[Title/Abstract] OR SOUTH AFRICA[Title/Abstract] OR SOUTH SUDAN[Title/Abstract] OR SUDAN[Title/Abstract] OR TANZANIA[Title/Abstract] OR TOGO[Title/Abstract] OR UGANDA[Title/Abstract] OR ZAMBIA[Title/Abstract] OR ZIMBABWE[Title/Abstract] OR "Sub-Saharan Africa"[Title/Abstract] OR "Africa, South of the Sahara"[Title/Abstract] OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	137	15
Overall STIs & Infertility	("sexually transmitted infection" OR "STI" OR "Gonorrhea"[Mesh] OR "Neisseria gonorrhoeae"[Mesh] OR gonorrhoea* OR gonorrhea* OR "N. gonorrhea" OR "N. gonorrhoeae" OR "Neisseria gonorrhea" OR "Neisseria gonorrhoeae" OR "syphili*" or "Treponema pallidum" or "T. pallidum" or "Treponem*" OR "Syphilis, Latent"[Mesh] OR "Syphilis"[Mesh] OR "Syphilis, primary" [Supplementary Concept] OR "Syphilis, secondary" [Supplementary Concept] OR "Syphilis tertiary" [Supplementary Concept] OR "Treponema pallidum"[Mesh] OR "Mycoplasma genitalium"[Mesh] OR "M. genitalium" OR "Mycoplasma genital*" OR "Mycoplasma Infections"[Mesh] OR Mycoplasma OR Mycoplasm* OR "Trichomonas vaginalis"[Mesh] OR "Trichomonas vaginalis" OR "T. vaginalis" OR trichomoniasis OR trich* OR "Chlamydia*"[MeSH Terms] OR "Chlamydia trachomatis"[MeSH Terms] OR "Chlamydiaceae"[MeSH Terms] OR "Chlamydiales"[MeSH Terms]) AND (infertility OR inferti* OR "Infertility, Female"[Mesh]) AND ("Sub-Saharan Africa" OR SSA OR "Africa South of the Sahara "[MeSH Terms] OR "India"[Title/Abstract])	161	54

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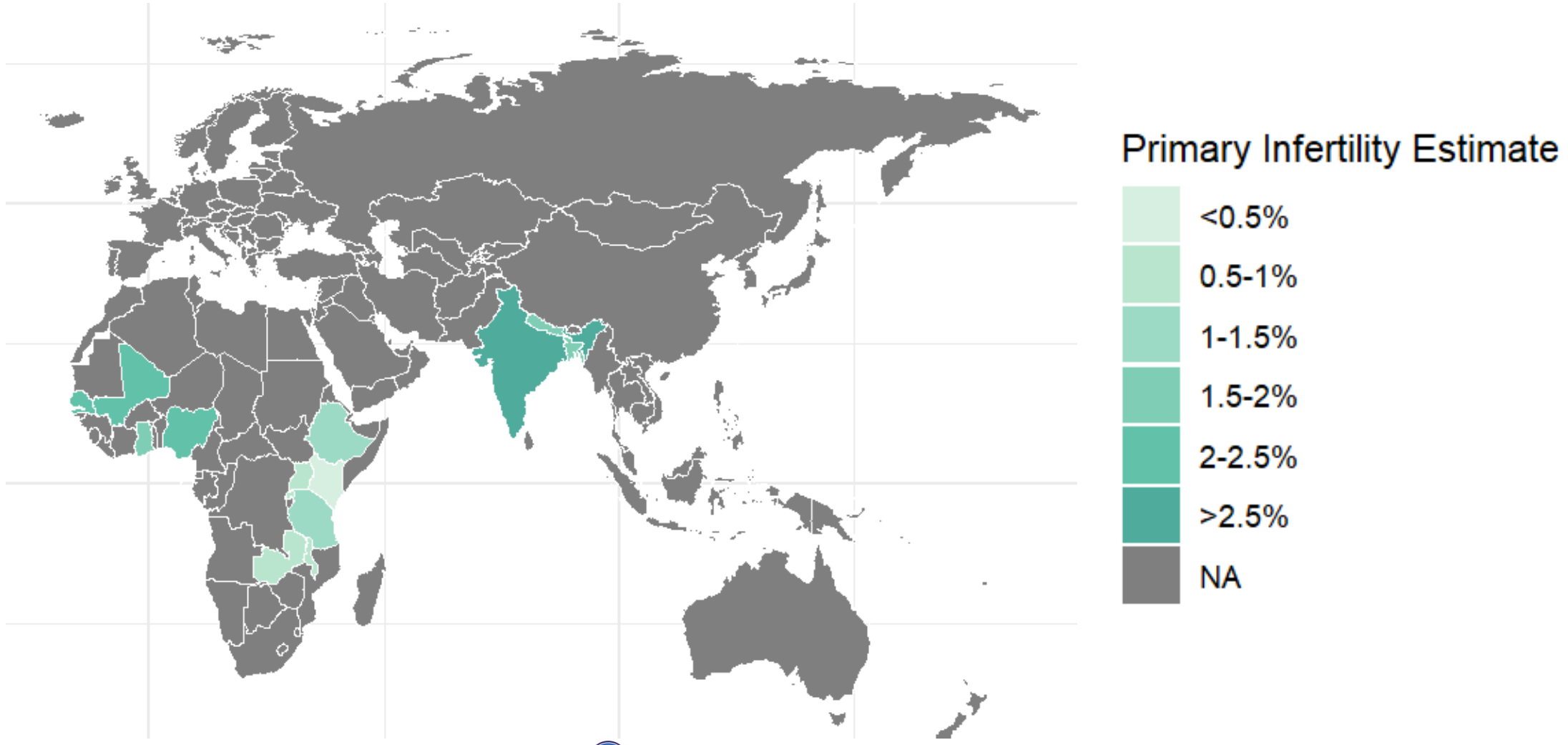
APPENDIX C

Unadjusted, age-standardized primary infertility prevalence; women aged 20-49 (DHS 2021)



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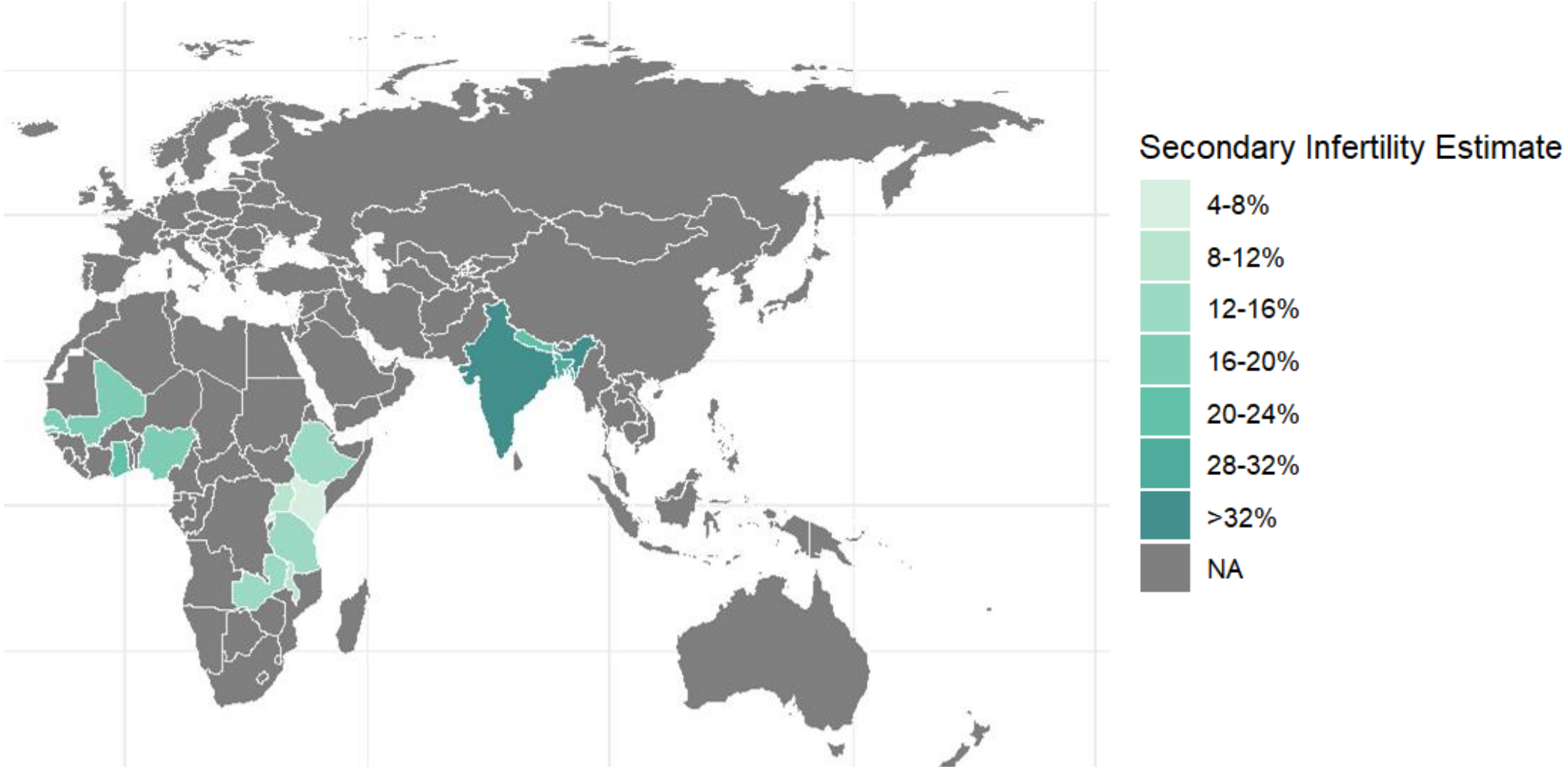
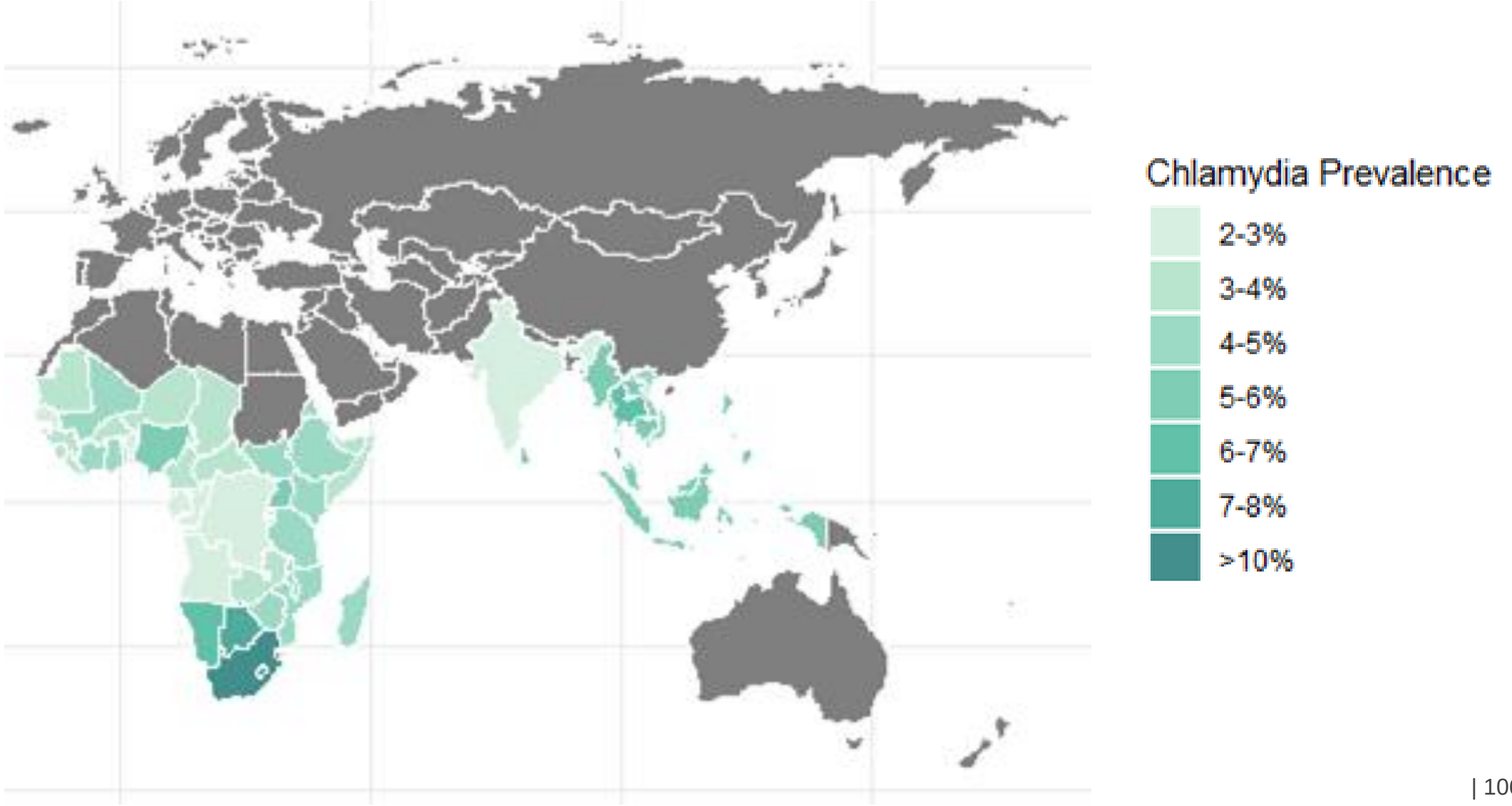
APPENDIX C (CONTINUED)

Unadjusted, age-standardized secondary fertility prevalence; women aged 20-49 (DHS 2021)



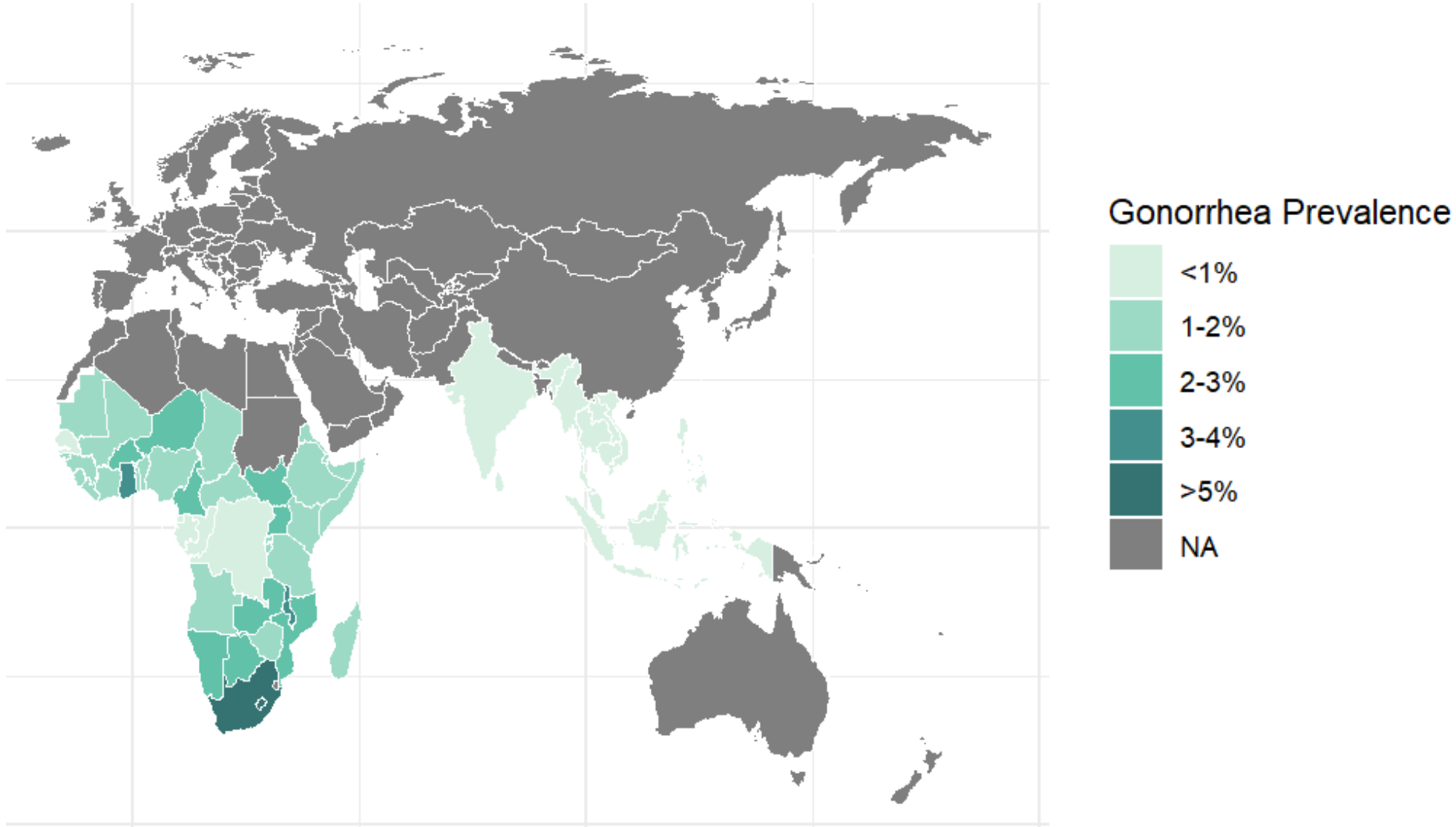
APPENDIX C (CONTINUED)

GBD Estimates of Chlamydia Prevalence by Country (2019)



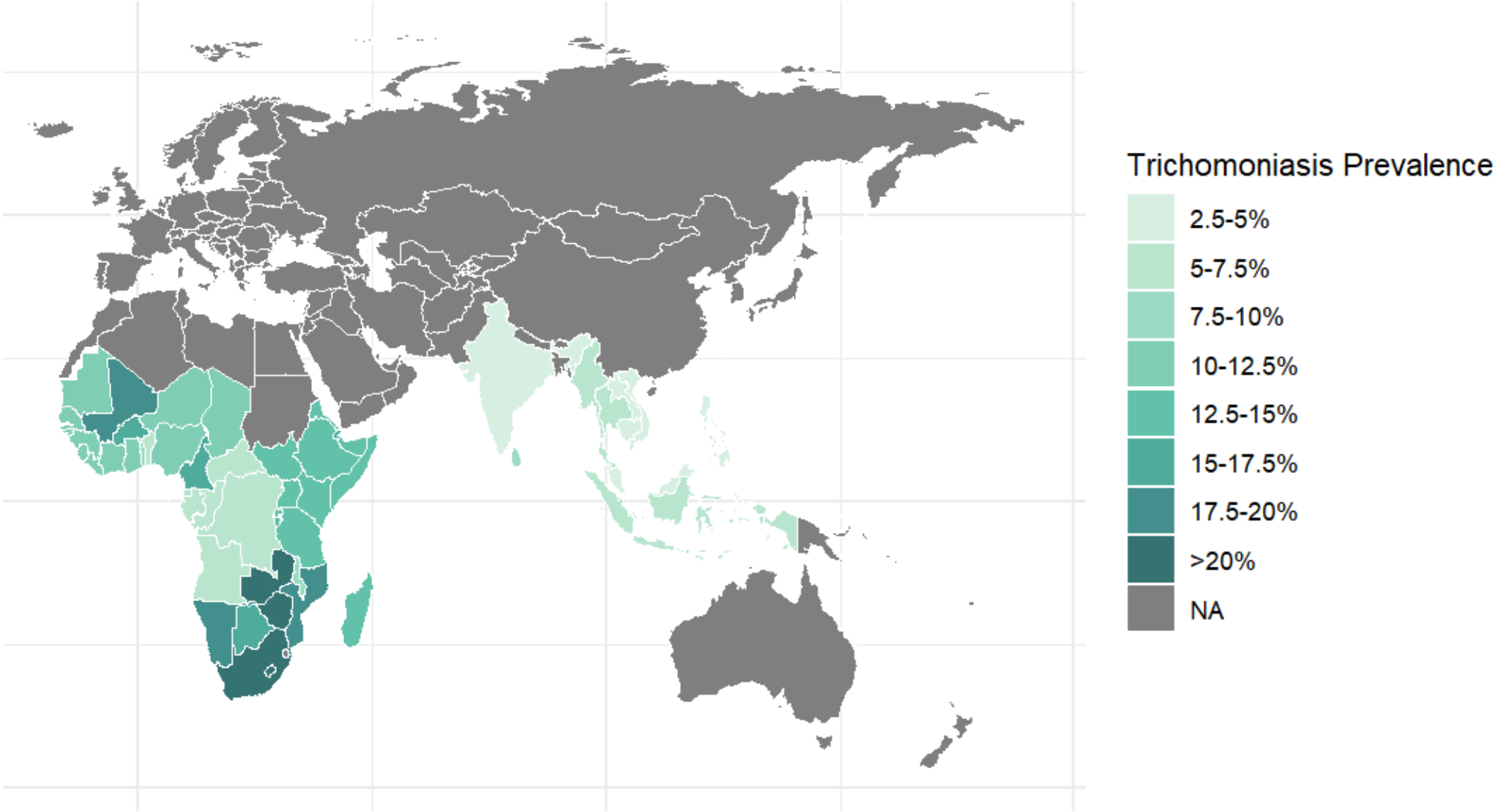
APPENDIX C (CONTINUED)

GBD Estimates of Gonorrhea Prevalence by Country (2019)



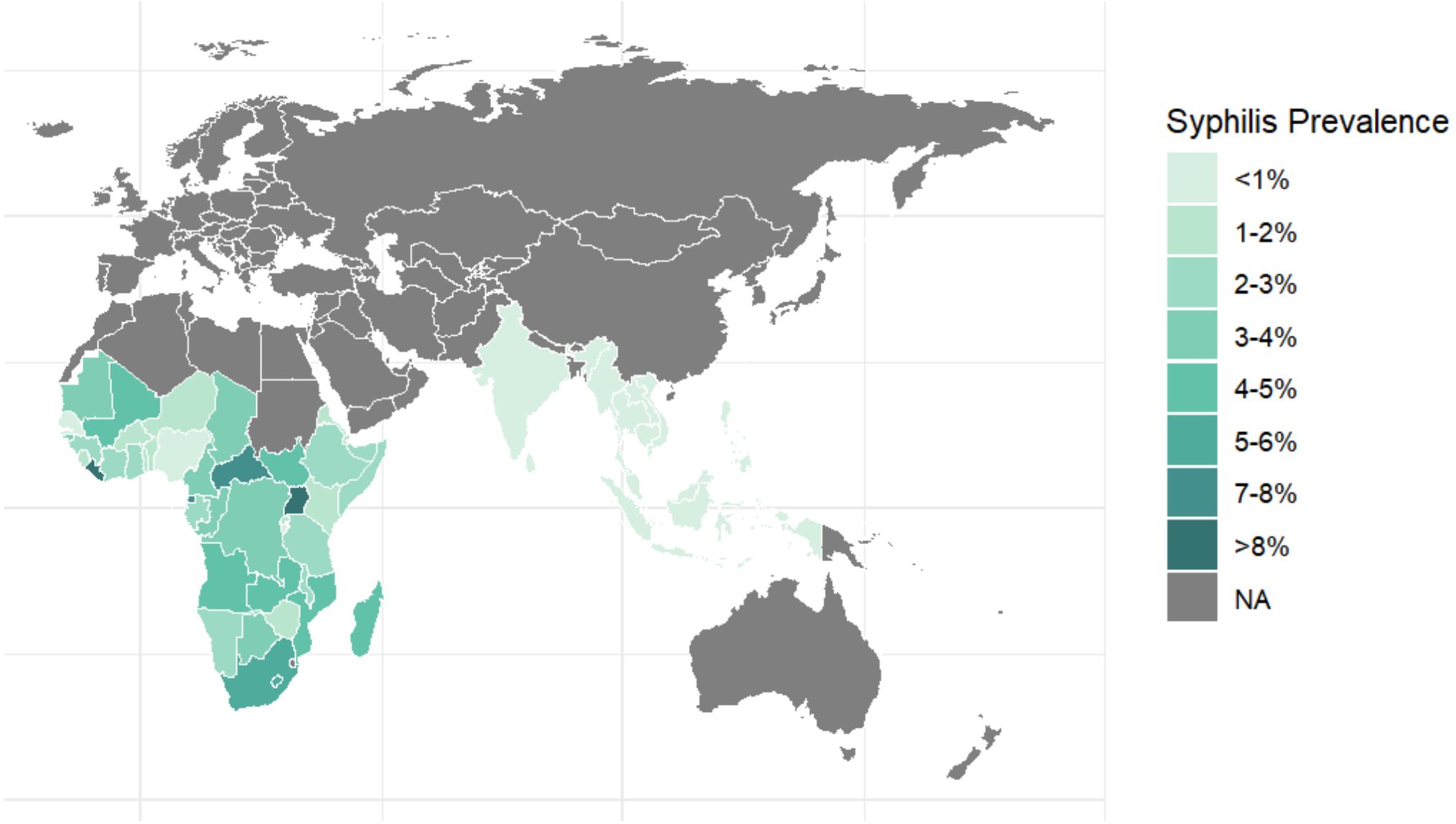
APPENDIX C (CONTINUED)

GBD Estimates of Trichomoniasis Prevalence by Country (2019)



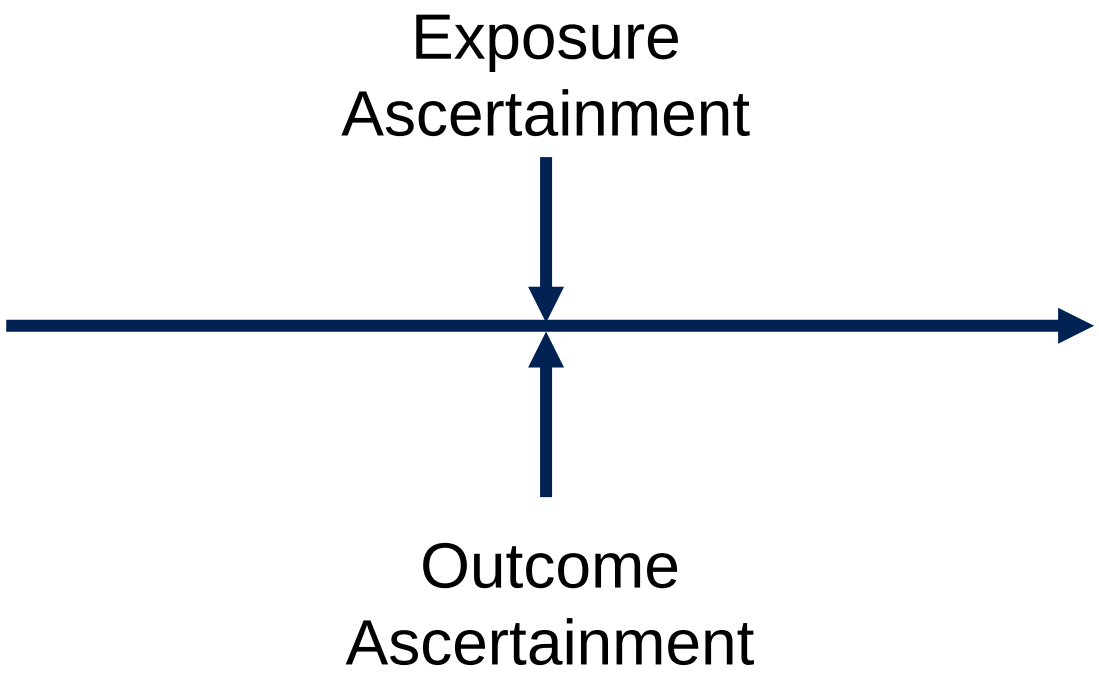
APPENDIX C (CONTINUED)

GBD Estimates of Syphilis Prevalence by Country (2019)



APPENDIX D

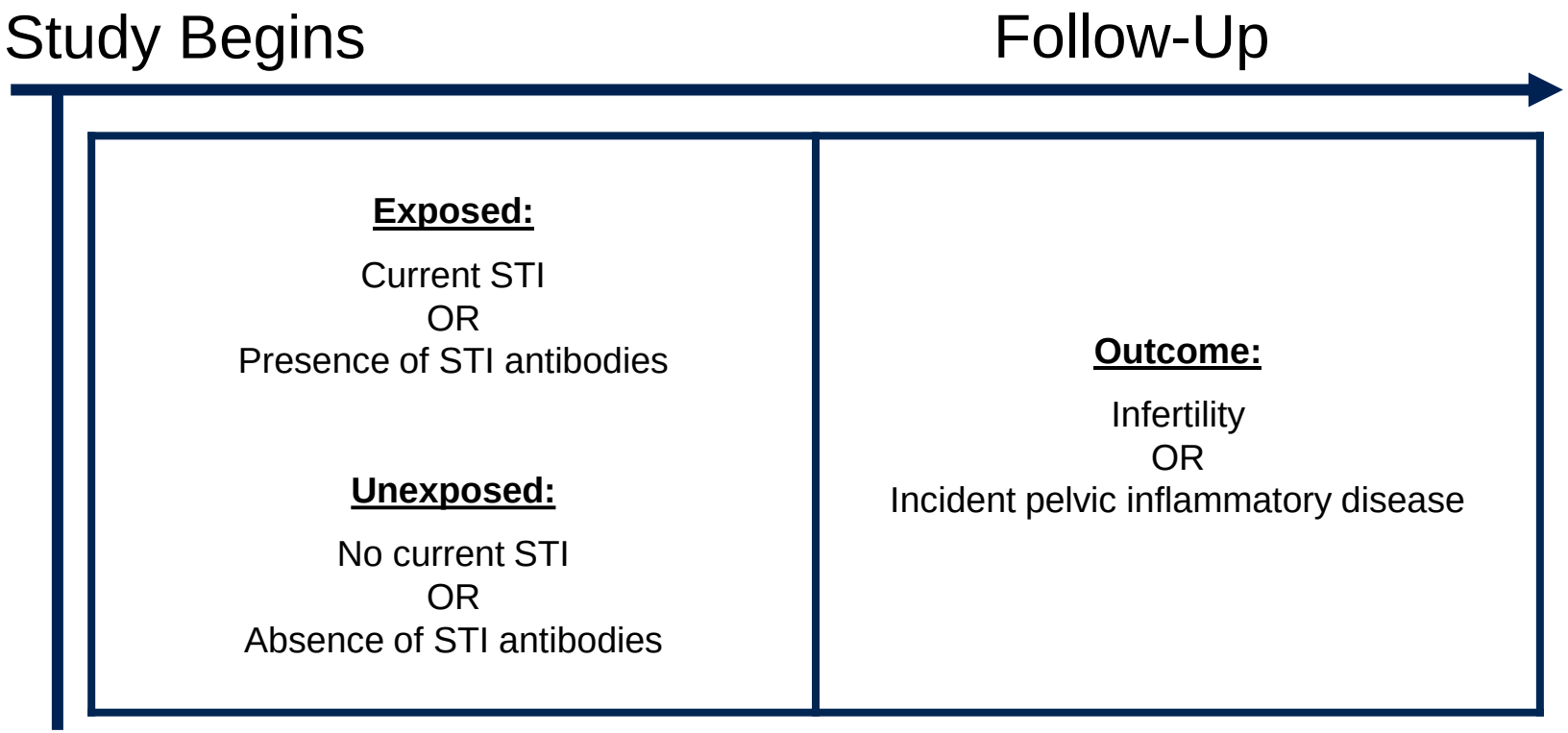
Methodological Challenges: Cross-Sectional Studies



- Limited ability to assess causality
- Antibody testing provides some degree of certainty about exposure timing, but antibody testing is limited to chlamydia

APPENDIX D (CONTINUED)

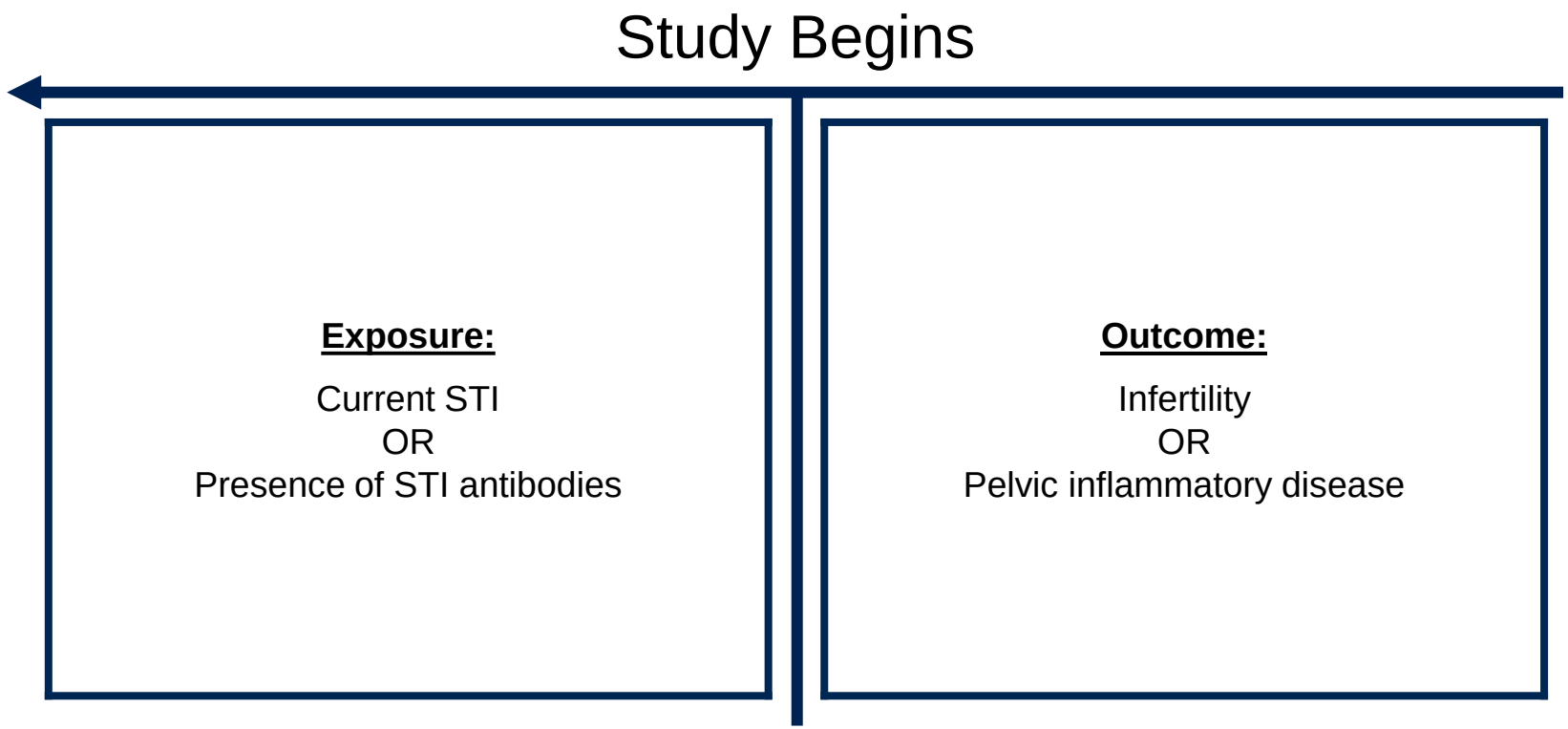
Methodological Challenges: Prospective Cohort Studies



- STIs must be treated following diagnosis
- Inability to determine exact timing of infertility or PID diagnosis
- Remaining questions about etiologically-relevant period following STI diagnosis

APPENDIX D (CONTINUED)

Methodological Challenges: Case-Control Studies



- May be most useful design for assessing relationship between STIs and infertility
- Relies on well-maintained medical records and frequent STI testing prior to study initiation
- Prevalence of STIs in case-control don't really inform the question