STIs & ADVERSE PREGNANCY OUTCOMES, PHASE II

FINAL PRESENTATION

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STRATEGIC ANALYSIS,
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START OVERVIEW

Leverages leading content expertise from across the University of Washington

Provides high quality research and analytic support to the Bill & Melinda Gates Foundation and global and public health decision-makers

Provides structured mentorship and training to University of Washington graduate research assistants

PROJECT OVERVIEW

PROJECT GOALS

OVERARCHING OBJECTIVE: to build a comprehensive case regarding the impact of STIs on women's health.

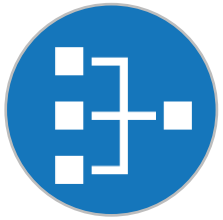
- **Building on Phase I findings focusing on the impact of STIs as a cause of infertility.**
- **Broadening this scope to adverse pregnancy outcomes.**

KEY OBJECTIVES

Employ a tiered evidence search strategy (with limited study designs) to understand the relationship between STIs and key adverse pregnancy and neonatal outcomes

Complete a literature review matrix of the relationship between STIs and key adverse pregnancy and neonatal outcomes

Highlight data gaps and suggest studies that would be needed to fill them



Develop quantitative summaries (forest plots) of study findings to inform modeling and data investments.

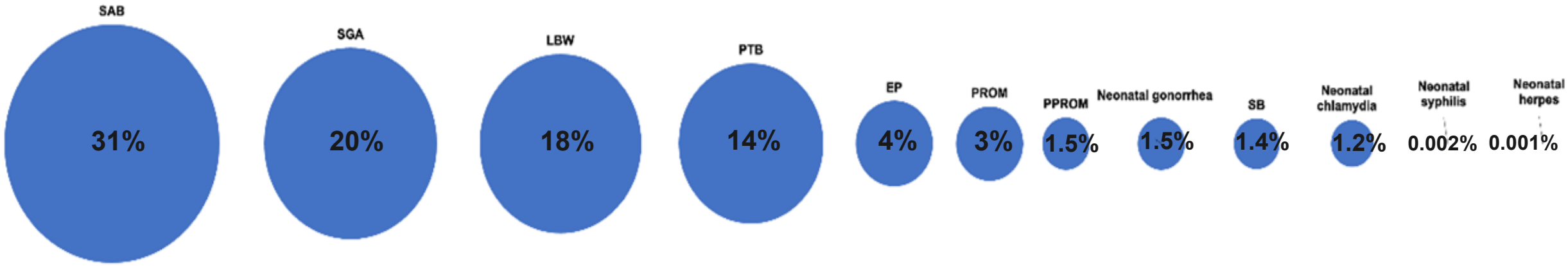
KEY SEXUALLY TRANSMITTED INFECTIONS

- *Treponema pallidum* (Syphilis)
- *Neisseria gonorrhoeae* (Gonorrhea)
- *Chlamydia trachomatis* (Chlamydia)
- *Mycoplasma genitalium (*M. gen*)*
- *Trichomonas vaginalis (*Trichomoniasis*)*
- Herpes simplex virus (HSV)
- *Bacterial vaginosis (*BV*)*

ADVERSE PREGNANCY OUTCOMES (APOs)

- Spontaneous abortion (SAB)
- Ectopic pregnancy (EP)
- Preterm birth (PTB)
- Low birthweight (LBW)
- Small for gestational age (SGA)
- Premature rupture of membranes (PROM)
- Preterm PROM (PPROM)
- Stillbirth (SB)
- Neonatal infection

INCIDENCE* OF APOs



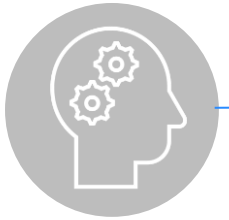
*APO incidence for SAB, PTB, EP, and SB was derived from Global Burden of Disease Study 2019 (GBD 2019) Reference Life Table for Low-Middle SDI countries.[1] Estimates for SGA, LBW, PROM, PPROM, neonatal gonorrhea, neonatal chlamydia, neonatal syphilis, and neonatal herpes were obtained through UpToDate.[2-7]

METHODS

TIERED EVIDENCE SEARCH STRATEGY OVERVIEW

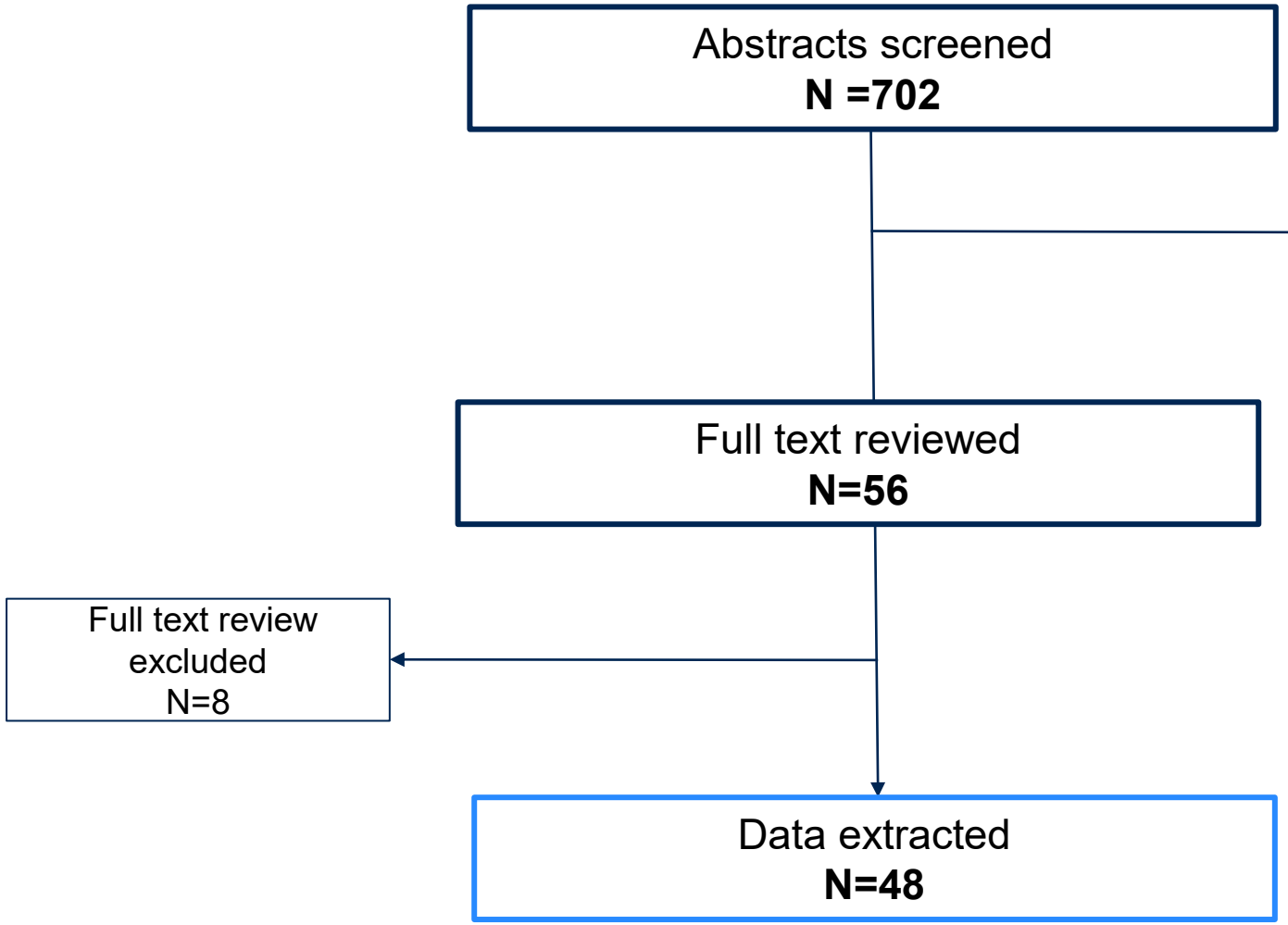
Prioritizing systematic reviews, meta-analyses, and randomized controlled trials (RCTs)

Full text extraction of the most recent systematic review and/or meta-analysis for each STI & APO combination



Further review of more recent RCTs and any other strong studies

TIERED EVIDENCE SEARCH RESULTS



Exclusion criteria:

- Quantifies the burden of disease but not the association or relationship between the STI and APO
- Protocol with no analysis yet completed
- Explores factors associated with an APO in an exposure-wide way (ie, not looking specifically at STIs as a cause)
- Examines an exposure that is upstream of an STI (e.g., bacterial colonization ahead of BV) and quantifies the proportion of individuals with the STI but does not link to an APO

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LITERATURE REVIEW MATRIX OVERVIEW

		STIs						
		Syphilis	Gonorrhea	Chlamydia	M. Genitalium	Trichomoniasis	HSV	BV
Adverse pregnancy outcomes	Spontaneous abortion							
	Stillbirth							
	Preterm birth							
	Low birthweight							
	Small for gestational age							
	Ectopic pregnancy							
	Premature rupture of membranes (PROM & PPROM)							
	Neonatal infection							

LITERATURE REVIEW MATRIX OVERVIEW

TIERS OF EVIDENCE

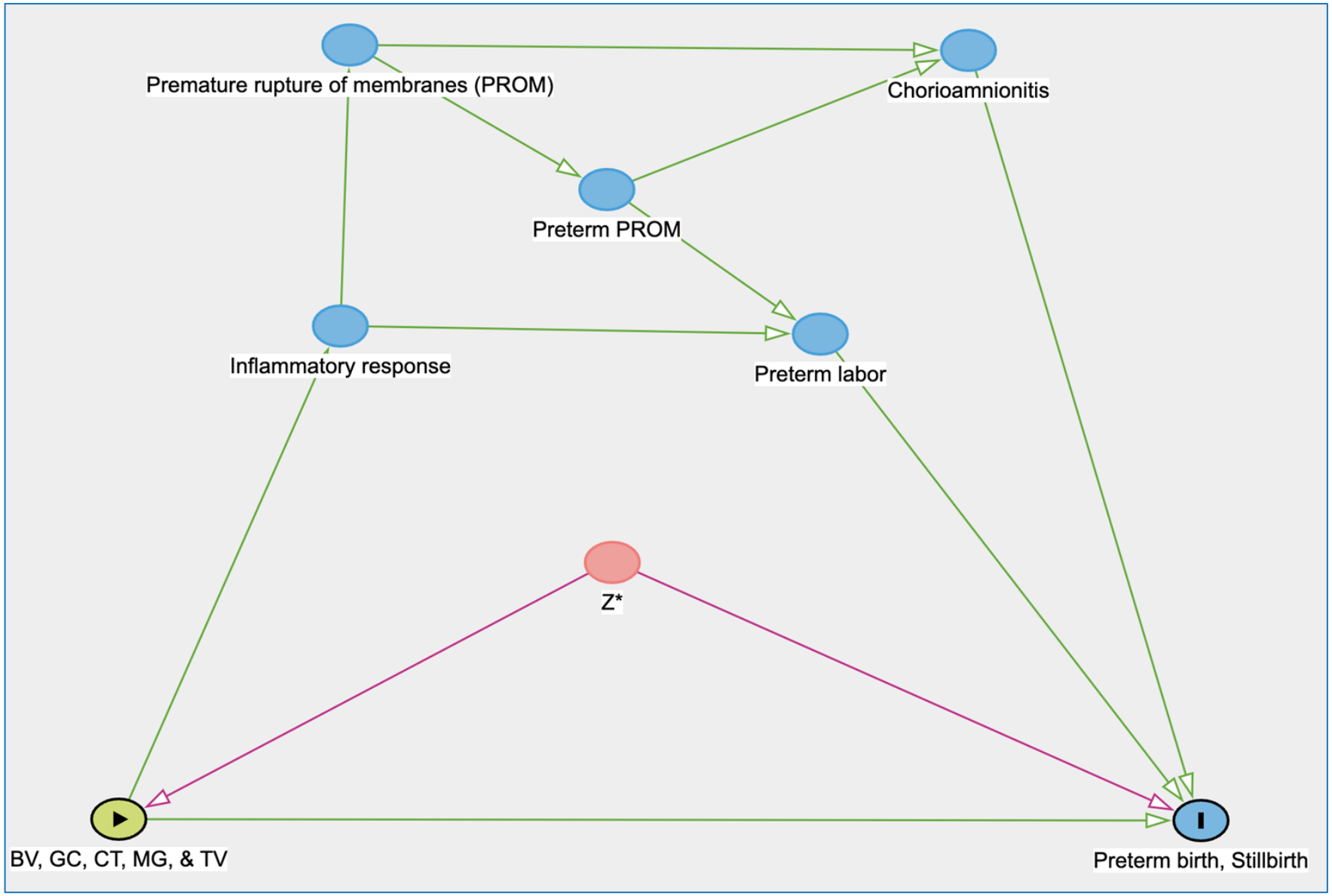
1. Systematic reviews, meta-analyses, RCTs
2. Cohort or case-control studies
3. Cross-sectional studies
4. No evidence found during review

LITERATURE REVIEW MATRIX FINDINGS

STRENGTH OF ASSOCIATION

1. Very strongly associated: effect estimates, on average, greater than 2.5
2. Strongly associated: effect estimates 1.5-2.5
3. Weakly to moderately associated: effect estimates 1.0-1.5
4. Not associated: effect estimates less than or equal to 1.0
5. No evidence found during review

STI & APO DAG EXAMPLE



***Z:** vector of confounding variables including but not limited to the age, socioeconomic status, adequacy of prenatal care received, and coinfection status with other STIs of the birthing person

FOREST PLOT OVERVIEW

- Building on the approach taken in Phase I, we developed forest plots depicting the measures of association between each STI and adverse pregnancy outcome.

- We used a directed acyclic graph (DAG) (see Appendix C) to group inter-related outcomes to reduce the dimensionality of the data. Thus, we broke out the APOs into the following categories:
    - SAB
    - EP
    - PTB, LBW, PROM, PPROM, SB
    - SGA
    - Neonatal infection

KEY FINDINGS

LITERATURE REVIEW MATRIX OVERVIEW

		STIs						
		Syphilis	Gonorrhea	Chlamydia	M. Gen	Trich	HSV	BV
Adverse pregnancy outcomes	Preterm birth	**5*:** Absolute difference in PTB between women w and without syphilis: 6.9%, p=0.000; **14*:** OR: 3.29 (1.93 - 5.61); 37: PTB: Crude OR: 1.66 (1.16, 2.39); Adjusted OR: 1.60 (1.12, 2.30); Very PTB: Crude OR: 1.75 (0.82, 3.71); Adjusted OR: 1.64 (0.77,3.51); Syphilis independent, PTB: Crude OR: 1.68(1.14, 2.46); aOR: 1.60(1.09, 2.35)	**4*:** OR: 1.55 (95% CI 1.21, 1.99), aOR1.90 (95% CI 1.14 to 3.19); **18*:** adjusted OR = 1.36 (95%CI: 1.07 - 1.72);	**8*:** Unadjusted OR between IgG Chlamydia & PL: 1.13 [0.79, 1.62], **25***: C. trachomatis infection was associated with a higher risk of preterm birth [OR (95% CI): 1.731 (1.343–2.230);	**10***: Unadjusted OR: 1.91 (95% CI 1.29 to 2.81, I2=0%) among 7 studies	**21*:** increased risk of preterm birth (RR, 1.42; 95% CI, 1.15–1.75; 9 studies; n = 81,101; I2 = 62.7%); **26***: Detection of T. vaginalis, was not associated with increased PTB (PR: 1.19, 95% CI 0.58-2.45; aPR: 1.19, 95% CI 0.58-2.43); **28***: Testing positive for T. vaginalis at the repeat visit was significantly associated with preterm births (OR 2.37; 95% CI: 1.11–5.03)	**28***: Testing positive for HSV-2 at the repeat visit was also likely associated with experiencing a preterm birth or any adverse pregnancy outcome (OR 3.39; 95% CI: 0.86–13.3) (P = 0.096); **30***: Genital HSV-2 shedding were not associated with preterm deliveries: OR = 0.9 (0.5 to 1.7); aOR = 0.9 (0.5 to 1.7); **31***: There was an increased risk of occurrence of preterm delivery among cohorts with incident HSV-2 infection relative to those who did not seroconvert (RR = 25.1 (95% CI: 23.9-26.3))	**2*:** Overall RR 1.44 (95% CI: 1.19 - 1.73); **19*:** 7/9 studies reported significant positive association between BV and PTB but the subgroups between studies were not comparable so therefore could not combine estimates (OR range: 1.83 - 16.44); **20*:** Intention-to-treat analysis of preterm birth showed no evidence of a reduction in the rate with the screen and treat strategy compared with usual care (no systematic screening or treatment); **24*:** OR 1.76 (95% CI: 1.41 - 2.12).

*Study IDs correspond to **Appendix D: Literature Extraction Sheet**.

LITERATURE REVIEW MATRIX OVERVIEW

TIERS OF EVIDENCE

		STIs						
		Syphilis	Gonorrhea	Chlamydia	M. Gen	Trich	HSV	BV
Adverse pregnancy outcomes	Spontaneous abortion							
	Stillbirth							
	Preterm birth							
	Low birthweight							
	Small for gestational age							
	Ectopic pregnancy							
	Premature rupture of membranes (PROM & PPROM)							
	Neonatal infection		*	*			*	

KEY

- Systematic reviews, meta analyses & RCTs
- Case-control & cohort studies
- Cross-sectional studies
- No evidence found during review

*While there was no recent evidence found during our review, neonatal infection following maternal infection with gonorrhea, chlamydia, or HSV is well-established.

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LITERATURE REVIEW MATRIX FINDINGS

STRENGTH OF ASSOCIATION

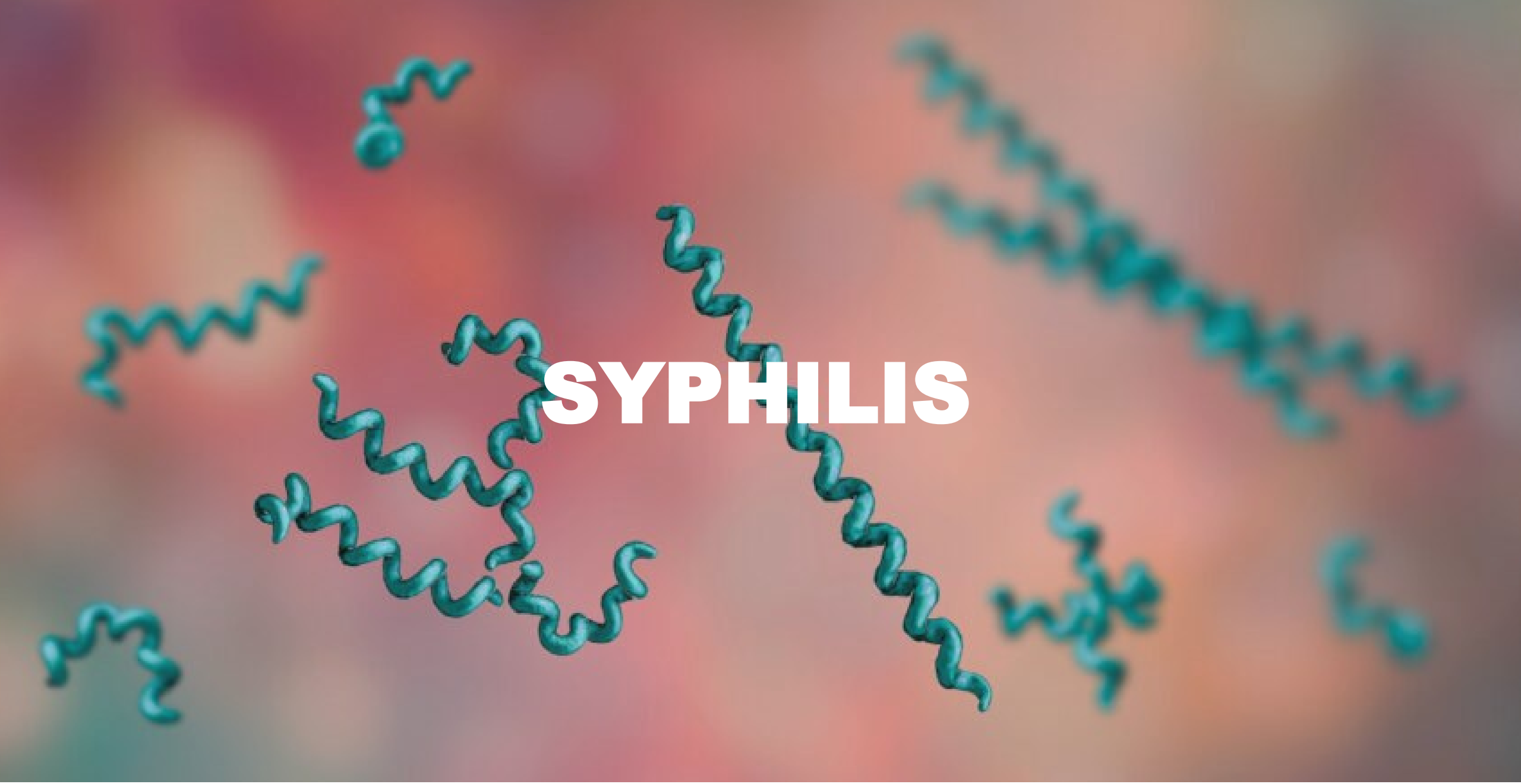
		STIs						
		Syphilis	Gonorrhea	Chlamydia	M. Gen	Trich	HSV	BV
Adverse pregnancy outcomes	Spontaneous abortion							
	Stillbirth							
	Preterm birth							
	Low birthweight							
	Small for gestational age							
	Ectopic pregnancy							
	Premature rupture of membranes (PROM & PPROM)							
	Neonatal infection		*	*			*	

KEY

- Very strongly associated
- Strongly associated
- Weakly to moderately associated
- Not associated**
- No evidence found during review

**No association refers to no association in the available literature, but may be due to imprecise and, thus, inconclusive results. For more information on uncertainty in the STI/APO measures of association, see forest detailed forest plots.

*While there was no recent evidence found during our review, neonatal infection following maternal infection with gonorrhea, chlamydia, or HSV is well-established.



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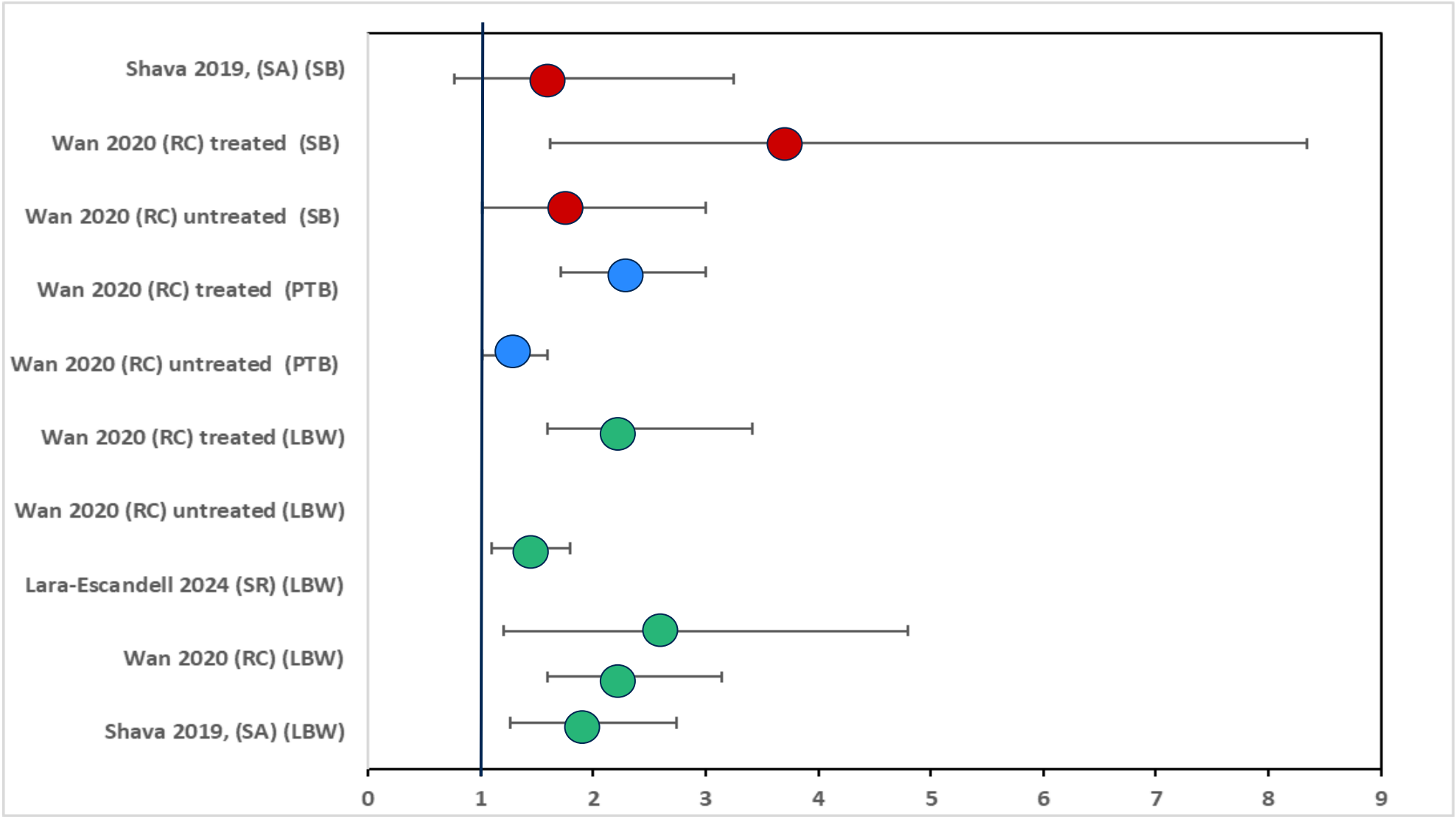
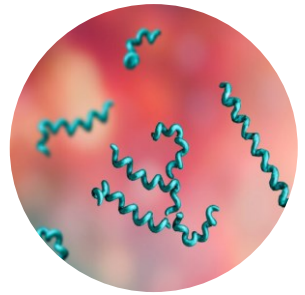
MEASURES OF ASSOCIATION:

SYPHILIS & PTB, VERY PTB, PROM, PPROM, LBW, AND SB (ODDS RATIOS)





Qin 2014 (SR)
Absolute Diff = 8.7% (**LBW**), 6.9% (**PTB**) and 8.8% (**SB**)

Studies didn't adjust for Co-infection with other STIs.
Shava 2019 (**SA**)
Prev= 24.1% (**LBW**) among (Syphilis+HIV) compared to 12.1% among controls)

Key
SA = Secondary Analysis
RC = Retrospective Cohort
CS = Cross Sectional
SR = Systematic Review

MEASURES OF ASSOCIATION:

PROPORTIONS OF APOs AMONG WOMEN WITHOUT SYPHILIS

Additional context on studies:

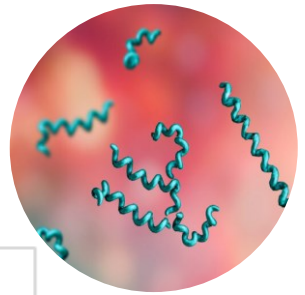
- LBW prevalence among control subjects (5.4%, *P* = 0.052) – Laktabai, 2022

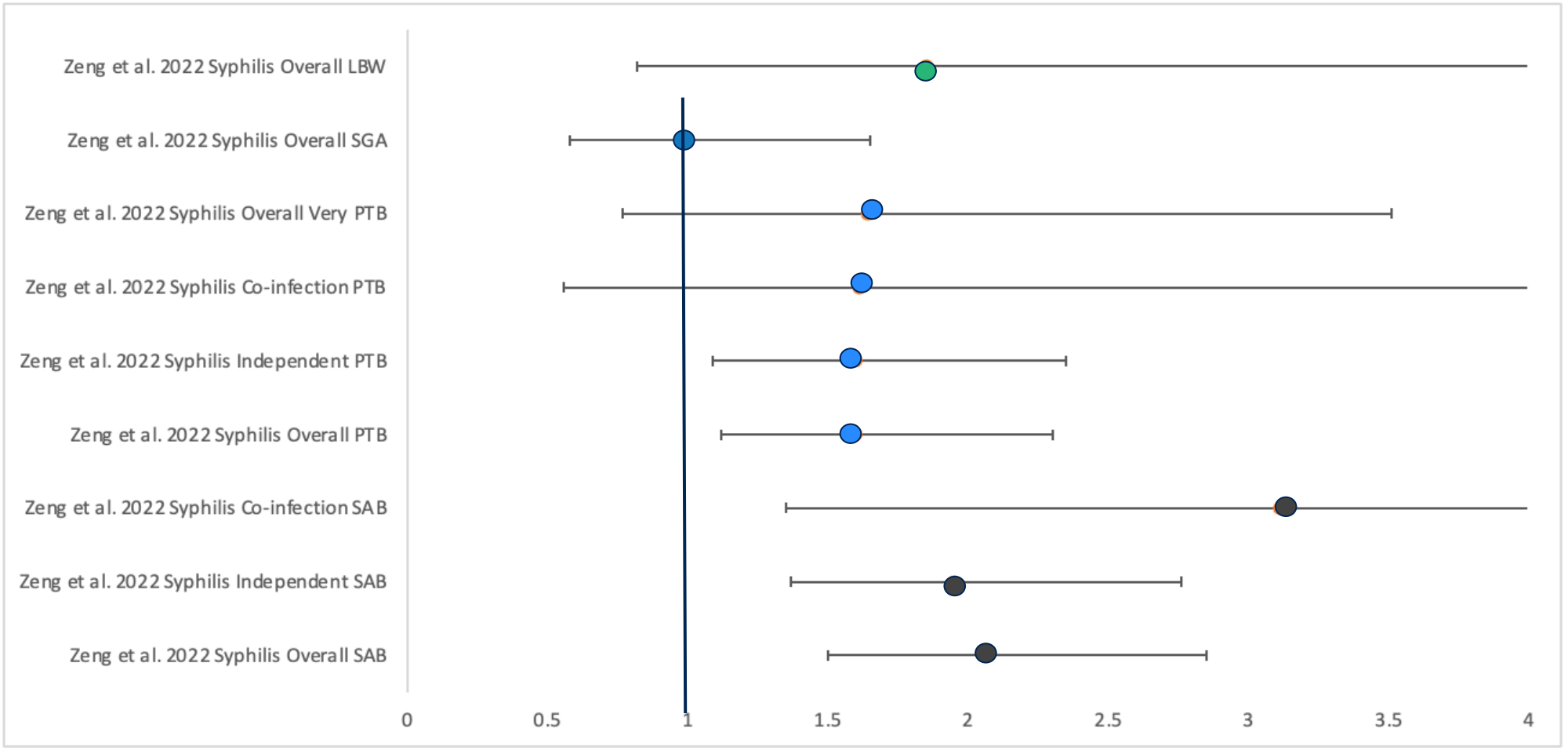
- Congenital Syphilis prevalence (0%) for control subjects – Laktabai, 2022

- Pooled proportion estimates for both women with and without syphilis (LBW, SB, PTB) Qin, 2014 (Table 2)

MEASURES OF ASSOCIATION:

PRE-CONCEPTION SYPHILIS & SAB, PTB, VERY PTB, SGA

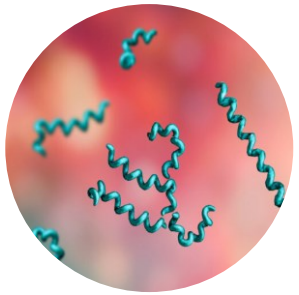


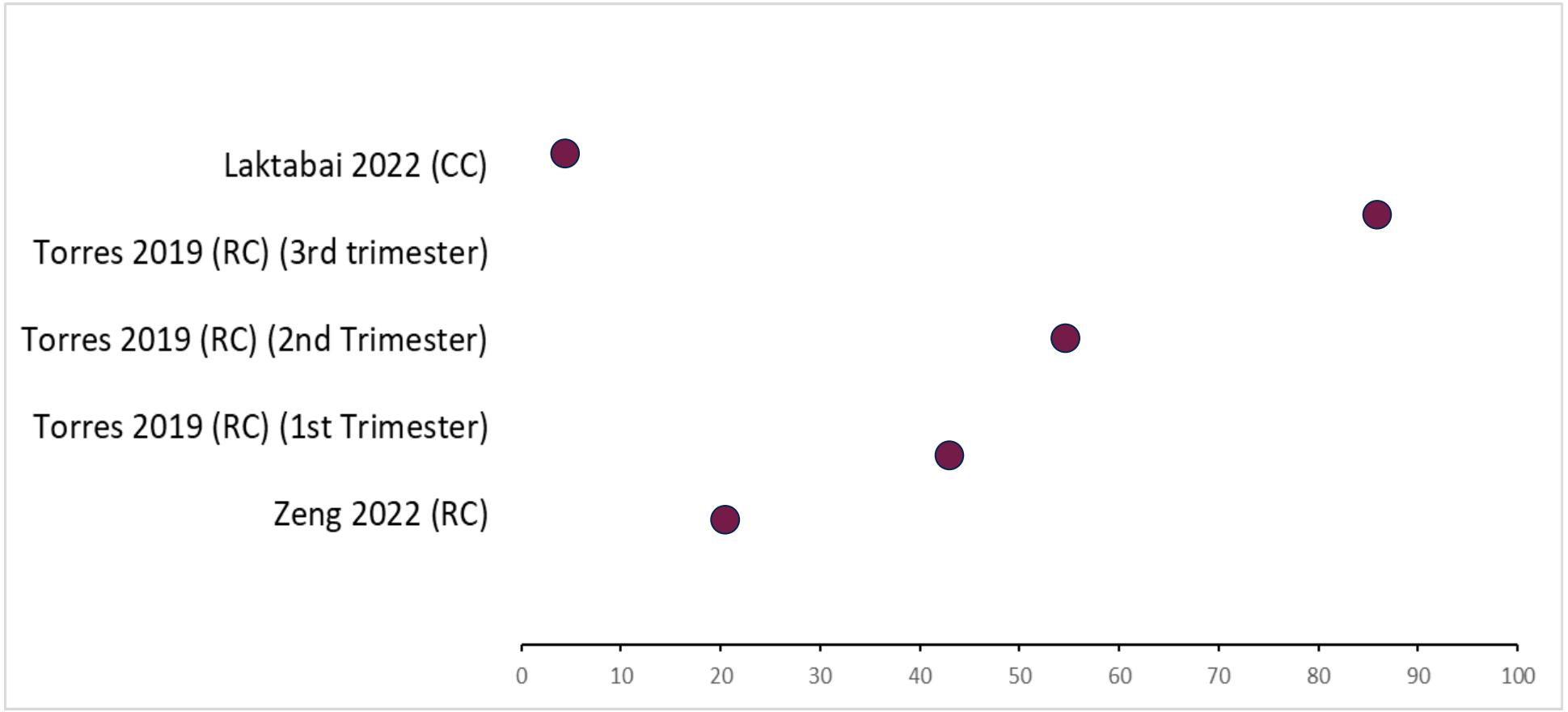


NB: OR adjusted for **history of preterm birth, history of spontaneous abortion, history of induced abortion**, socio-demographic and lifestyle factors. For more information about Zeng et al. study methods**, see Appendix C.**

MEASURES OF ASSOCIATION:

SYPHILIS & NEONATAL INFECTION (PREVALENCE ESTIMATES)

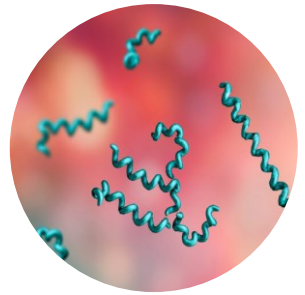




Wan 2022 (RC)
Odds Ratio= 3.63
(95% CI: 1.80-7.31)

KEY
CC= Case control
RC = Retrospective cohort

SUMMARY OF FINDINGS: SYPHILIS & APOs

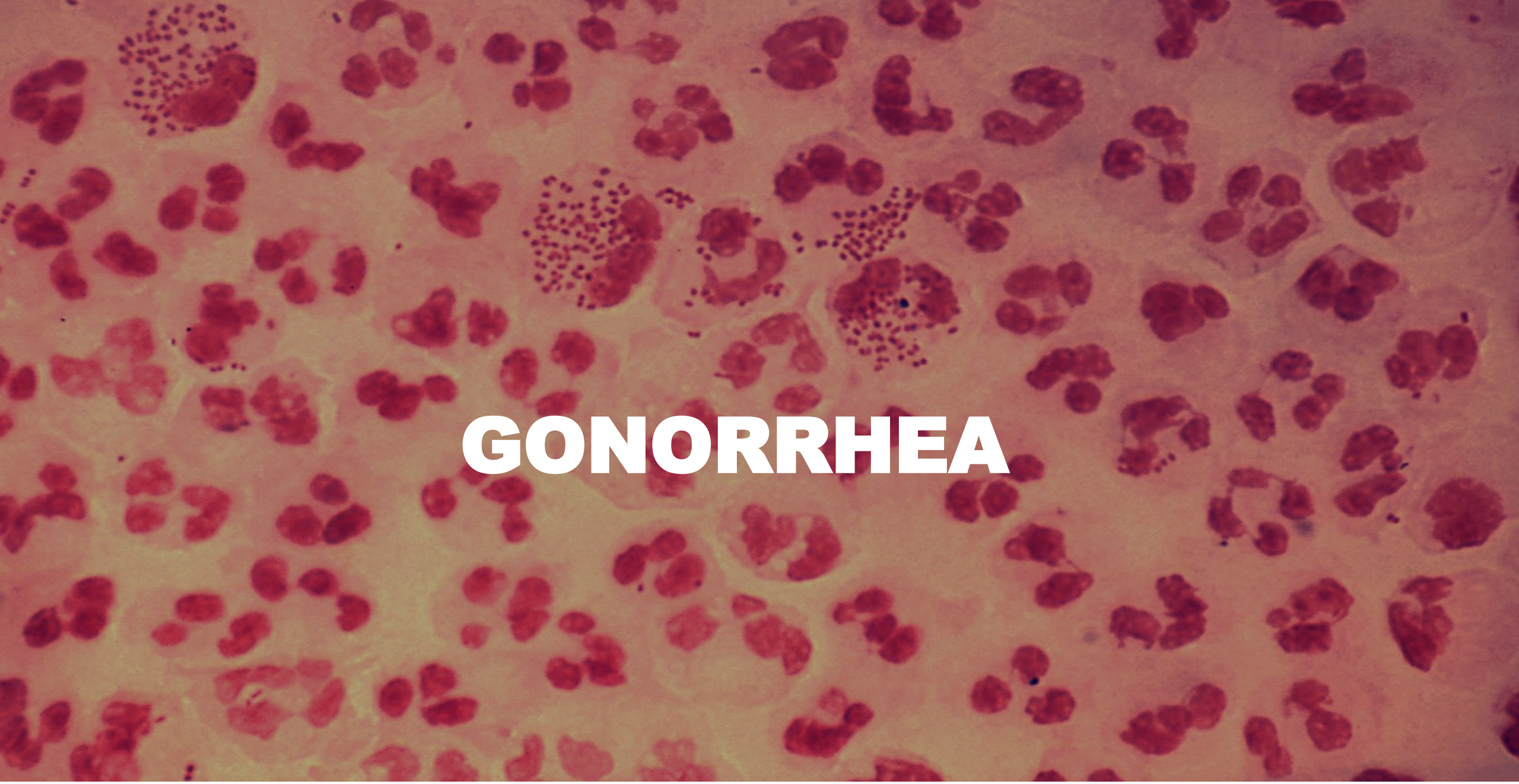


1. There is strong evidence of an increased risk of **stillbirth**, **preterm birth,** and **low birth weight** following maternal syphilis infection

2. Clearly established strong association between **preconception syphilis** and spontaneous abortion

3. **Congenital syphilis** is prevalent among infants born to mothers with syphilis. **Prevalence of congenital syphilis has been shown to** increase with progression of pregnancy (with higher proportions being detected in the later trimesters)

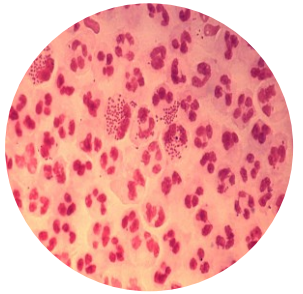
4. There were **limited findings** in recent literature for its association with **SGA** and **no recent evidence** for **PROM, PPROM** and **ectopic pregnancy**

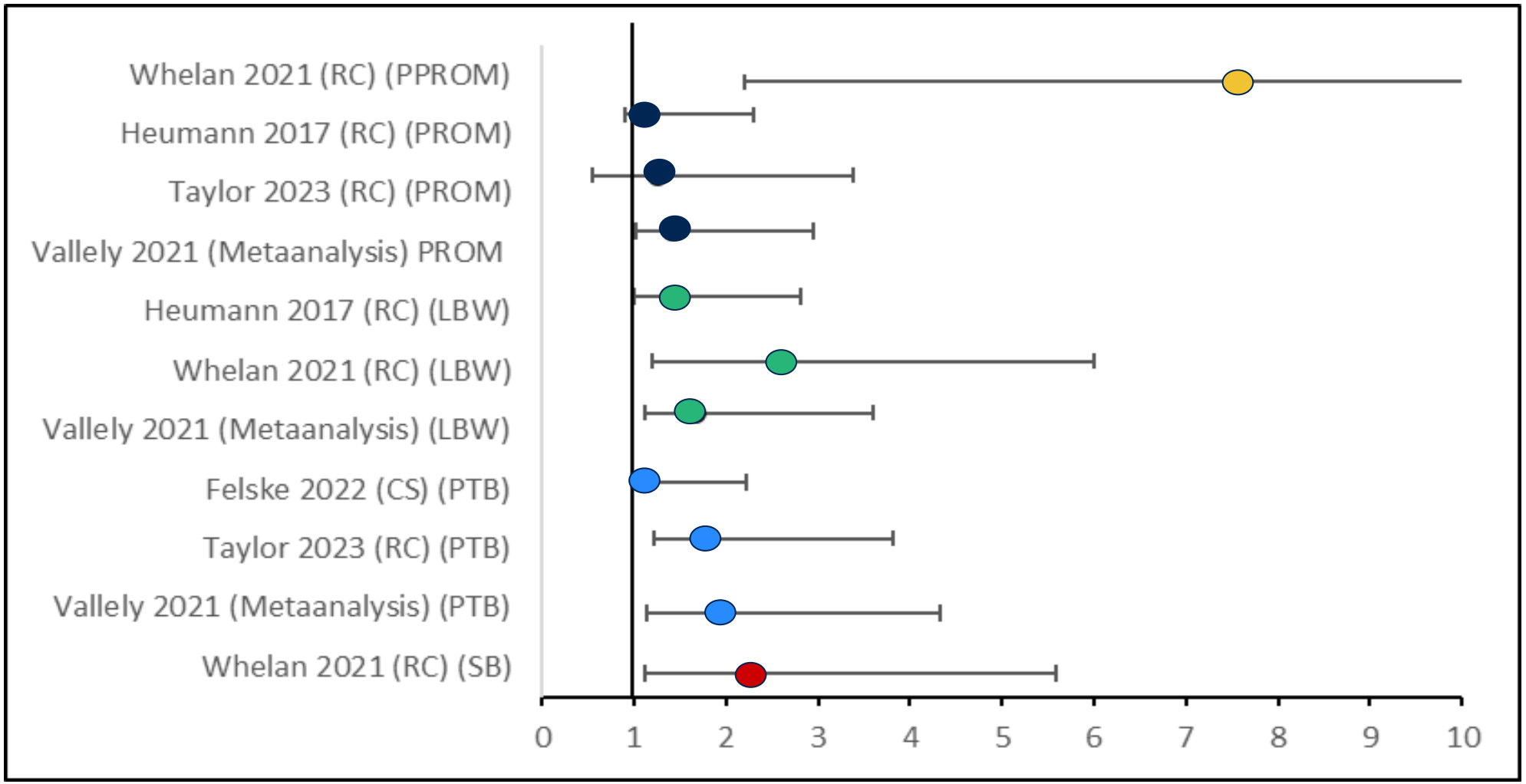


GONORRHEA

MEASURES OF ASSOCIATION:

GONORRHEA & PTB, PROM, PPROM, LBW, AND SB (ODDS RATIOS*)





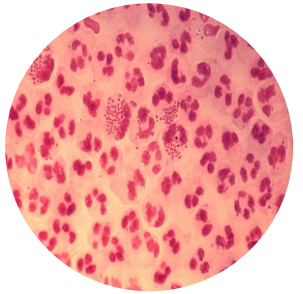
* **Studies did not adjust for co-infections with other STIs; Felske (2022)** adjusted for Hep B and C status

KEY

CS = Cross sectional

RC = Retrospective cohort

MEASURES OF ASSOCIATION:



GONORRHEA & SGA

STUDIES

1. Heumann et al; 2017 (retrospective cohort)

   measure: Odds ratio; **1.6** (95% CI: 1.3, 2.0)

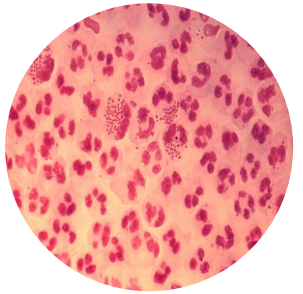
2. Felske et al; 2022 (cross sectional)

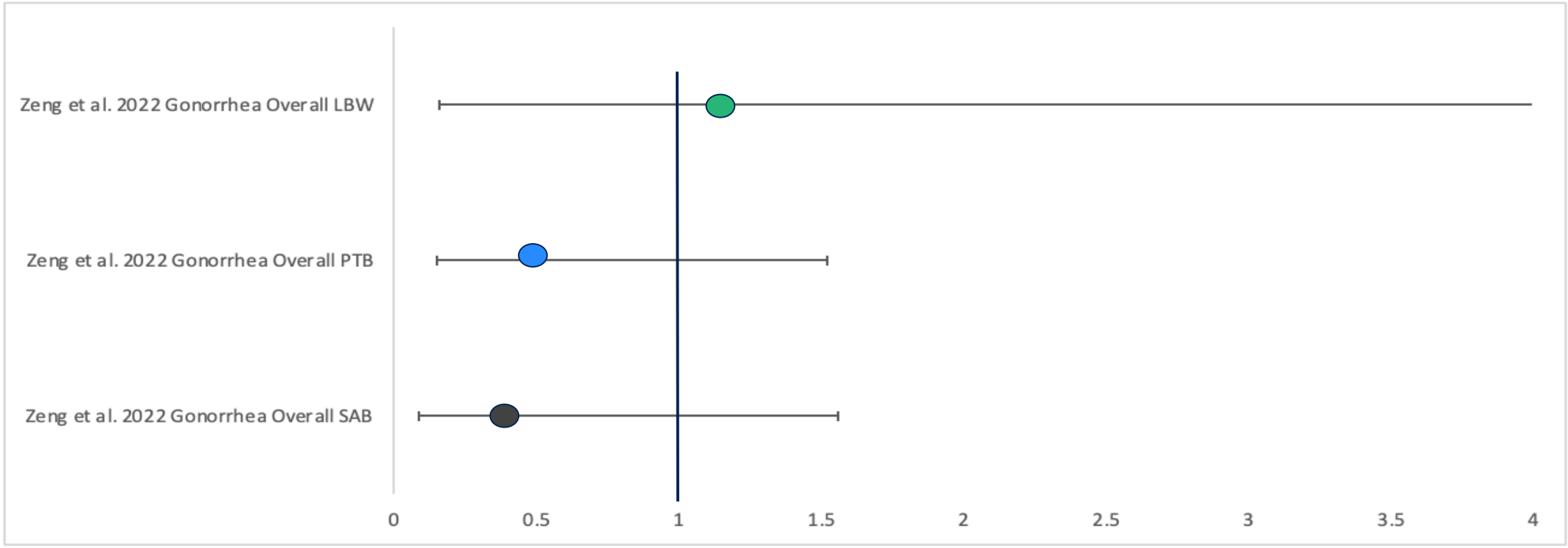
   measure: Adjusted prevalence ratio; 0.95 (95%CI: 0.85, 1.06)

NB: **Prevalence ratio adjusted for** sociodemographic and health-related factors like **adequacy of prenatal care**, smoking status during pregnancy, Hepatitis B and C status
***Studies did not adjust for co-infections with other STIs**

MEASURES OF ASSOCIATION:

PRE-CONCEPTION GONORRHEA & SAB, PTB, & LBW (ODDS RATIOS)





NB: OR adjusted for **history of preterm birth, history of spontaneous abortion, history of induced abortion**, socio-demographic and lifestyle factors. For more information about Zeng et al. study methods**, see Appendix C.**

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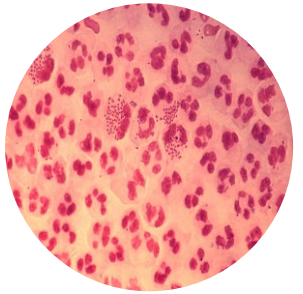
MEASURES OF ASSOCIATION:

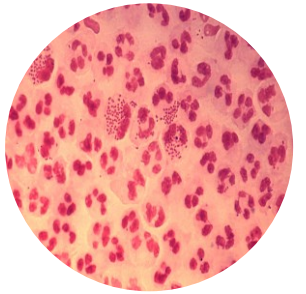
GONORRHEA & NEONATAL INFECTION



- There has been extensive, less established evidence of neonatal eye infection following maternal gonorrheal infection **(strongly association)**.

- This is supported by the standard practice of providing routine ophthalmologic prophylaxis for newborns of gonorrhea-infected mothers

SUMMARY OF FINDINGS: GONORRHEA & APOs



1. Overall, the evidence establishing a significant association between gonorrhoea and all the APOs is less consistent. There evidence is moderate for **preterm birth**, **low birth weight**, and **stillbirth**

2. Gonorrhea had a consistent positive association with **PROM**. There was a significantly high risk of **PPROM following maternal gonorrheal infection** (Whelan 2021), suggesting that gonorrhea has a substantial impact on the likelihood of PPROM

3. There is an established increased risk of **SGA infants** following maternal gonorrhea infection (Heumann, 2017), however with **limited** findings in recent literature for its association with **spontaneous abortion,** and **lack** of recent evidence for its association with **neonatal infection** and **ectopic pregnancy**


CHLAMYDIA

MEASURES OF ASSOCIATION:

CHLAMYDIA & SPONTANEOUS ABORTION

STUDY

He et al; 2020 **(**Systematic Review**)**

Zuo et al; 2023 (Systematic Review of Antibody Association)

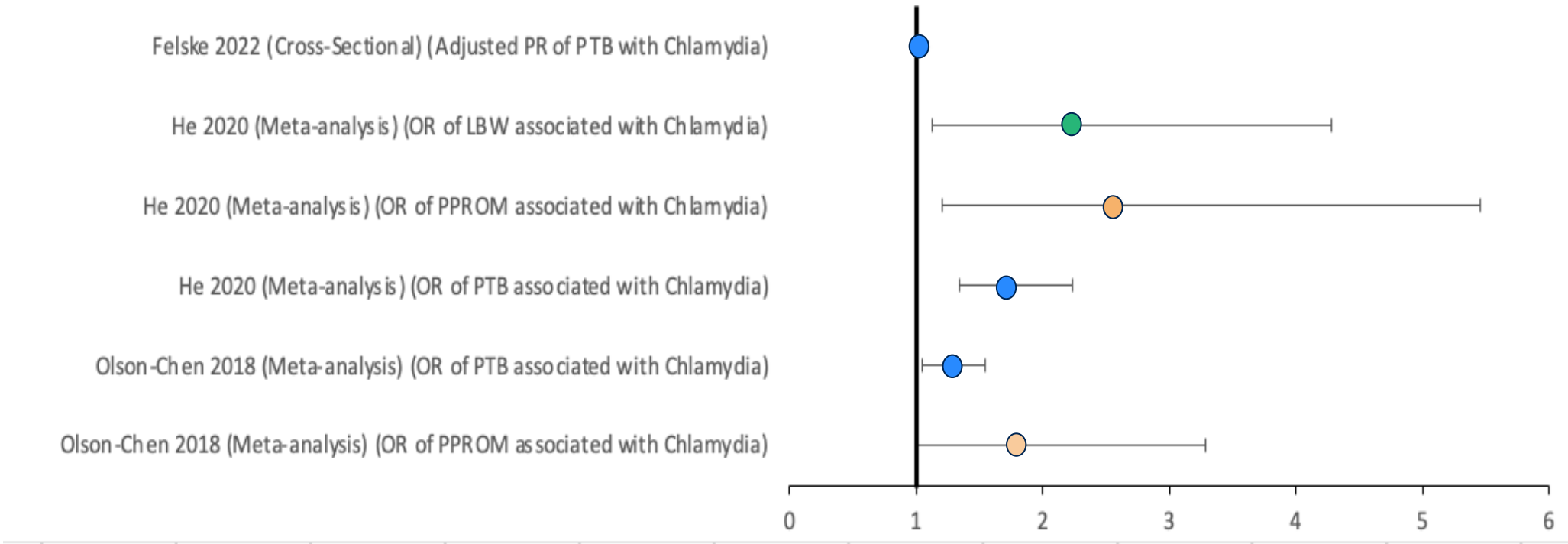
MEASURE

Crude OR: 1.231 (0.990–1.530)

Association of IgG CT Antibody Unadjusted OR: 1.60 (1.24– 2.07)

MEASURES OF ASSOCIATION:

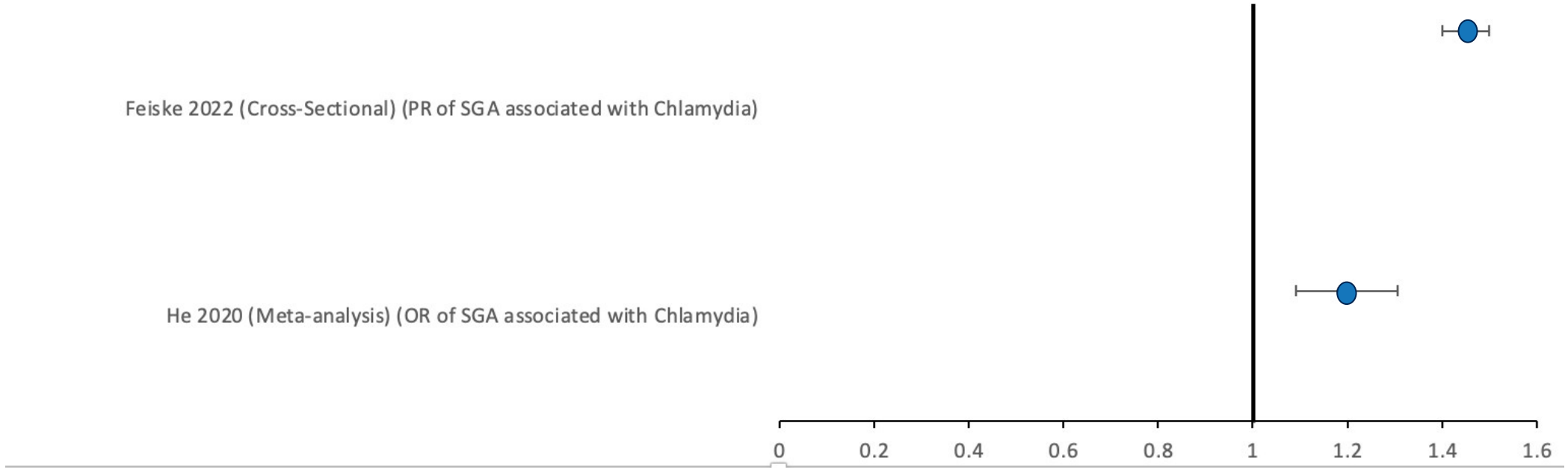
CHLAMYDIA & PTB, VERY PTB, PROM, PPROM, LBW, AND SB



Felske: Prevalence ratio (PR) adjusted for maternal age, race/ethnicity, education, BMI, marital status, adequacy of prenatal care, insurance status, smoking status during pregnancy, and hep B and C status

MEASURES OF ASSOCIATION:

CHLAMYDIA & SGA



Felske: PR adjusted for maternal age, race/ethnicity, education, BMI, marital status, adequacy of prenatal care, insurance status, smoking status during pregnancy, and hep B and C status

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MEASURES OF ASSOCIATION:

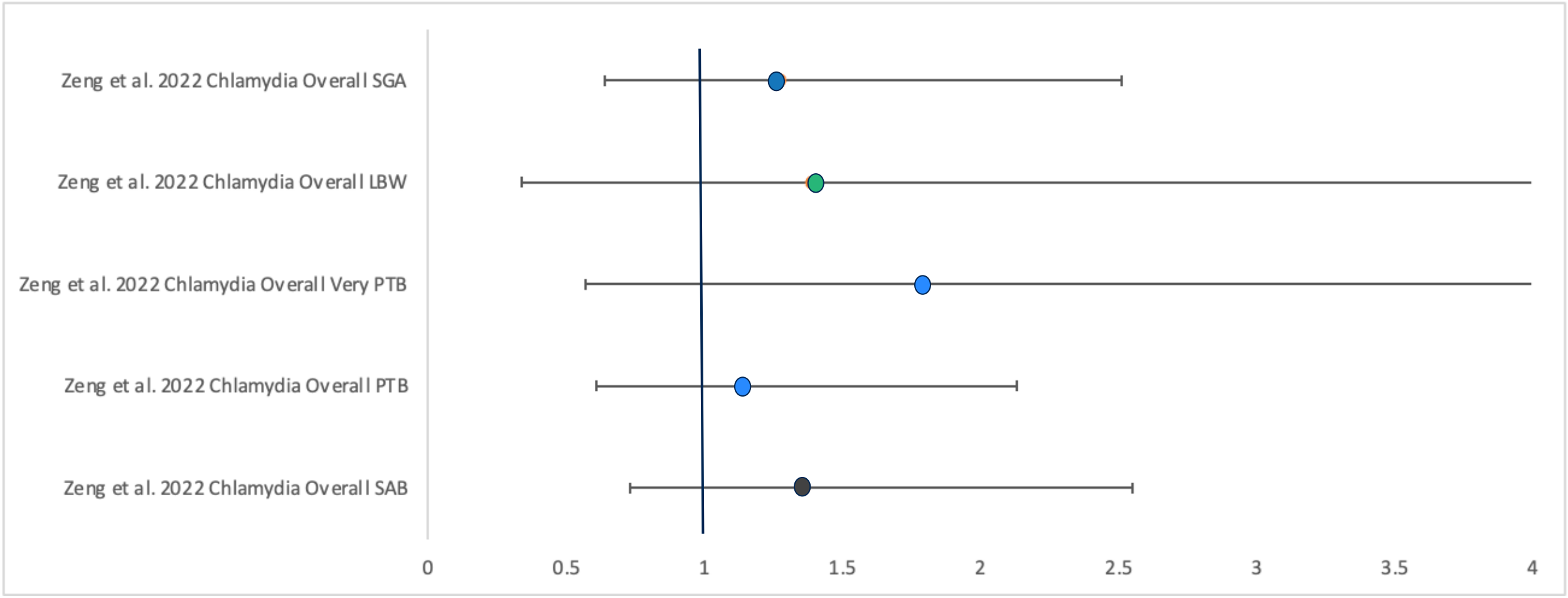
CHLAMYDIA & NEONATAL INFECTION

- There is a history of association of neonatal infection from Chlamydia, impacting mucous membranes of eyes, oropharynx, etc., hence screening and treatment recommended during pregnancy

- Limited findings on this association in recent literature

MEASURES OF ASSOCIATION:

PRE-CONCEPTION CHLAMYDIA & SAB, PTB, VERY PTB, LBW, SGA (ODDS RATIOS)



For more information about Zeng et al. study methods**, see Appendix C.**

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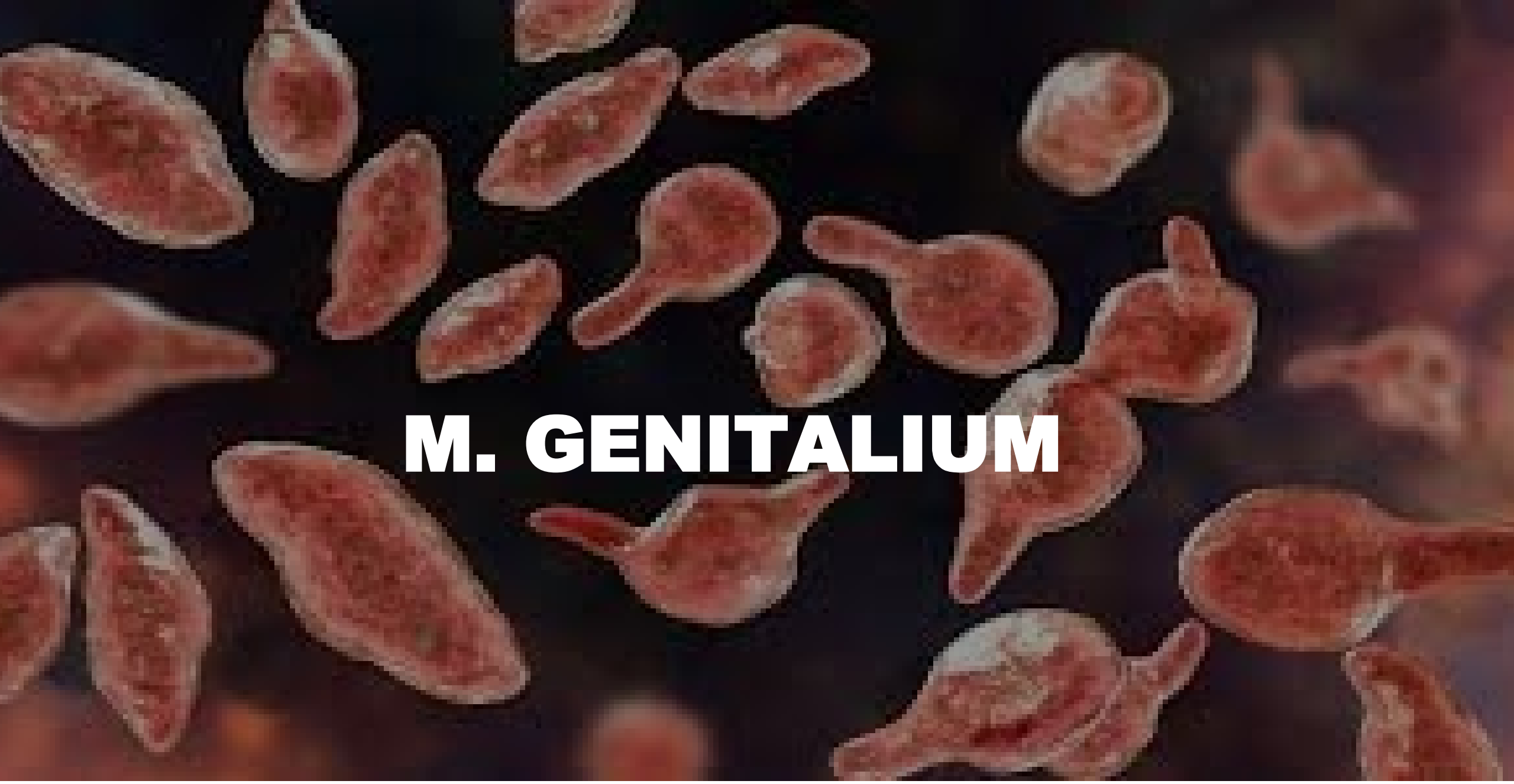
SUMMARY OF FINDINGS: CHLAMYDIA & APOs

1. Higher number of studies, though primarily of lower quality, are readily available and inform increased risk of *Chlamydia* for all adverse pregnancy outcomes studied (particularly with **spontaneous abortion** where data was more limited, but significant association seen)

2. Positive association seen among **preterm birth**, **PPROM** & **low birth weight,** with lower association established for **small for gestational age** among neonates

3. Lack of recent data for association with **neonatal infection**, with recommendation for screening and treatment in pregnancy, and **ectopic pregnancy**


M. GENITALIUM

MEASURES OF ASSOCIATION:

M.GEN & SPONTANEOUS ABORTION

STUDY

Frenzer et al; 2022 **(**Systematic Review**)**

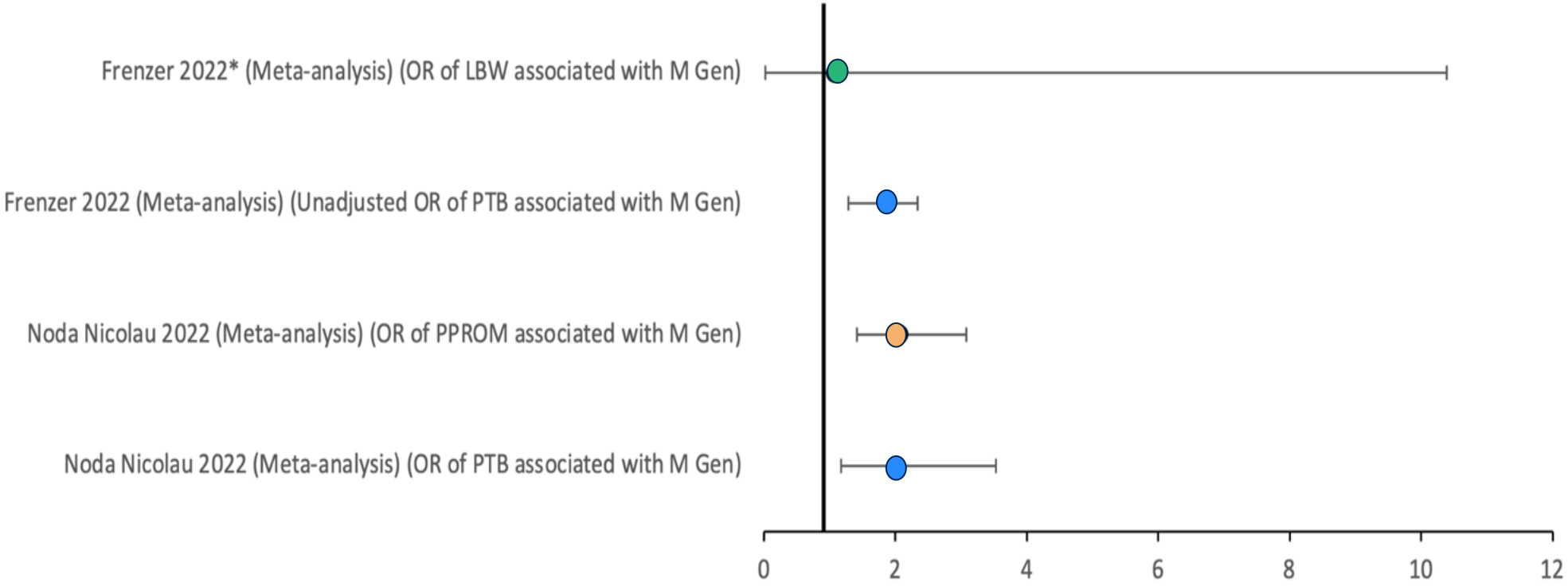
MEASURE

Crude OR: 1.0 (95% CI: 0.53,1.89) and **Adjusted OR in one study:** 0.9 (95% CI 0.2 to 3.8).

Frenzer: OR adjusted for **history of spontaneous abortion, smoking, age and gestational age**.

MEASURES OF ASSOCIATION:

M. GEN & PTB, VERY PTB, PROM, PPROM, LBW, AND SB



***: Frenzer et al 2022 contains OR for LBW based on one Cohort study**

SUMMARY OF FINDINGS: M. GENITALIUM & APOs

1. Among smaller pool of findings, studies show inconsistencies in association with adverse pregnancy outcomes. More evidence based required for significant takeaways

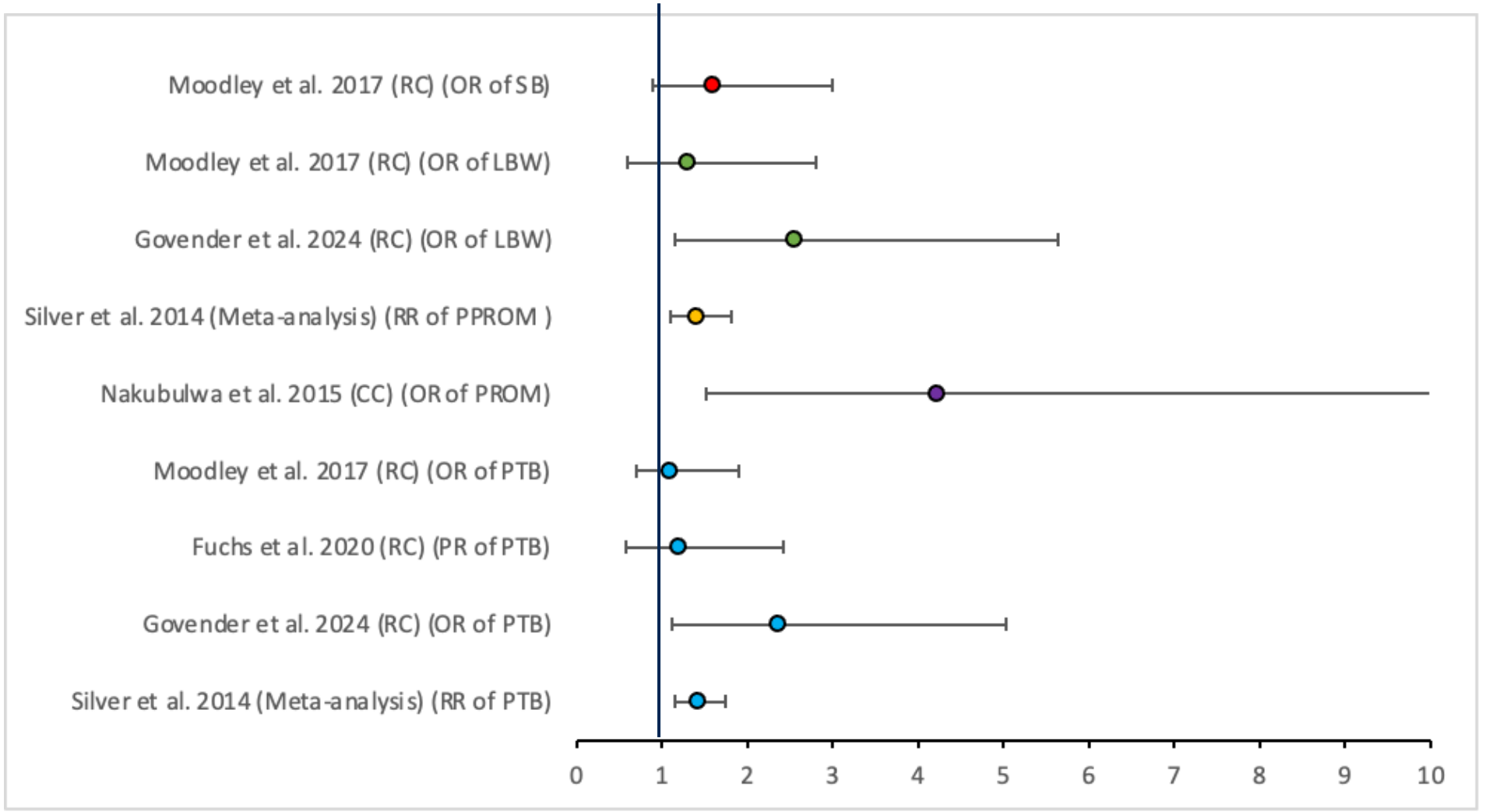
2. Absence of evidence requiring screening/treatment during pregnancy could allow for future opportunities for innovative research design

TRICHOMONIASIS

START CENTER

MEASURES OF ASSOCIATION

TRICHOMONIASIS & SB, LBW, PROM, PPROM, AND PTB



KEY
CC = Case-control
RC = Retrospective cohort

START CENTER

MEASURES OF ASSOCIATION:

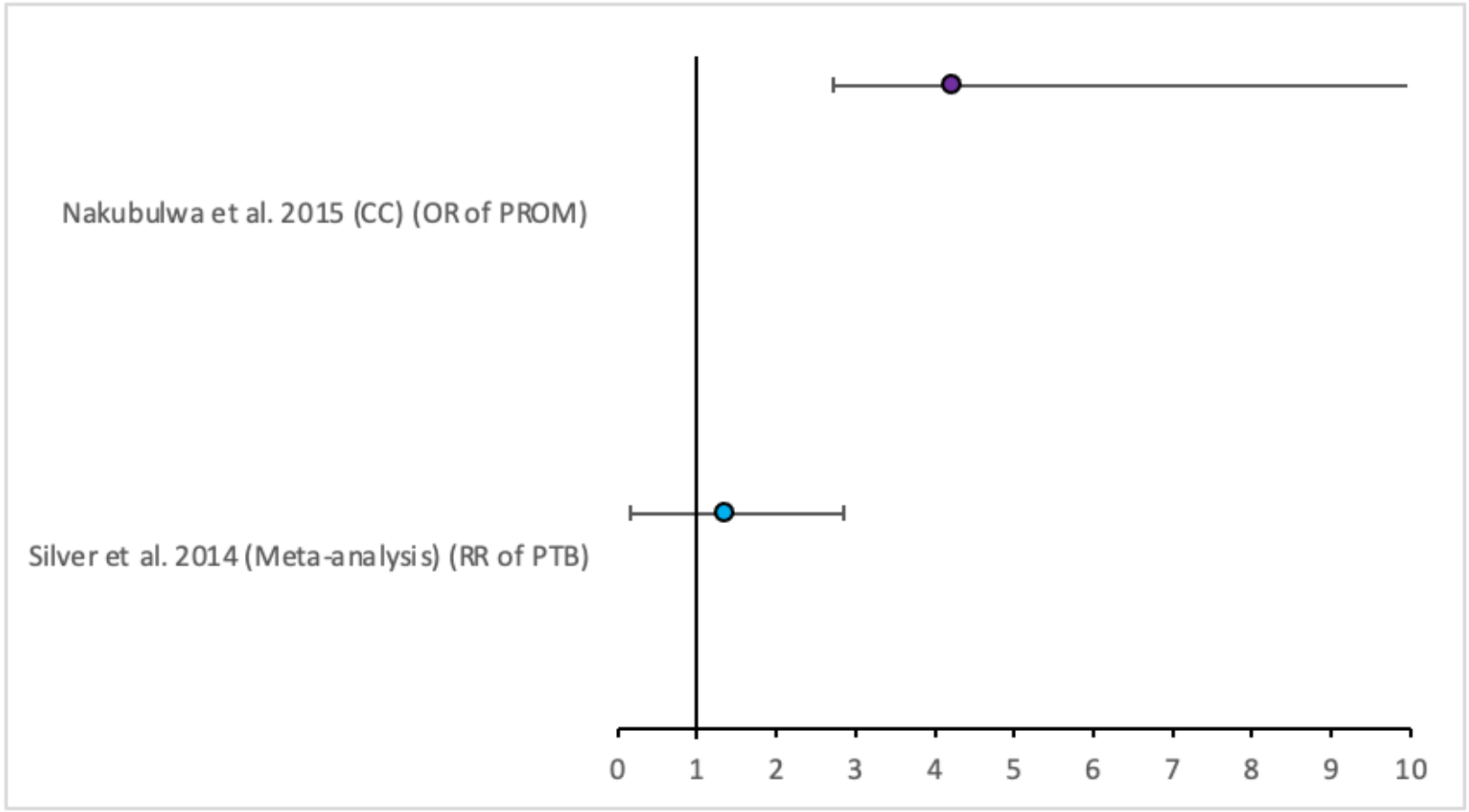
TRICHOMONIASIS & SGA

- Meta-analysis study
- *T. Vaginalis* in pregnancy was associated with an increased risk of small for gestational age infants:
  - RR, 1.51; 95% CI,1.32-1.73; 2 studies; n = 14,843; I = 0.0%

Silver, Bronwyn J., et al. (2014)

MEASURES OF ASSOCIATION

TRICHOMONIASIS & OTHER CO-INFECTION WITH PRO & PTB



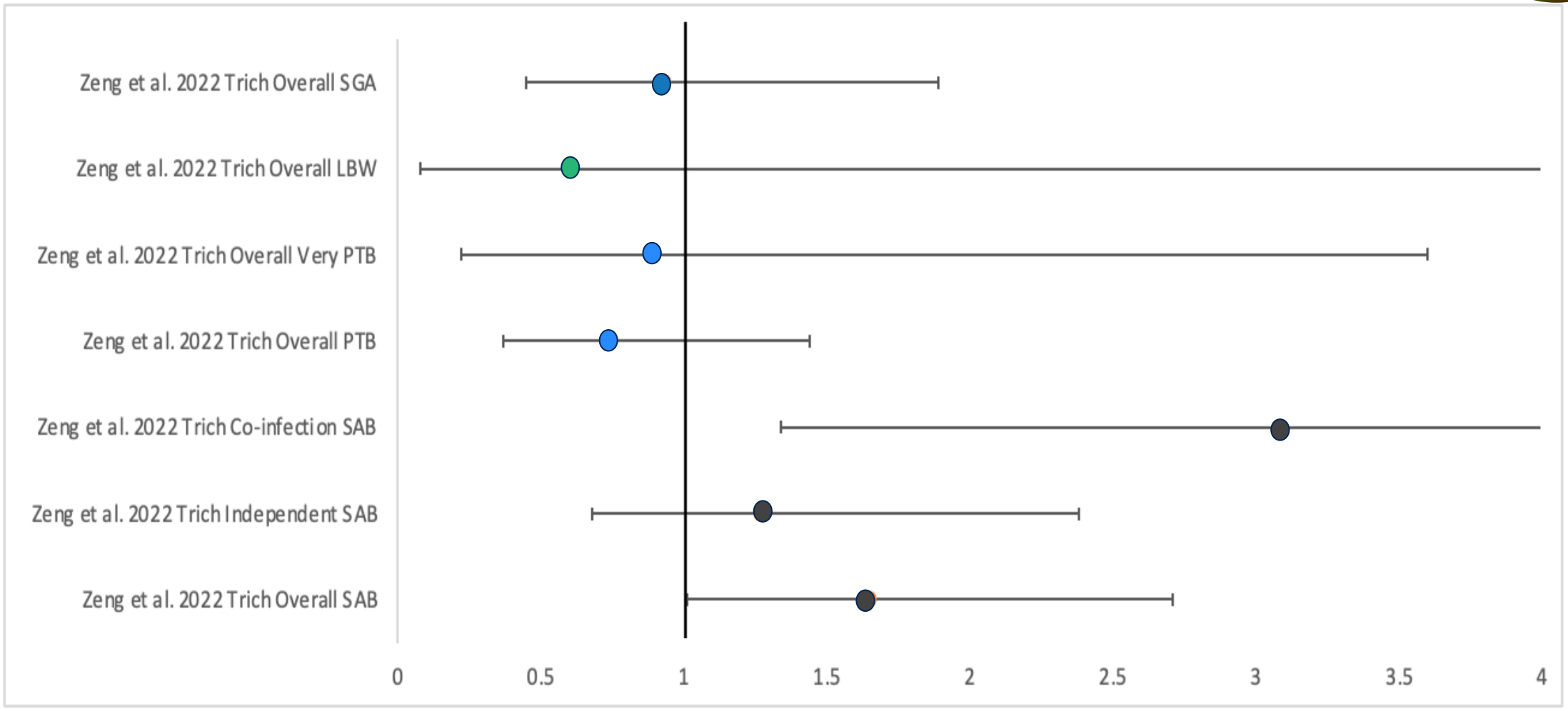
T. Vaginalis & adjusted for C. trachomatis

KEY
CC = Case-control

6 studies adjusted for STI coinfection: Chlamydia trachomatis, Bacterial vaginosis, Group B Streptococcus, Candida, Neisseria gonorrhoea, Syphilis

MEASURES OF ASSOCIATION:

PRE-CONCEPTION TRICHOMONIASIS & SAB, PTB, VERY PTB, LBW, & SGA (ODDS RATIOS)



For more information about Zeng et al. study methods**, see Appendix C.**

START CENTER

SUMMARY OF FINDINGS: TRICHOMONIASIS & APOs

1. There are inconsistent findings between trichomoniasis and various APOs. Further evidence-based studies are needed

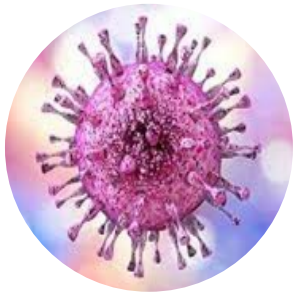
2. There was a moderate to high association between *T. Vaginalis* and PTB, PROM/PPROM, LBW, spontaneous abortion, and SGA

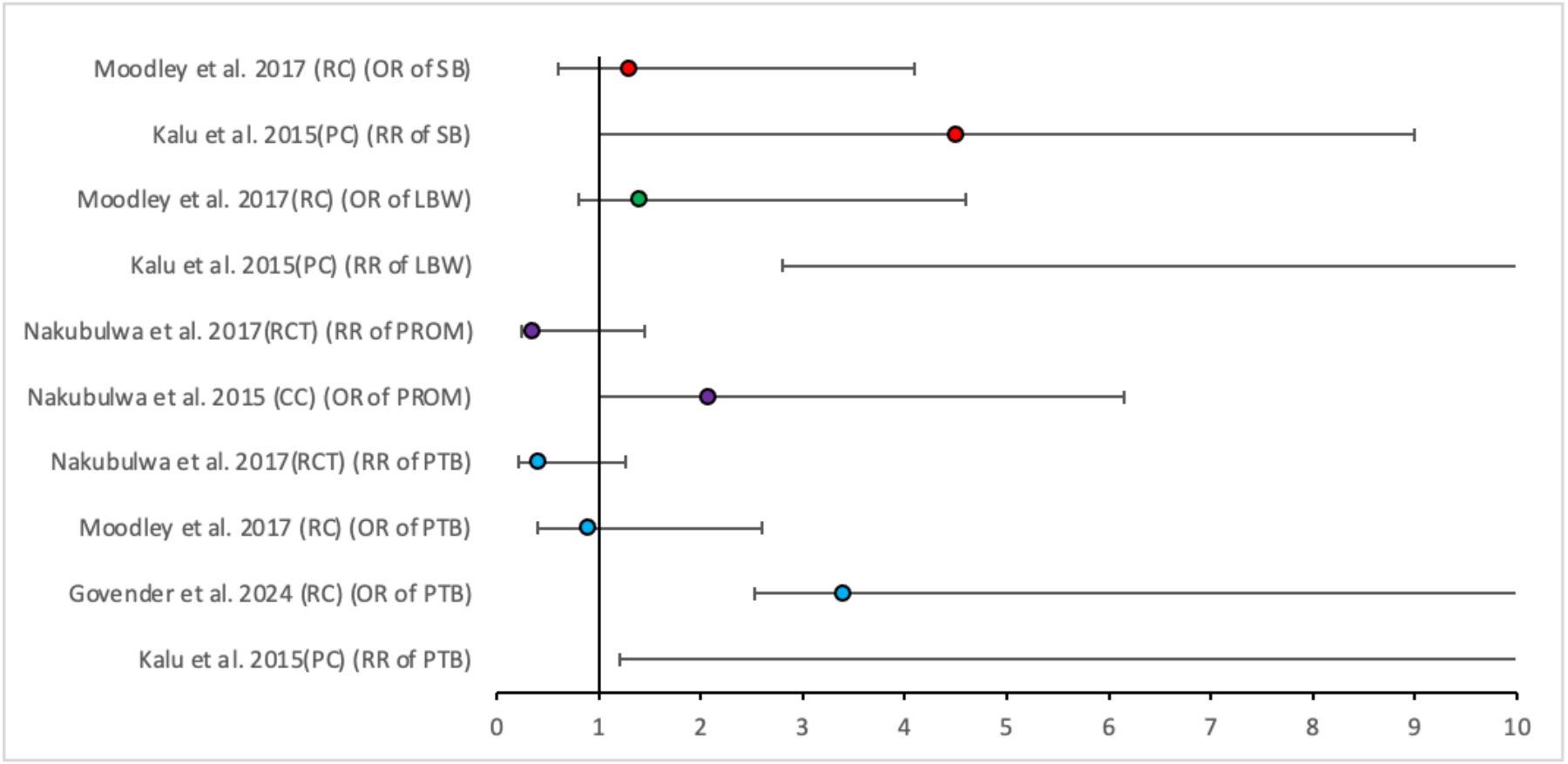
3. The strength of the association between T. Vaginalis & APOs (particularly SAB & PROM) was attenuated after adjusting for co-infection with other STIs


HSV

MEASURES OF ASSOCIATION:

HSV & PTB, PROM, PPROM, LBW, AND SB



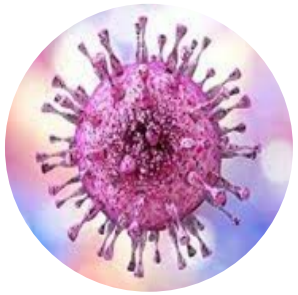


KEY

RC = Retrospective Cohort
CC = Case-control

MEASURES OF ASSOCIATION:

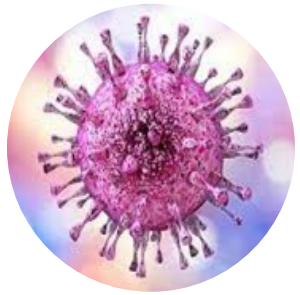
HSV & NEONATAL INFECTION



- HSV infection during pregnancy poses a significant risk to the developing fetus
- Neonates can acquire HSV infection by intrauterine, perinatal, or postnatal transmission of the virus; most cases are acquired perinatally
- Neonatal HSV infection is rare but results in significant morbidity and mortality

Riley et al. (2022)

SUMMARY OF FINDINGS: HSV & APOs



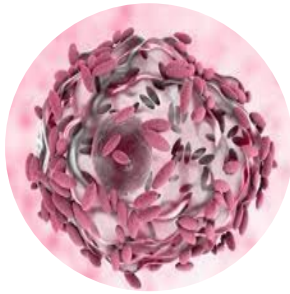
1. There are inconsistent findings between HSV and different APOs. More evidence-based studies are warranted

2. There was a moderate to strong association between HSV and PTB, PROM, LBW, and SB

3. Although no recent literature was included, HSV is a very well known neonatal infection with devastating consequences. Serological tests for HSV-2 and vaccines are needed


BV

MEASURES OF ASSOCIATION



BV & SPONTANEOUS ABORTION

STUDY

Kenfack-Zamguin et al; 2023 **(**Meta-analysis**)**

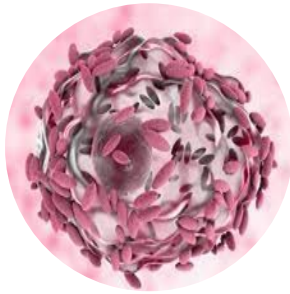
MEASURE

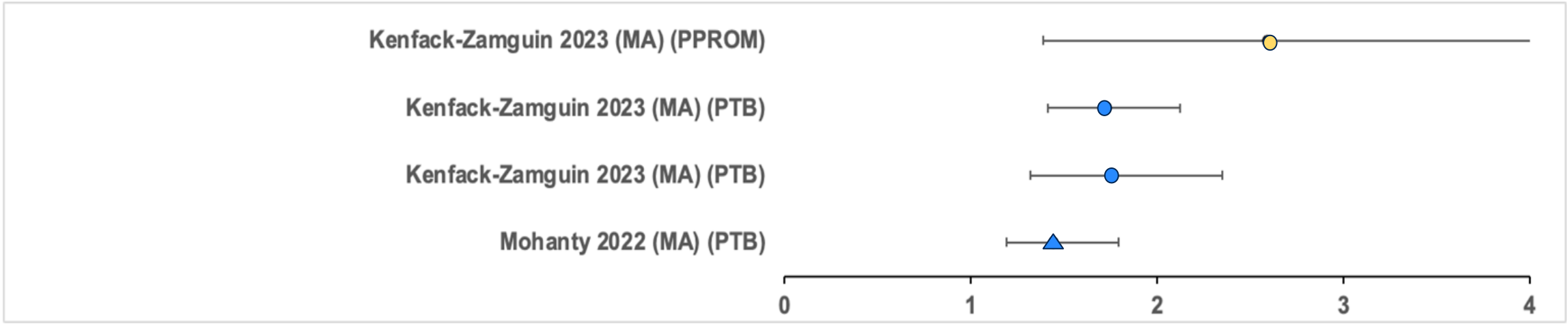
OR for SAB**: 2.34** (95%CI: 1.18, 4.64)

*Meta-analysis did not discuss adjustment for STI co-infection.

MEASURES OF ASSOCIATION

BV & PTB, PPROM





KEY:

- Risk Ratio
- Odds Ratio

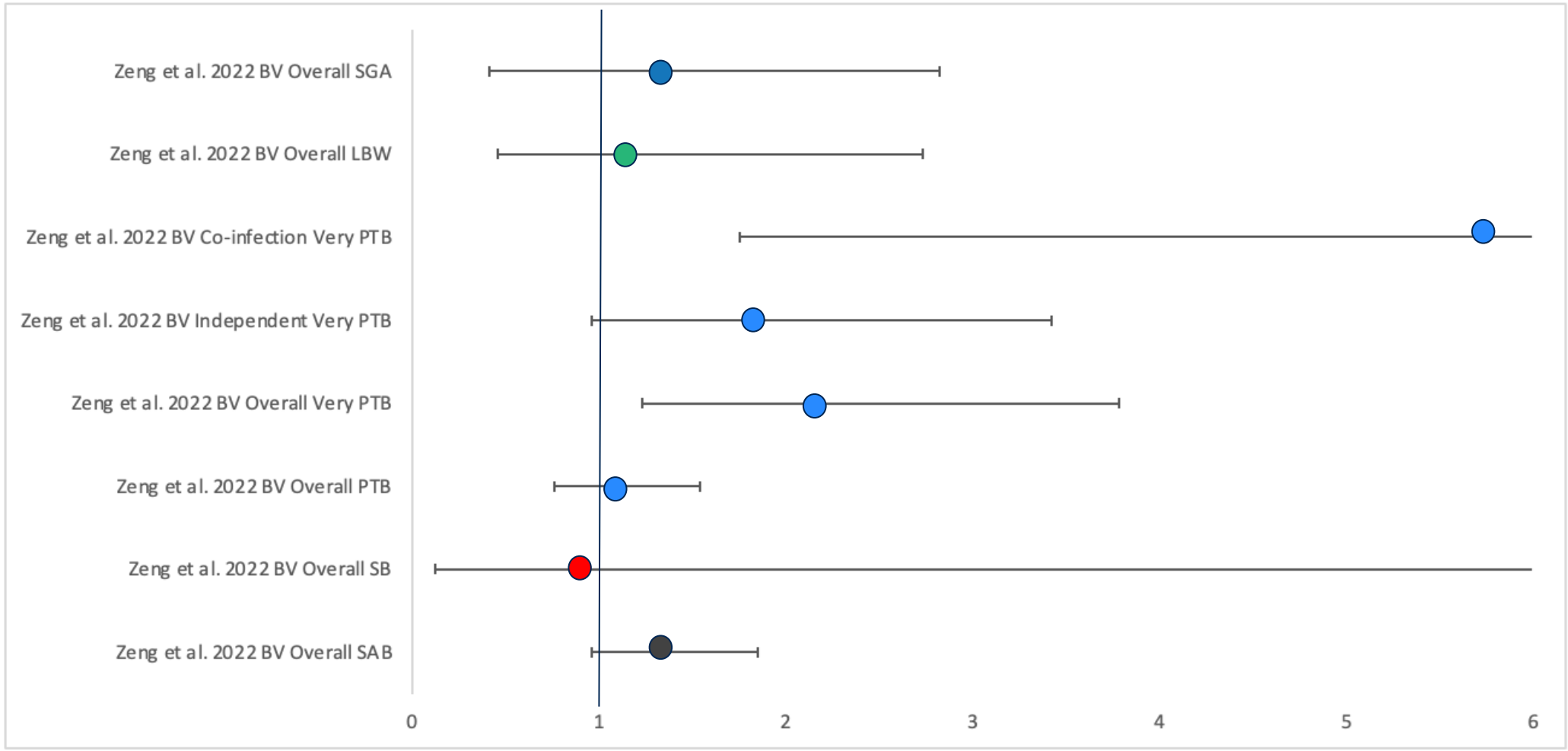
Meta-analysis (MA)

Cohort Study (CS)

*Studies did not discuss adjustment for STI co-infection.

MEASURES OF ASSOCIATION

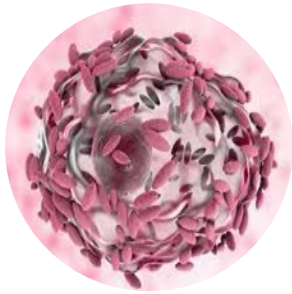
PRE-CONCEPTION BV & SAB, PTB, VERY PTB, LBW, SGA (ODDS RATIOS)



*For more information on Zeng et al. study methods, **see Appendix C.**

START CENTER

SUMMARY OF FINDINGS: BV & APOs



1. Clear association between *BV* and **PTB** in all three systematic reviews & meta-analyses examined and **preterm PROM** in one systematic review & meta analysis

2. Studies examining the effect of treating *BV* on reducing the rate of PTB, however, have all yielded null results (including RCT published in 2023)

3. Pre-conception *BV* was associated with very PTB (gestational age 28-32 weeks), but this association was attenuated when stratifying by co-infection status and examining independent infection with *BV*

4. Evidence regarding the association between BV and other APOs is mixed

CONCLUSIONS & OPPORTUNITIES

CONCLUSIONS

1

Strong Evidence for Syphilis & APOs:

- The link between syphilis and nearly every APO is well-established.
- Treating syphilis reduces these outcomes, but in lower resource settings, screening and treatment is implemented poorly.

2

Moderate to Mixed Evidence for Chlamydia, Gonorrhea, BV & APOs:

- Chlamydia, gonorrhea, and BV are all associated with certain APOs, but no clinical trials showing that screening and treating these STI reduces the risk of APOs.

3

Limited Evidence for Trichomoniasis, HSV, M. gen & APOs:

- Trichomoniasis, HSV, and M. gen show inconsistent results, with some studies indicating significant risks for preterm birth, PROM, and low birth weight, and others reporting null findings.

4

Quantification of the association between STIs and APOs, and determining whether these associations are causal, is limited by a lack of RCTs, variably defined outcomes, mixed study results, and limited data on coinfection and other confounding factors.

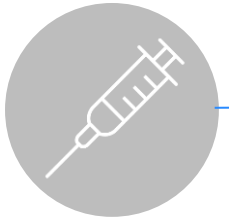
FUTURE OPPORTUNITIES

Clinical trials showing that screening and treating gonorrhea, chlamydia, and BV reduces APOs.

- However, there are several study design challenges that must be considered including whether single screen and treat will be adequate, ethical considerations, etc.

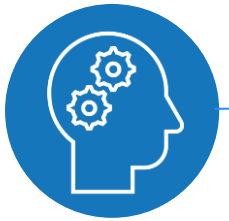
Building the evidence base for M. gen & trichomoniasis and APOs.

- Evidence is currently insufficient to recommend screening/treatment so filling in these gaps in the literature could be essential to informing recommendations.



Vaccines for syphilis and HSV

- Given the well-established relationship between syphilis and nearly all APOs and HSV and neonatal herpes, there is a huge need for syphilis and herpes vaccines to avert poor neonatal and maternal health outcomes



Better understanding how coinfection with BV (and other STIs) impacts risk of APOs.

- Evidence suggesting that *BV* with other STIs might result in different outcomes than BV alone or other STIs alone.

THANK YOU

Questions?

START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

APPENDICES

APPENDICES

- A Gaps & Opportunities
- B STI Co-infection Findings
- C Zeng et al. Study Methods - Preconception STIs & APOs
- D Literature Extraction Sheet
- E References

APPENDIX A:
Gaps & Opportunities

APPENDIX A:

GAPS & OPPORTUNITIES - SYPHILIS & APOS

GAPS

- Varied definitions for APOs especially for stillbirth across studies
- Lack of robust, large-scale clinical trials or longitudinal studies specifically designed to evaluate the effectiveness of POCT for syphilis in improving pregnancy outcomes (direct evidence)

OPPORTUNITIES

- Additional RCTs establishing a reduction in APOs by screening and treating syphilis are not necessarily needed due to WHO's screening and treatment recommendations during pregnancy
- Huge need for syphilis vaccine to avert poor neonatal and maternal health outcomes
- The need to develop additional implementation strategies for syphilis evidence-based interventions

APPENDIX A:

GAPS & OPPORTUNITIES - GONORRHEA & APOS

- High quality evidence was generally lacking, with high heterogeneity across studies, limited or inconclusive data, and lack of adjustment for coinfection

- Need for clinical trials to demonstrate the benefit of screening and treatment for GC to reduce APOs, however with substantial challenges and further questions

Notably,

1. Having a trial that could establish these associations as causal and at the same time demonstrating **efficacy** of an intervention for reducing APOs
2. Ethical considerations for the trial design, as screening and treating is recommended (cluster randomized stepped wedge or pre-post may need to be considered)

3. Need to establish rates of GC infection in **potential trial populations** of pregnant women

4. Single-screen and treat may be inadequate due to treatment failures and reinfection as there is need to first demonstrate that it is possible to **substantially reduce GC infection** during the **entire** pregnancy

- Partner treatment
- Rescreening

APPENDIX A:

GAPS & OPPORTUNITIES - CHLAMYDIA & APOS

GAPS

- While meta-analysis showed increased association for preterm birth, there are conflicting findings about prevalence of *Chlamydia* in preterm birth (high range in degree of association)

- Limited findings about confounders (if *Chlamydia* was causal vs. High-risk population status), co-infection & mixed definitions for adverse pregnancy outcomes

- Higher quality studies (NOS >= 6) for those examining certain outcomes, like stillbirth, but lower when examining low birthweight and PPROM (lost significance when only including high quality studies)

OPPORTUNITIES

- Similar needs for clinical trial to demonstrate need for screening and treatment as seen with *Gonorrhea*, with the similar concerns of causality, ethical concerns and considerations for treatment

APPENDIX A:

GAPS & OPPORTUNITIES - M. GEN & APOS

GAPS

- Lower availability of data: Pre-term birth (7 studies), low birthweight (1) and PPROM (1) examined with differing magnitudes of association

- Data gap particularly important in LMICs where higher burden for *M.Gen* & adverse pregnancy outcomes occurs

- Lower quality of studies (10 total in systematic review) & possibility of bias

APPENDIX A:

GAPS & OPPORTUNITIES - M. GEN & APOS

GAPS

- Association of *M. Gen* & APOs is largely understudied, particularly in spontaneous abortion or miscarriage

- Understanding of co-infection with other pathogens or *BV* is limited

OPPORTUNITIES

- Evidence is currently insufficient to recommend screening/treatment for asymptomatic *M. Gen* in pregnant women, so understanding gaps could be essential to informing recommendations (concerns about AMR vs. Concern for APOs)

- Since screening/treatment is not currently recommended in pregnant women, considerations for clinical trial lack same ethical concerns applied to *Gonorrhea* and *Chlamydia*, so RCT may be rigorous and ethically sound

APPENDIX A:

GAPS & OPPORTUNITIES - TRICHOMONIASIS & APOS

GAPS

- Inconsistent findings/concerns about the safety of treating *T. Vaginalis* in pregnancy:
- An RCT in the 1990s - asymptomatic women assigned to treatment with metronidazole found an increased risk of preterm birth and/or LBW
- Treatment with metronidazole in pregnancy is currently only advised in symptomatic cases or if asymptomatic, after 37 weeks' gestation
- Conversely, a review in 2012 of metronidazole use in pregnancy among 2829 women found no association with preterm birth or LBW

  Silver, Bronwyn J., et al. (2014)

OPPORTUNITIES

- Treatment of asymptomatic women in different trimesters
- Therefore, whether there are indeed risks or benefits associated with treatment in pregnancy remains unclear, and further studies are needed to answer this important question to ensure clinical practice and guidelines are supported by a solid evidence base

  Silver, Bronwyn J., et al. (2014)

APPENDIX A:

GAPS & OPPORTUNITIES - HSV & APOS

GAPS

- Vaccine are not available to treat neonatal herpes

OPPORTUNITIES

- Need for good serological tests to identify those who carry HSV-2
- Need for a vaccine; most current efforts are focused on therapeutic vaccines that would reduce symptomatic recurrences in people with HSV-2
  Corey., et al. (2010)

APPENDIX A:

GAPS & OPPORTUNITIES - BV & APOS

GAPS

- Evidence suggesting that *BV* with other STIs might result in different outcomes than BV alone or other STIs alone, particularly *BV* with *M. Gen*. However, the impact of *BV* and other STIs such as *Chlamydia, Gonorrhea, and T. Vaginalis* on APOs is a gap in the literature

- Coinfection is prevalent but the extent to which it is clinically important remains unknown

OPPORTUNITIES

- Better understanding the impact of coinfection on APOs

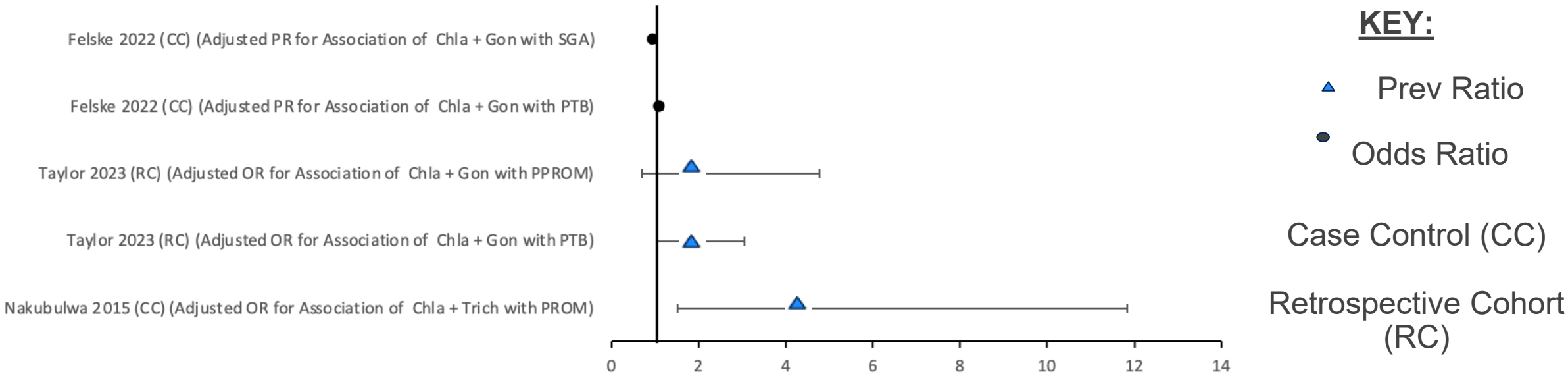
- How to treat *BV* more effectively. Studies looking into the impact of treating *BV* on reducing adverse pregnancy outcomes like pre-term birth are complicated by lack of effective treatment regimens

- Newer treatment approaches such as combinations of antimicrobial and microbiota approaches

APPENDIX B:
STI Co-infection Findings

APPENDIX B: MEASURES OF ASSOCIATION

STI CO-INFECTION & ADVERSE PREGNANCY OUTCOMES



APPENDIX C:
Zeng et al. Study Methods – Pre-conception STIs & APOs

APPENDIX C:

ZENG ET AL. STUDY METHODS: PRECONCEPTION STIs & APOs

- Zeng evaluated the risk of APOs associated with pre-conception (before pregnancy within one year) STIs and whether co-infection influenced the association between STIs and APOs.

- First, Zeng assessed the risk of APOs associated with each STI (irrespective of co-infection status).

- Initial findings that were statistically significant were then further evaluated in a stratified analysis to assess whether co-infections influenced the significant association between the independent infection and the APO.
    - Those infected with exclusively one of the STIs (i.e., independent infection) were considered separately from those with STI co-infection (e.g., those with syphilis alone were examined separately from those with syphilis and another STI.

APPENDIX D:

LITERATURE EXTRACTION SHEET

ID#	Title	Author	Year	Link	Article Type	Geography	Sample Size	STI	Trimester of infection detection	Symptomatic vs. asymptoma	Sample and diagnostic used	Adverse Pregnancy Outcome	Other Adverse Pregnancy Outcome, specify
1	Effect of Antibiotic Exposure on Nugent Score Among Pregnant Wome	Anderson et al.	2011	https://www.ncbi.	RCT	US	547	BV	Unknown	Asymptoma	Gram stain	Pre-term birth	
2	Effect of bacterial vaginosis on preterm birth: a meta-analysis	Mohanty et al.	2022	https://link.springe	Systematic review and meta-analysis		290,397	BV	Unknown			Pre-term birth	
3	Asymptomatic bacterial vaginosis and intermediate flora as risk factor	Leitich et al.	2007	https://www.scier	Systematic review and meta-analysis		24,190	BV	Unknown	Asymptoma	Gram stain	Pre-term birth	
4	Adverse pregnancy and neonatal outcomes associated with Neisseria	Vallely et al.	2021	https://sti.bmj.con	Systematic review and meta-analysis		60,396	Gonorrhea			Culture and/or	Pre-term birth	
5	Reported estimates of adverse pregnancy outcomes among women v	Qin et al.	2014	https://journals.pk	Systematic review and meta-analysis		9,430	Syphilis				Neonatal infection	
6	The impact of antenatal syphilis point of care testing on pregnancy out	Dana et al.	2021	The impact of ant	Systematic review ONL	Latin America, Asia	14834	Syphilis	at first visit, at third GA		POC syphilis	Other	Neonatal mortality
7	Sexually Transmitted and Blood-Borne Infections in Pregnant Women	D'Aiuto et al.	2020	Sexually Transmi	Retrospective cohort	Montréal, Québec	3460	Syphilis	<37 weeks			Low birthweight	
8	Associations of Chlamydia trachomatis serology with fertility-related ar	Zuo et al.	2023	https://www-clinic	Systematic review and meta-analysis		128,625	Chlamydia				Ectopic Pregnancy	
9	Genital Mycoplasmas and Biomarkers of Inflammation and Their Asso	Noda Nicolau e	2022	https://www.ncbi.	Systematic review and meta-analysis			M.Gen	primarily delivery, some		Culture and/or	Pre-term birth	
10	Adverse pregnancy and perinatal outcomes associated with *Mycoplas*	Frenzer et al.	2022	https://sti.bmj.con	Systematic review and meta-analysis		2446	M.Gen			NAAT	Pre-term birth	
11	Chlamydia trachomatis and Adverse Pregnancy Outcomes: Meta-ana	Olson-Chen et	2018		Systematic review and meta-analysis		614892	Chlamydia			NAAT, antibody	Preterm PROM (PPROM)	
12	Chlamydia trachomatis immunoglobulin G3 seropositivity is a predictor	Steiner et al.	2015	https://www.scier	Prospective cohort	USA	1251	Chlamydia	Pre-pregnancy		Serology	Ectopic Pregnancy	
13	The impact of antenatal syphilis point of care testing on pregnancy out	Brandenburger	2021	The impact of ant	Systematic review ONL	Global	278	Syphilis	primarily de	Syphilis	POCT, RPR	Stillbirth	
14	The association between non-viral sexually transmitted infections and	Lara-Escandel	2024	The association b	Systematic review ONL	Latin America and	8360	Syphilis	primarily de	Syphilis	ELISA, VDRL, I	Pre-term birth	
15	Readily treatable reproductive tract infections and preterm birth among	French et al.	2006	https://pubmed-nc	Prospective cohort	Denver, Colorado	1038	T.Vaginalis	< 29 weeks followed thro		microbiologic m	Pre-term birth	
16	Sexually transmitted infections during pregnancy and subsequent risk	Warr et al.	2018	https://sti.bmj.con	Prospective cohort	Kenya	1221	T.Vaginalis	pregnancy and followed		wet mount micr	Stillbirth	
18	Systematic Literature Review and Quantitative Analysis of Health Prob	Whelan et al.	2021	Systematic Liter	Systematic review and meta-analysis		103	Gonorrho	primarily d	Gonorrhea	NAAT, culture	Preterm PROM (PP	
19	The Association Between Vaginal Microbiota Dysbiosis, Bacterial Vagi	Juliana et al.	2020	https://www.fr	Systematic review ON	Sub-Sarahan Afri	6 studies	BV			Gram Stain	Low birthweight	
20	Effectiveness and Costs of Molecular Screening and Treatment for Ba	Bretelle et al.	2023	https://waterm	RCT	France	6671	BV	<20 weeks		qPCR assays t	Pre-term birth	
21	Trichomonas vaginalis as a Cause of Perinatal Morbidity A Systematic	Silver et al.	2014	https://pubmed-nc	Systematic review and r	Global	11 studies - size	T.Vaginalis	The most frequently rep		The method of	Pre-term birth	
22	Trichomonas vaginalis as a cause of perinatal morbidity: a systematic	Chico et al.	2012	https://jamanetwo	Systematic review and r	Sub-Sarahan Afri	171 studies - pro	T.Vaginalis	pregnancy		wet mount microscopy		
23	Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newbo	ARABSALMAN	2017	https://www-ncbi-	Systematic review and r	Iran	5 studies , includ	HSV	pregnancy		Not specified		
24	Systematic review and meta-analysis of maternal and fetal outcomes	Kenfack-Zangu	2023	https://www.scier	Systematic review and r	Global	13 studies (1537	BV			Gram Stain	Low birthweight	
25	Effect of Chlamydia trachomatis on adverse pregnancy outcomes: a meta	He et al.	2020	Downloaded	Systematic review and r	Global	50 studies	Chlamydia				Miscarriage	
26	Influence of Sexually Transmitted Infections in Pregnant Adolescents on	Fuchs et al.	2020	https://www.ncbi.	Retrospective cohort	USA	739 adolescent m	T.Vaginalis	full pregnancy		VPIII	Pre-term birth	Chorioamnionitis
27	Genital infections and risk of premature rupture of membranes in Mulago	Nakubulwa et a	2015	https://bmcresnot	Case-control	Uganda	174 (87 cases and	T.Vaginalis	third trimester of pregnan		wet preparation	Premature rupture of membranes (PROM)	
28	Sexually transmitted infections in pregnancy and adverse pregnancy outc	Govender et al	2024	https://obgyn-onli	Retrospective cohort	South Africa	752 pregnant won	T.Vaginalis	<28 weeks of gestation; as		Roche Light Cycl	Pre-term birth	Lowbirth weight, stillb
29	Point-of-care testing and treatment of sexually transmitted and genital infe	Riddell et al.	2024	https://www.thela	RCT	Guinea	4526 women were	T.Vaginalis	26 weeks' gestation or ear		GeneXpert platfo	Pre-term birth	Low birth weight or bo
30	Pregnancy Outcomes in Association with STDs including genital HSV-2 shed	Moodley et al.	2017	https://sti.bmj.cor	Retrospective cohort	South Africa	615 women	T.Vaginalis	34 weeks gestation with s		BD Probetec ET A	Pre-term birth	stillbirth, low birth we
31	Obstetric outcomes of human herpes virus-2 infection among pregnant wor	Kalu et al.	2015	https://journals.lw	Prospective cohort	Nigeria	674 pregnant won	HSV-2	full pregnancy		ELISA kit by Dia.	Low birthweight	Pre-term birth, stillbir
32	Effect of suppressive acyclovir administered to HSV-2 positive mothers from	Nakubulwa et al	2017	https://reproducti	RCT	Uganda	200 HSV-2 positive	HSV-2	28 weeks of gestation		HerpeSelect HSV	Premature rupture of	Pre-term birth
33	Prevalence of 7 sexually transmitted organisms by multiplex real-time PCR i	Ashshi et al.	2015	https://bmcinfecto	Case-control	Saudi Arabia	135 Saudi women	HSV-1/2	first trimester		Multiplex-PCR	Ectopic Pregnancy	
35	Syphilis in Pregnancy: The Reality in a Public Hospital	Torres et al.	2019	SciELO - Brazil - Syp	Retrospective cohort	Brazil	268 pregnant won	Syphilis	(n= 80, 29.8 in the 1st trim		non-treponemic	Preterm birth	
37	Preconception reproductive tract infections status and adverse pregnancy c	Zeng. et al.	2022	https://bmcpregna	Retrospective cohort	China	57,586	T. Vaginalis				Other	Spontaneous abortion
38	The Impact of Neisseria gonorrhoeae Mono- and Coinfection on Adverse Pre	Taylor et al.	2023	https://www.ncbi.	Retrospective cohort	US	29,821	Gonorrhea				Pre-term birth	
39	Comparing adverse neonatal and maternal outcomes of chlamydia, gonorrh	Felske et al.	2022	https://onlinelibra	Cross-sectional	US	63,391	Chlamydia				Pre-term birth	
40	Maternal syphilis treatment and pregnancy outcomes: a retrospective study in J	Wan Z et al.	2020	Maternal syphilis t	Retrospective cohort	China	4210 syphilis infe	Syphilis	≥28 gestational weeks		non-treponemal	stillbirth	
41	Associations between Antenatal Syphilis Test Results and Adverse Pregn	Laktabai et al.	2022	Associations betwe	Case-control	Kenya	51 cases (wom	Syphilis	less than 32 weeks ges		POCT and RPR	Stillbirth	
42	High Rates of Adverse Birth Outcomes in HIV and Syphilis Coinfected Wo	Shava et al.	2019	Brief Report: High I	Secondary Analysis	Botswana	76,466 women, S	Syphilis	>24 weeks gestational age		RPR and Serolo	Still birth	
43	Adverse Birth Outcomes and Maternal *Neisseria gonorrhoeae* Infection: A	Heumann et al.	2017	Adverse Birth Outc	Retrospective cohort	USA	819 Women (were	Gonorrhoea	full pregnancy		Not specified: cl	LBW	
44	Chlamydia and Gonorrhea in HIV-Infected Pregnant Women and Infant H	Adachi et al.	2015	Chlamydia and Go	sub-study of a phase 3,	Brazil, South Africa,	1684 HIV-infected	Gonorrhoea + Chla	>32 weeks gestational age		NAAT, culture	**PRIOR** Still birth	

APPENDIX D:

LITERATURE EXTRACTION SHEET

Co-Infection	Measures of Association	Other Key Results (Receipt of treatment, partner treatment, etc)	Notable Tables/Figures	Comments
None	Frequency of preterm birth not significantly different between BV+	Primary outcome of interest was effect of antibiotics on BV- women. Rec	Table 4	
None	The overall RR of preterm birth is 1.44 (95% Confidence Interval 1.19-1.73).			
None	OR: 2.16 (1.56 - 3.00), p<0.0000001		Table 4	
None	1.55 (95% CI 1.21, 1.99; I2 61.1%; prediction interval (	Eleven studies were from high-income countries4 8 29 32–34 37 39 41 4	Table 2	Eleven studies were from high-income countries4 8 29 32–34 37 39 41 43 45 (table 1). NG was more strongly
None	Pooled estimate: 20.6% of infants born to people with syphilis had	Congenital Syphilis	Table 4	
None	Latin America:0,82 adverse pregnancy outcomes (of which 0,42 stillbirths) averted after Syphilis POCT; Asia: 0,83 (of which 0,43 stillbirths		Table 2	
None	Prev: 8(15.7%) in Pregnancies resulting in birth withsexually transmitted and blood-borne infections; n = 51, and prev: 186 (10.2) in Pregna		Table 4	
None	Pooled adjust OR between antibodies for chlamyddia & EP: poole	d adjusted OR = 3.00, 95% CI 1.66–5.40	Table 1, Figure B	
None	OR for odds of M.Gen in women with pre-term birth compared to	full-term pregnancies: OR: 2.04; CIL 1.18–3.53; I2: 20%	Figure 7 & 8	
None	Unadjusted OR: 1.91 (95% CI 1.29 to 2.81, I2=0%) among 7 stud	Adjusted OR: 2.34 (95% CI 1.17 to 4.71, I2=0%, 2 studies	figure 1	
None	(OR = 1.82) which bordered significancewith p = 0.05 and 95% CI	1.0–3.29	NA	note sample size is among total studies
None	RR of seropositive chlamydia and Ectopic preg: 2.7 (95% CI 1.40–5.34)		Table 1	
None	Risk proportion: 93% Significant reduction of congenital syphilis c	Risk proportion with non-treponemal rapid RPR: 58% reduction of misca	Table 2	note sample size is among total studies
None	OR: 3.29 (1.93 - 5.61)	73 pre-term births among 134 syphilis positive mothers	Table 1	note sample size is among total studies
Chlamydia trachomatis,	Up to 42% of preterm births among black women were attributab	The risk for preterm birth among infected black women who received C	Table 4	a) a secondary analysis of combined data from a prospective cohort study and 3 clinical trials; b) preterm birt
BV, vaginal yeast, CT, N	Prev of TV: 6%; Overall, 19/1221 (2%) women experienced stillbi	Women were counselled to have their partner come to the study clinic fo	Table 2	Overall, among 1221 women, 55% had STIs or genital infections detected: vaginal yeast (25%), BV (22%), TV
None	adjusted OR = 7.6 (95%CI: 2.2 - 26.4)		Table 1	
Yes; different betwee	2 studies in Nigeria found very large effects (OR 3.56 (95%CI:1.3-9.7) and OR 19.93 (95%CI: 5.3-75.0)) with very wide confidence interva		Table 3	
	Intention-to-treat analysis of preterm birth sho	No differences in other exploratory outcomes (PROM, IUGR, endometritis, spontaneous abortion, late miscarriage, fetal death, preecla		
Not specified	increased risk of preterm birth (RR, 1.42; 95% CI, 1.15–1.75; 9 st	Sensitivity analyses of studies that accounted for coinfection with other s	Figure 2, 3 & 4	Our review provides strong evidence that T. vaginalis in pregnancy is associated with an increased risk of pre
malaria, syphilis, Neisse	pooled prevalence estimates for TV - East and Southern Africa: 29.1% (20.9%-37.2%; n=5502); and West and CentralAfrica: 17.8% (12.4%		Table 1 & Figure 2	The dual prevalence of malaria and STIs/RTIs in pregnancy among womenwho attend antenatal care facilities
None	pooled prevalence of HSV: 0.64% (95% CI: 0.10- 1.18)	pooled prevalence of studies on both HSV-1 and HSV-2 was 0.91% (CI:	Figure 2	The prevalence of HSV infection in pregnant women in Iran was higher. HSV infection of the central nervous s
Not specified	Pooled prevalence: 14.2 (9.1 -20.1); OR: 1.73 (95% CI: 1.41-2.12)		Table 1 & Figure 2	
	Chlamydia did not increase prevalence of misscarriage in fixed-effect model (OR (95%CI): 1.231 (0.990–1.530), P=0.062)			
Not specified	Detection of T. vaginalis, was not associated with increased PTB	Infection with T. vaginalis significantly increased the likelihood of any chorioa	Table 2	The overall prevalence of STIs during pregnancy was 16.5% (Trichomonas vaginalis: 3.7%, n = 27) In this
C. trachomatis, candidias	T. vaginalis (OR = 2.98, 95 % CI 1.18–7.56 and AOR = 4.22, 95 %	Co infection with T. vaginalis and C. trachomatis was associated with PROM (O	Table 2 & 3	
Not specified	Testing positive for T. vaginalis at the repeat visit was significantly	associated with preterm births (OR 2.37; 95% CI: 1.11–5.03), low birth v	Table 2,3&4	During study follow-up visits, pregnant women symptomatic for STIs were treated; These specimen collection procedu
Not specified	The proportion of preterm birth, low birthweight, or both, in the inte	There was no group difference in the primary outcome among women with C t	Table 2 & 3	Of 858 women with C trachomatis, N gonorrhoeae, or T vaginalis in the intervention group at enrolment, 98·6% (846 c
Not specified	Genital HSV-2 shedding, HIV-1, Neisseria gonorrhoea, Chlamydia	However with stratification by treatment for a STI, asymptomatic women who	Table 3 & 4	Genital HSV-2 shedding in pregnancy does not appear to alter pregnancy outcomes. Untreated curable STIs (T.vaginalis,
h, spontaneous abortion	There was an increased risk of occurrence of LBW delivery, preterm delivery, and stillbirths among cohorts with incident HSV-2 infection r		Table 6	First episode HSV-2 infection among pregnant women in Benin, Nigeria is associated with an increased risk of occurren
None	There was tendency towards reduction of incidence of PROM at 36 weeks but this was not statistically significant (4.0% versus 10.0%; RR		Table 2	
≥ 2 pathogens	Binary logistic regression also showed that infection with ≥ 2 pathogens (OR 4.9; 95 % CI: 2.2 – 11.6; P = 0.006), CT (OR 3.07; 95 % CI: 1.		Data not shown	The observed high rates of co-infection advocate the necessity of establishing national guidelines and/or screening prog
	Prev: 61 (25.9%) had preterm births, OF THESE, 36 (59.0%) had la	The median gestational age at birth was 38 weeks and 2 days.		
	Crude OR: 1.82 (1.12-2.97); Adjusted OR: 1.65 (1.01-2.71)		Table 3	
	Crude OR: 1.81 (1.24, 2.62); Adjusted OR: 1.78 (1.22-2.6)			Adjusted for maternal age, ethnicity and smoking. Did not end up adjusting for STI co-infection due to collinearity
	Unadjusted PR: 1.24 (1.22, 1.27); Adjusted PR: 1.05 (1.03, 1.08)		Table 3	Adjusted for maternal age, race/ethnicity, education, BMI, marital status, adequacy of prenatal care, insurance status,
	Adjusted OR (aOR) = 1.74, 95% CI, 1.01–3.00, P = 0.045)	This comparism was for Infants born to untreated mothers (n=1364) (who were at significantly higher risk) compared to treated mothers (n=2846) after adjustment for confounding factors.		
	Prev overall = 4.8%, (7/147), among cases = (6.1%, (3/49) and among controls = 4.1% (4/98), overall p-value = 0.584			
HIV	Stillbirth Prev: 5.8% of coinfected women, compared with 1.9% with no HIV/syphilis (OR = 3.09; 95% CI: 1.83 to 5.23); 3.4% with HIV alone (OR = 1.75; 95% CI: 1.03 to 2.9			Women with multiple pregnancies were excluded from analysis, as were those who delivered before arrival at health
	aOR = 1.4, 95% CI: 1.0–1.8). Women with gonorrhea during pregnancy had a 40% increased odds of having an LBW infant compared to women without gonorrhea, when adjusted for marital status and smoking status			
Chlamydia + Gonorrhoea	Unadjusted OR = 0.32; (95%CI: 0.11 - 0.88) For any CT infection i.e CT o	Of the 1373 HIV-infected pregnant women included in this analysis, 938 (68.3%), 409 (29.8%), 19 (1.4%), and 7 (0.5%) women were enrolled from study sites in Brazil, South Africa, Argentina, and the United States, res		

APPENDIX E:

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