DIRECTIONALITY OF HPV INFECTION TRANSMISSION WITHIN HETEROSEXUAL COUPLES

A SYSTEMATIC REVIEW & META-ANALYSIS

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INTRODUCTION

- Most literature on HPV infection comprised of individual-based studies
- EUROGIN 2014 Roadmap suggested greater rates of female-to-male (F-M) compared to male-to-female (M-F) transmission.
  - No formal meta-analytic procedures to assess a differential HPV transmission
- Objective: Assess the evidence for a differential transmission rate hypothesis in heterosexual couple-based studies considering genital-to-genital α-HPV transmission.

SEARCH STRATEGY

Database	Ovid Medline	EMBASE	Scopus	Cochrane Library	ProQuest
Dates	June 7, 2019 & August 15, 2019	June 7, 2019 & August 15, 2019	June 10, 2019 & August 15, 2019	June 10, 2019 & August 15, 2019	June 11, 2019 & August 15, 2019
Terms	(hpv.tw,kf. OR Papillomavirus Infections/tm [Transmission] OR (hpv adj5 transmission).tw,kf OR Papillomaviridae) AND (Heterosexuality/ OR (Male and Female).mp) AND (coitus/ or courtship/ OR Sexual Partner/ OR couples.tw,kf.)	(hpv.tw,kf. OR Papillomavirus Infections/tm [Transmission] OR (hpv adj5 transmission).tw, kf OR Papillomaviridae/) AND (Heterosexuality/ OR (Male and Female).mp) AND (coitus/ or courtship/ OR Sexual Partner/ OR couples.tw,kf.)	HPV OR "papillomavirus infections" OR papillomaviridae AND couples OR "sexual partners" AND heterosexuals	HPV AND couples	HPV OR "Human papillomavirus" AND heterosexual AND couples

No language or year restrictions
Publication dates from inception until search dates

STUDY SELECTION CRITERIA

- Transmission rates of alpha-HPV types reported
- Population included heterosexual couples aged 18 years and over
- Genital samples collected from couples

DATA EXTRACTED

Study Features

- Sample size at baseline
- Sample size used for analysis
- Follow-up length
- Study period
- Geographic location
- Publication Year

Participants' Characteristics

- Age
- Relationship status
- Relationship Length
- Monogamy
- Circumcision status

HPV Detection

- HPV types & species
- Genotyping method
- Sampling interval
- Sample collection
- Sexual activity instructions prior to visit

Quantitative Data

- Events and person-time
- F-M and M-F transmission rates
- HPV prevalence in both sexes
- Type-specific HPV rates

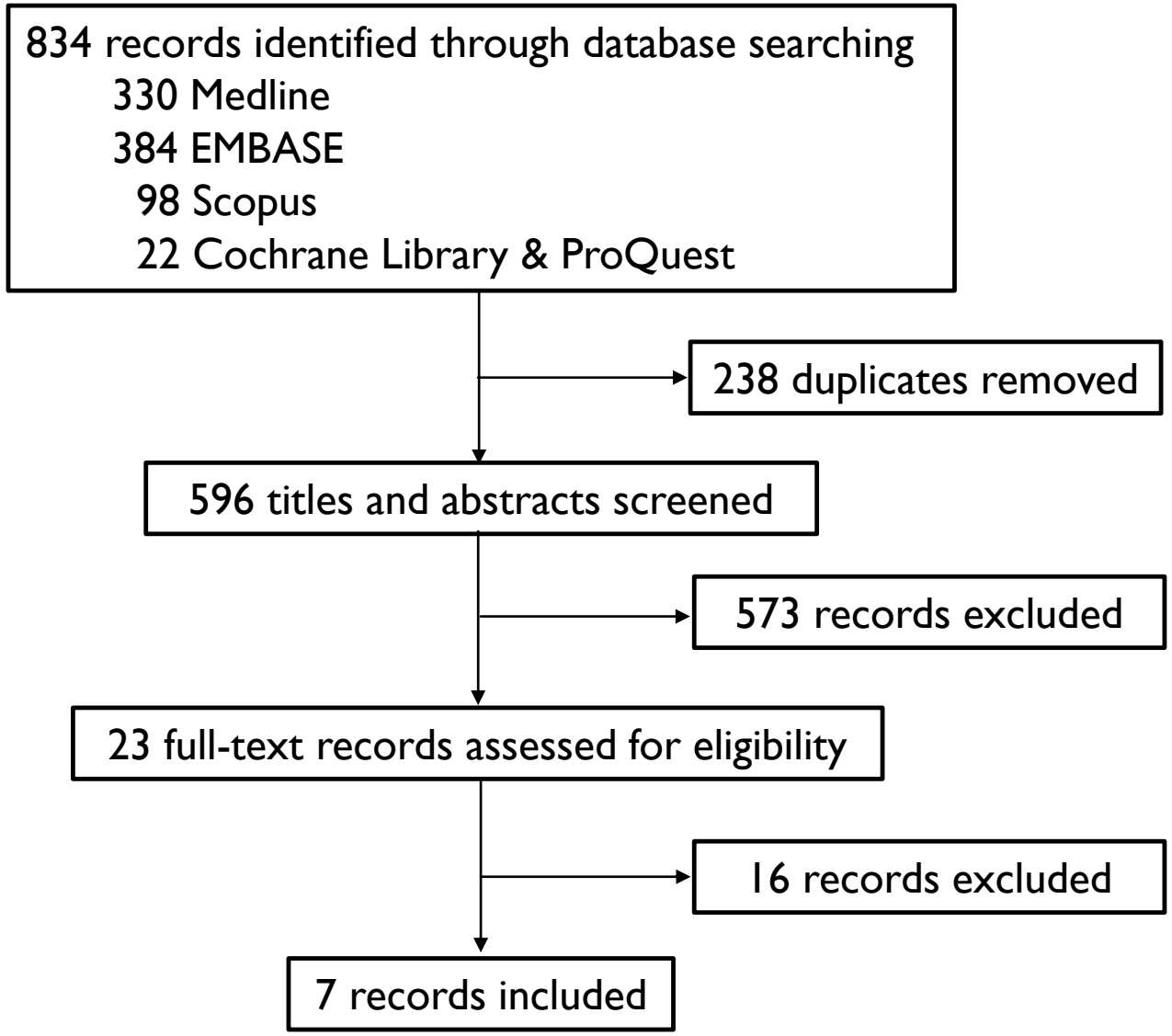
STATISTICAL ANALYSES

$$Rate = \frac{Events}{Person - Time}$$

$$Person - Time = \frac{Events}{Rate}$$

- *Metafor* to pool transmission rates with generalized linear mixed model and *Meta* to pool transmission rate difference with inverse variance method
- Removed outliers to explore their impact
- HPV type-specific preponderance – identified and counted occurrences of directionality preponderance (F-M or M-F) for each HPV type
- Subgenera HPV rates – summing type-specific HPV rates corresponding to HPV types in each subgenus group

FLOW CHART


834 records identified through database searching
330 Medline
384 EMBASE
98 Scopus
22 Cochrane Library & ProQuest
238 duplicates removed
596 titles and abstracts screened
573 records excluded
23 full-text records assessed for eligibility
16 records excluded
7 records included

STUDY CHARACTERISTICS

Authors, year	Country (study period)	Baseline (analysis) sample size	Follow-up length (months)	Mean age (years)	Relationship status
Hernandez et al., 2008	USA (2005 - 2006)	38 (25)	Mean: 7.5	Women: 26, range: 18-57 Men: 28, range: 18-59	Dating (48%), married (8%), separated (12%), cohabitating (32%)
Burchell et al., 2011	Canada (2005 - 2010)	308 (179)	Median: 5.5 (range 1.8-15.5)	Women: 21.5 Men: 23.9	Dating
Mbulawa et al., 2013	South Africa (2006 - 2009)	486 (NR)	24	Women: 35, range: 18-66 Men: 38, range: 19-67	Partner
Widdice et al., 2013	USA (2006 - 2007)	25 (25)	1.5	Women: 22.6 Men: 25.5	Partner
Nyitray et al., 2014	USA (2006 - 2010)	137 (65)	Median: 25	Women: 33, range: 18- 70 Men: 33, range: 18-70	Partner (dating, married, and cohabitating)
Liu et al., 2015	China (2009 - 2013)	874 (296)	Median for men: 35.7 Median for women: 30.5	Women: 44, range: 39-52.5 Men: 44, range: 39-54	Married
Su et al., 2019	China (2014 - 2016)	390 (97)	Median: 12.5	Women - median: 40, range: 32-46 Men - median: 42, range: 35-49	Married

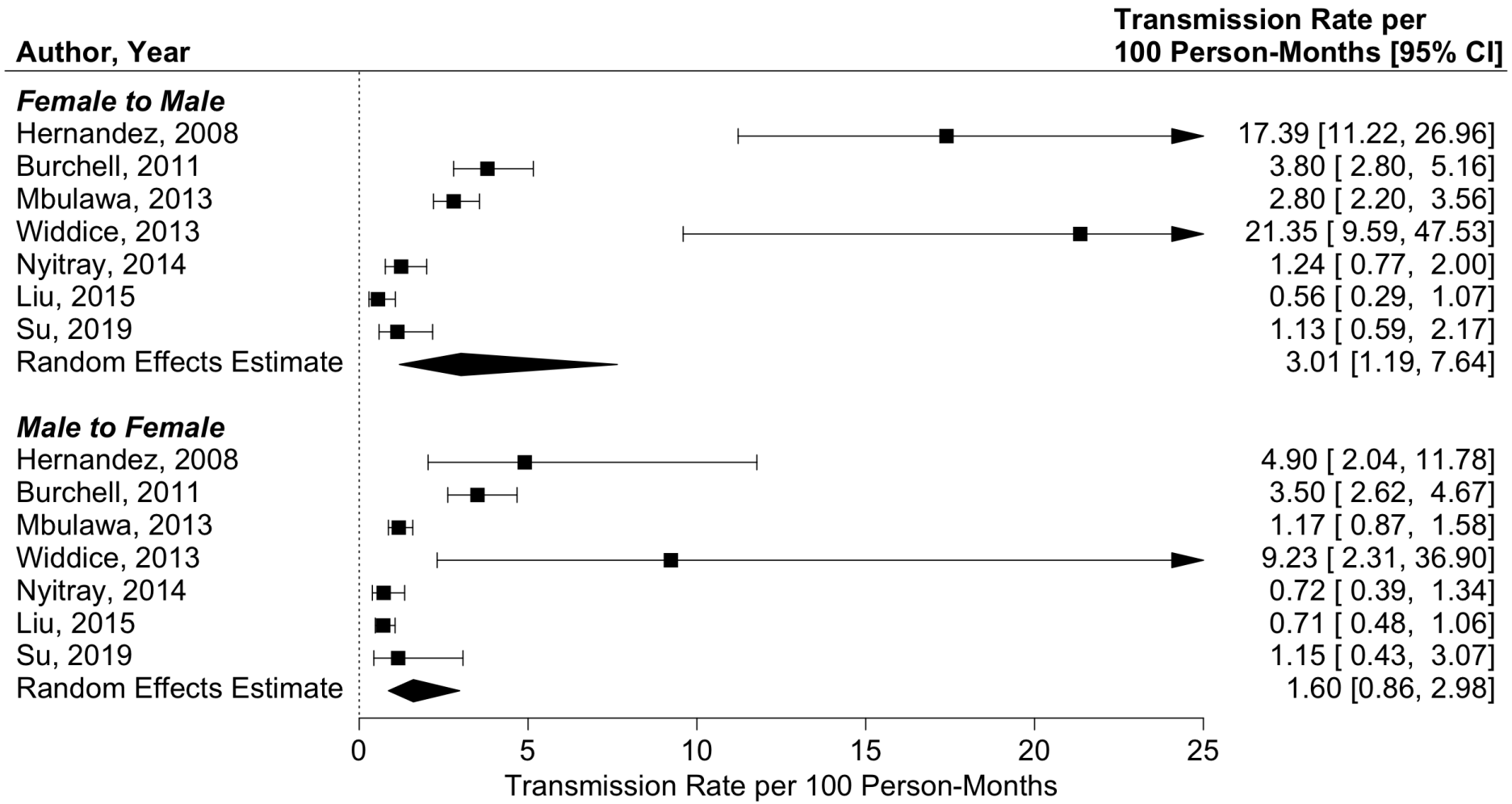
CHARACTERISTICS, *CONT'D*

Authors, year	Relationship length (months)	Reported monogamy	Instructions prior to visit	Circumcision (%)
Hernandez et al., 2008	NR	100% of couples	NR	80
Burchell et al., 2011	Mean: 4	65% of females and 74% of males were monogamous with transmitting partner	Abstain from oral, vaginal, or anal sex for 24 hours	57
Mbulawa et al., 2013	Median: 40.8	NR	NR	3.4
Widdice et al., 2013	- Women median: 32 - Men Median: 26	92% of couples	Intercourse 24 hours before visit 2 Abstain from sexual interaction before visit 3 Engage in normal sexual behaviors for remaining visits (4-6)	64
Nyitray et al., 2014	Median: 42	83% of men and women (6 months prior to enrollment)	Abstain from sexual activity for 48 hours	NR
Liu et al., 2015	NR	NR	No instructions given	NR
Su et al., 2019	NR	96.5% of men and 97.9% of women (year prior to enrollment)	Abstain from sexual activity for 48 hours	NR

SAMPLING & HPV DETECTION

- Sampling interval between visits ranged from 24 hours (Widdice et al.) to 6 months (Mbulawa et al., Nyitray et al., Liu et al., Su et al.)
- PGMY09/11 primer set to detect 36 HPV types
  - Burchell et al., Hernandez et al., Mbulawa et al., Nyitray et al., & Widdice et al.
- SPF1/GP6+ primer set to detect 46 HPV types
  - Liu et al.
- GP51/61 primer set to detect 16 HPV types.
  - Su et al.

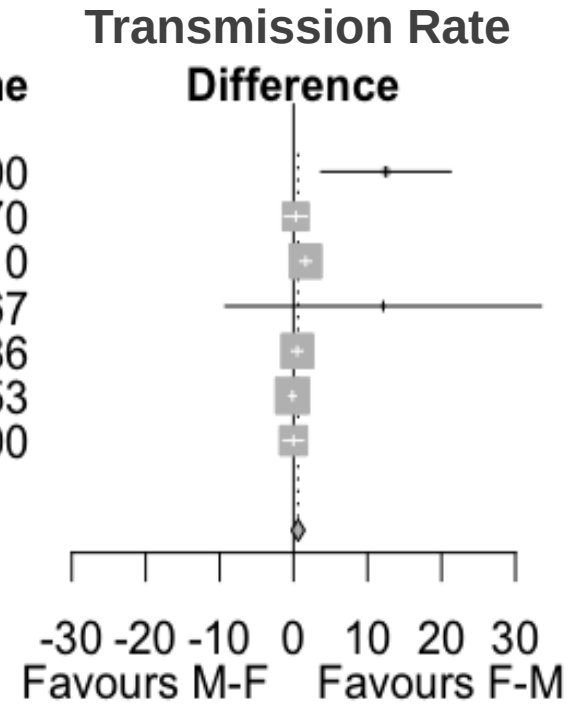
INDIVIDUAL & POOLED ESTIMATES



RATE DIFFERENCE

Study	F-M Events	F-M Time	M-F Events	M-F Time	TRD Estimate	95% CI	Weight
Hernandez et al., 2008	20	115.00	5	102.00	12.49	[3.74; 21.24]	1.0%
Burchell et al., 2011	41	1079.80	46	1313.70	0.30	[-1.25; 1.84]	14.5%
Mbulawa et al., 2013	66	2359.00	42	3586.10	1.63	[0.86; 2.39]	21.8%
Widdice et al.,2013	6	28.10	2	21.67	12.12	[-9.22; 33.47]	0.2%
Nyitray et al., 2014	17	1382.11	10	1369.86	0.50	[-0.24; 1.24]	22.0%
Liu et al., 2015	9	1618.71	24	3375.53	-0.16	[-0.62; 0.31]	24.3%
Su et al., 2019	9	796.00	4	347.00	-0.02	[-1.37; 1.33]	16.2%
Random effects model					**0.61**	**[-0.27; 1.49]**	**100.0%**

Heterogeneity: I^2 = 75%, τ^2 < 0.0001, p < 0.01



SENSITIVITY ANALYSIS

Study	F-M Events	F-M Time	M-F Events	M-F Time	TRD Estimate	95% CI	Weight
Burchell et al., 2011	41	1079.80	46	1313.70	0.30	[-1.25; 1.84]	13.2%
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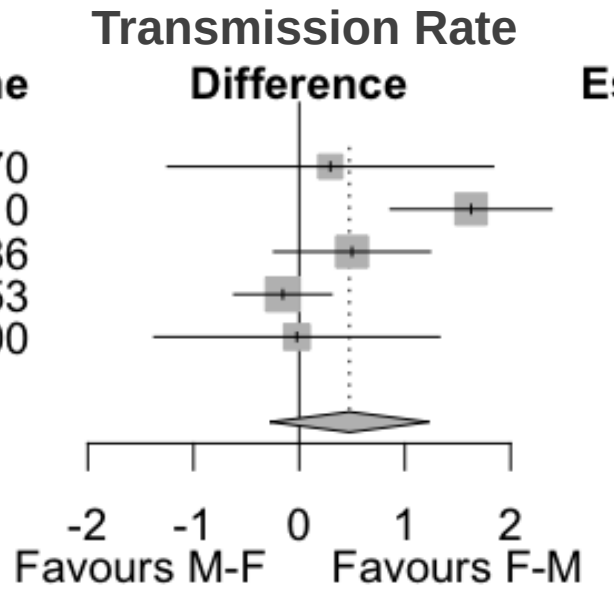
Su et al., 2019	9	796.00	4	347.00	-0.02	[-1.37; 1.33]	15.1%
Random effects model					**0.48**	**[-0.28; 1.23]**	**100.0%**

Heterogeneity: I^2 = 75%, τ^2 < 0.0001, p < 0.01



HPV TYPE-SPECIFIC RATES DIRECTIONALITY PREPONDERANCE

HPV genotype	Incidence rates, Nyitray et al., 2014		Incidence rates, Mbulawa et al., 2012		Transmission rates, Liu et al., 2015	
	Men	Women	Men	Women	M-F	F-M
HPV11	0.15	0.00	0.19	0.04	0.00	2.70
HPV16	0.38	0.28	0.32	0.20	1.09	0.25

	Nyitray et al., 2014	Mbulawa et al., 2012	Liu et al., 2015
No. of M-F > No. of F-M transmission rates	0	0	1
No. of F-M > No. of M-F transmission rates	2	2	1

HPV TYPE-SPECIFIC RATES

HPV genotype	Incidence rates, Nyitray et al., 2014[2]		Incidence rates, Mbulawa et al., 2012[¤]		Transmission rates, Liu et al., 2015 [†]	
	Men	Women	Men	Women	M-F	F-M
HPV2	NT	NT	NT	NT	0	0
HPV3	NT	NT	NT	NT	0.00	4.18
HPV6	0.32	0.32	0.17	0.18	15.79	0.00
HPV7	NT	NT	NT	NT	0	0
HPV10	NT	NT	NT	NT	0	0
HPV11	0.15	0.00	0.19	0.04	0.00	2.70
HPV16	0.38	0.28	0.32	0.20	1.09	0.25
HPV18	0.10	0.16	0.34	0.11	0	0
HPV26	0	0	0.00	0.04	0	0
HPV27	NT	NT	NT	NT	0	0
HPV29	NT	NT	NT	NT	0	0
HPV30	NT	NT	NT	NT	1.40	0.00
HPV31	0.14	0.19	0.14	0.04	15.46	0.00
HPV32	NT	NT	NT	NT	0	0
HPV33	0.04	0.05	0.09	0.11	4.02	0.00
HPV34	0	0	NR	NR	NT	NT
HPV35	0.04	0.18	0.34	0.28	3.84	0.00
HPV39	0.29	0.14	0.31	0.22	0	0
HPV40	0.09	0	0.14	0.07	0	0
HPV42	0.09	0.09	0.14	0.11	0	0
HPV43	NT	NT	NT	NT	0	0
HPV44	0.14	0.28	0.35	0.07	0	0
HPV45	0	0.18	0.36	0.18	0.00	3.76
HPV51	0.36	0.32	0.32	0.20	0	0
HPV52	0.37	0.14	0.32	0.26	15.46	0.00
HPV53	0.29	0.24	0.43	0.23	0	0

HPV genotype	Incidence rates, Nyitray et al., 2014[2]		Incidence rates, Mbulawa et al., 2012[¤]		Transmission rates, Liu et al., 2015 [†]	
	Men	Women	Men	Women	M-F	F-M
HPV54	0.33	0.24	0.32	0.23	0.55	0.00
HPV56	0.14	0.09	0.09	0.15	0	0
HPV57	NT	NT	NT	NT	0.23	1.55
HPV58	0.05	0.05	0.46	0.21	1.18	0.49
HPV59	0.05	0.14	0.26	0.11	0	0
HPV61	0.09	0.14	0.76	0.44	NT	NT
HPV62	0.39	0.42	1.06	0.57	0	0
HPV66	0.29	0.20	0.55	0.22	NT	NT
HPV67	0.04	0.05	0.02	0.02	0.78	0.00
HPV68	0.14	0.09	0.44	0.09	2.70	0.00
HPV69	0	0	0.16	0.18	0	0
HPV70	0.14	0.09	0.47	0.20	0	0
HPV71	0	0	0.29	0.23	NT	NT
HPV72	0.18	0.09	0.52	0.37	NT	NT
HPV73	0.09	0.09	0.19	0.20	NT	NT
HPV74	NT	NT	NT	NT	0	0
HPV75	NT	NT	NT	NT	0	0
HPV81	0.05	0.14	0.32	0.16	0	8.15
HPV82	0.09	0.05	0.16	0.13	0	0
HPV83	0.23	0.23	0.32	0.27	0	0
HPV84	0.34	0.28	0.47	0.31	0	0
HPV87	NT	NT	NT	NT	1.96	1.59
HPV89	0.50	0.40	0.32	0.11	0.00	3.40
HPV90	NT	NT	NT	NT	0.84	0
HPV91	NT	NT	NT	NT	2.24	0
HPV94	NT	NT	NT	NT	0	0

HPV DIRECTIONALITY PREPONDERANCE

	Nyitray et al., 2014	Mbulawa et al., 2012	Liu et al., 2015
No. of M-F > No. of F-M transmission rates	11	6	14
No. of F-M > No. of M-F transmission rates	16	29	6

HPV GROUPED RATES

Subgenera	Nyitray et al., 2014 Incidence rates per 100 PM		Mbulawa et al., 2012 Incidence rates per 100 PM		Liu et al., 2015 Transmission rates per 100 PM	
	Male	Female	Male	Female	M-F	F-M
Subgenus 1 *(non-carcinogenic)*	1.12	0.93	0.94	0.62	18.58	2.70
Subgenus 2 *(carcinogenic)*	3.04	2.73	5.77	3.39	45.94	4.50
Subgenus 3 *(commensal)*	1.78	1.70	4.05	2.46	3.03	18.87

PM = Person-Months, M-F = Male-to-Female, F-M = Female-to-Male

CONCLUDING REMARKS

- First systematic review and meta analysis to examine genital-to-genital α-HPV transmission dynamics between heterosexual partners
- 2 more articles identified in addition to EUROGIN 2014 Roadmap
- Small evidence for differential transmission rate with higher F-M compared to M-F transmission
- Presence of substantial statistical heterogeneity

REFERENCES

Burchell, A. N., Coutlée, F., Tellier, P. P., Hanley, J., & Franco, E. L. (2011). Genital transmission of human papillomavirus in recently formed heterosexual couples. *Journal of Infectious Diseases*, *204*(11), 1723- 1729.

Hernandez, B. Y., Wilkens, L. R., Zhu, X., Thompson, P., McDuffie, K., Shvetsov, Y. B., ... & Goodman, M. T. (2008). Transmission of human papillomavirus in heterosexual couples. *Emerging infectious diseases*, *14*(6), 888.

Liu, M., He, Z., Zhang, C., Liu, F., Liu, Y., Li, J., ... & Pan, Y. (2015). Transmission of genital human papillomavirus infection in couples: a population-based cohort study in rural China. *Scientific reports*, *5*, 10986.

Mbulawa, Z. Z., Johnson, L. F., Marais, D. J., Coetzee, D., & Williamson, A. L. (2013). The impact of human immunodeficiency virus on human papillomavirus transmission in heterosexually active couples. *Journal of Infection*, *67*(1), 51-58.

Nyitray, A. G., Lin, H. Y., Fulp, W. J., Chang, M., Menezes, L., Lu, B., ... & Giuliano, A. R. (2013). The role of monogamy and duration of heterosexual relationships in human papillomavirus transmission. *The Journal of infectious diseases*, *209*(7), 1007-1015.

Su, Y., Wei, F., Huang, X., Li, Y., Qiu, L., Hu, F., ... & Wu, T. (2019). Prevalence, Concordance, and Transmission of Human Papillomavirus Infection Among Heterosexual Couples in Liuzhou, China: An Observational Perspective Study. *The Journal of infectious diseases*.

Widdice, L., Ma, Y., Jonte, J., Farhat, S., Breland, D., Shiboski, S., & Moscicki, A. B. (2013). Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *The Journal of infectious diseases*, *207*(8), 1286-1294.