Quantifying HIV transmission by age from cross-sectional viral phylogenetic deep sequence data: a population-based study in Rakai, Uganda

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Imperial College London

PANGEA HIV

Rakai Health Sciences Program
Improved Health Through Research

HIV transmission cycle

The cycle of infection in South Africa

Young women between 16 and 23 acquire HIV from older men.

Men between 23 and 35 have a high incidence of HIV.

Mean: 27

Women in their mid-20s infect and are infected by similarly aged men.

Mean: 18

Mean: 26

Age

16   20   25   30   35
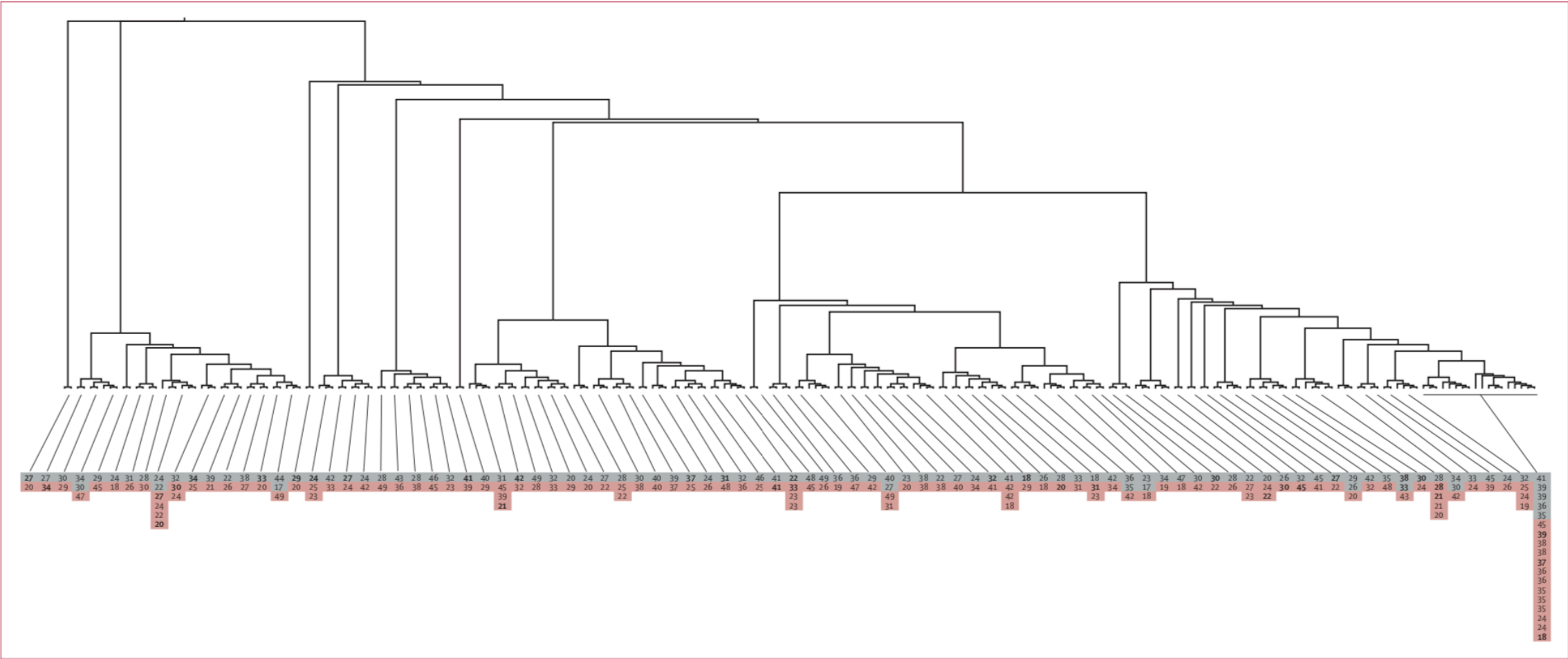
HIV phylogenetic analysis, KZN, 2014-2015

Figure 2: Maximum likelihood tree for 90 heterosexual transmission clusters
Clusters with a bootstrap support higher than 90% and whose sequences had an intraclade genetic distance of 4·5% or less. 123 women were linked to 103 men in the 90 heterosexual clusters. For better visualisation of the clusters, the tree is represented with proportional branch length transformation. The age (years) of the individuals in each transmission cluster is presented inside the boxes. Grey boxes represent men and red boxes represent women.

Figure from: de Oliveira et al. Lancet HIV 2017

HIV phylogenetic analysis, KZN, 2014-2015

		Men (n=103)			Total
		<25 years (7·6%)	25–40 years (40·3%)	41–49 years (47·2%)	
Women (n=123)	<25 years (22·3%)	18	37	5	60
	25–40 years (59·8%)	13	58	21	92
	41–49 years (50·1%)	2	24	10	36
Total		33	119	36	188

Figure 3: All possible pairings from 90 clusters of men and women stratified by age group
The community-based HIV prevalence in each age group is shown in parentheses.

- F<25 linked with M25+: 42/60 = 70% (95% CI 57%-80%)

- F<25 linked with any M: average age difference 8.7 yrs

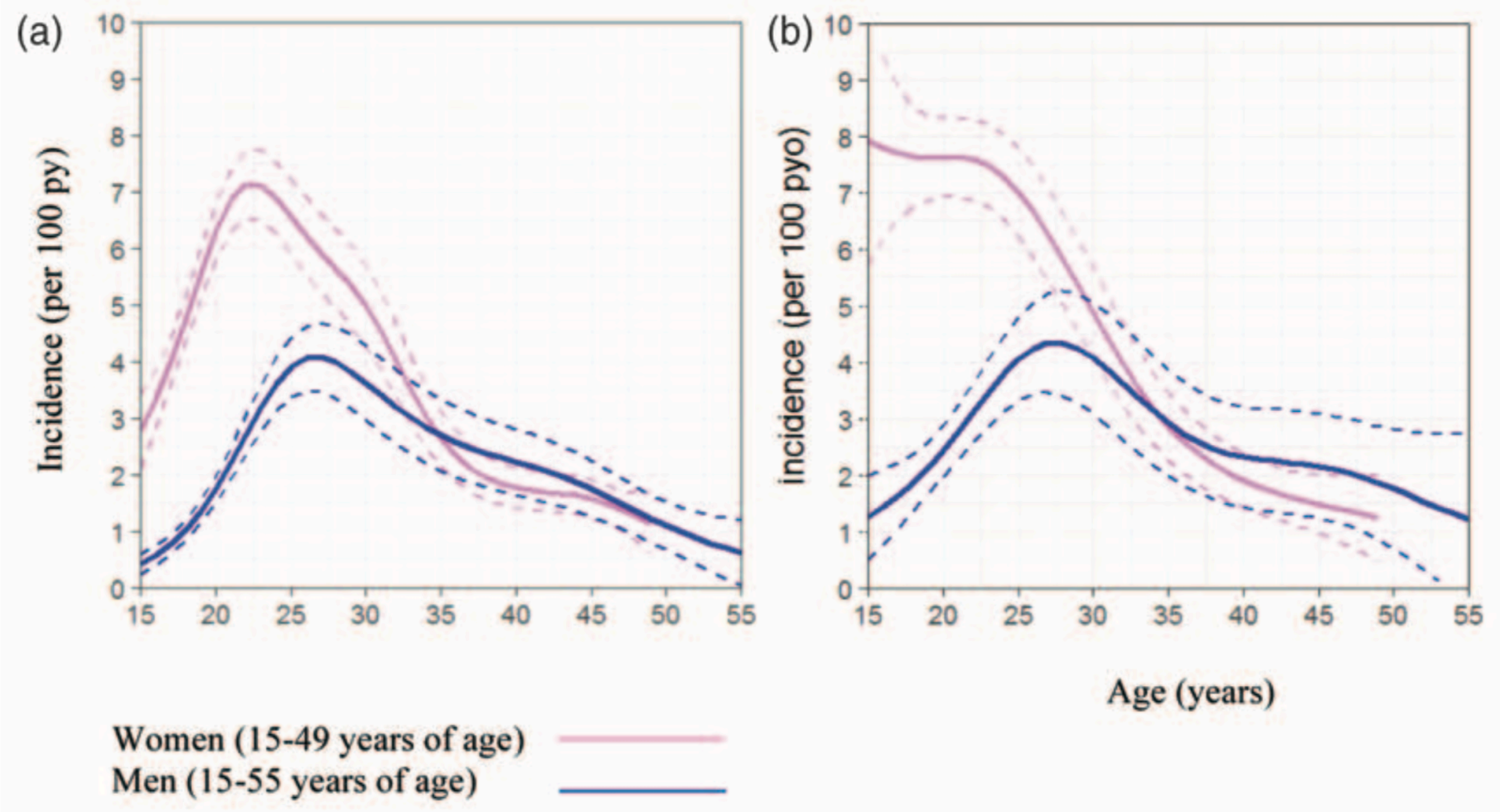- Suggesting that such age-discordant pairings may be important driver of epidemic

Figure from: de Oliveira et al. Lancet HIV 2017

Association HIV incidence with partner age, primarily Durban area, 2009-2012

TABLE 2. Association Between Age-Disparate Relationship and HIV-1 Infection Within 1 Year

|	HIV Infections/ Person-Years	HIV Incidence* (95% CI)	Univariate Model† HR (95% CI)	Multivariable Model‡ HR (95% CI)
Primary analysis				
All participants	243/3343.57	7.27 (6.41 to 8.24)		
Primary partner >5 yrs older				
Yes	67/871.84	7.68 (6.05 to 9.76)	1.10 (0.82 to 1.45)	1.17 (0.88 to 1.56)
Do not know partner age	5/70.36	7.11 (2.96 to 17.07)	0.97 (0.40 to 2.37)	0.98 (0.40 to 2.39)
No	171/2401.37	7.12 (6.13 to 8.27)	1.00	1.00
Primary partner >10 yrs older				
Yes	10/160.43	6.23 (3.35 to 11.58)	0.87 (0.46 to 1.64)	1.01 (0.53 to 1.92)
Do not know partner age	5/70.36	7.11 (2.96 to 17.07)	0.94 (0.39 to 2.29)	0.94 (0.38 to 2.28)
No	228/3112.78	7.32 (6.43 to 8.34)	1.00	1.00
Participants <25 yrs	172/1877.54	9.16 (7.89 to 10.64)		
Primary partner >5 yrs older				
Yes	47/480.43	9.78 (7.35 to 13.02)	1.09 (0.78 to 1.53)	1.13 (0.80 to 1.59)
Do not know partner age	4/35.30	11.33 (4.25 to 30.19)	1.17 (0.43 to 3.18)	1.13 (0.41 to 3.09)
No	121/1361.81	8.89 (7.43 to 10.62)	1.00	1.00

- VOICE trial, South African sites

- 3789 women, 2143 aged <25

- Suggesting age-discordant relationships may not be driver of epidemic among young women

Figure from: Baltus et al. JAIDS 2015

Incidence estimates may vary by reporting behavior

- Africa Centre DSS, 2004-2015

- 10260 women, 7251 reporting age of most recent partner

Women (15-49 years of age)
Men (15-55 years of age)

Figure from: Akullian et al. AIDS 2017

Association HIV incidence with partner age, KZN, predicted at 2009
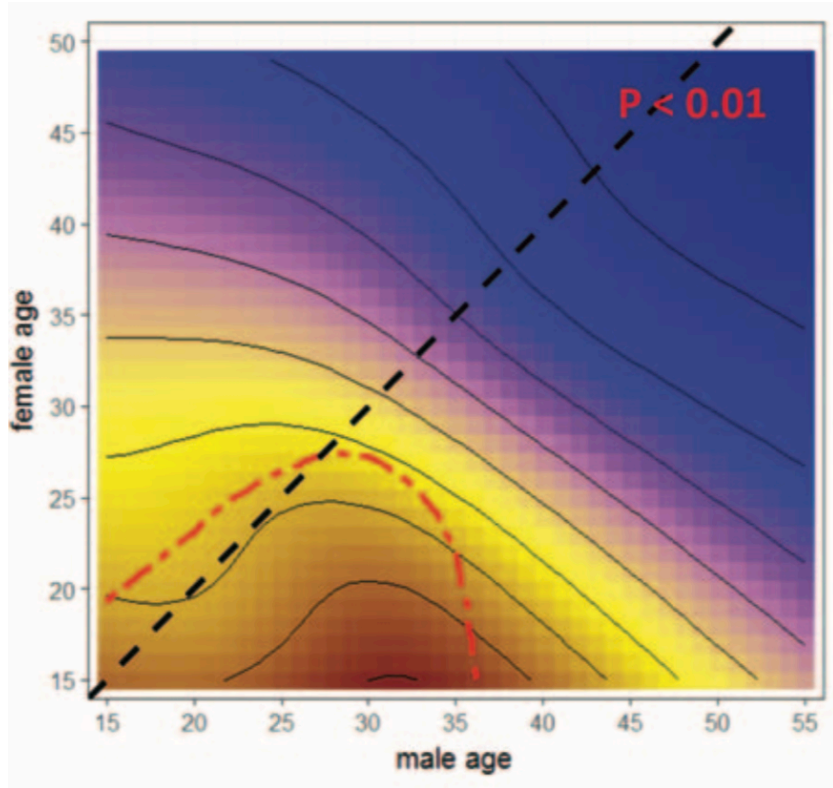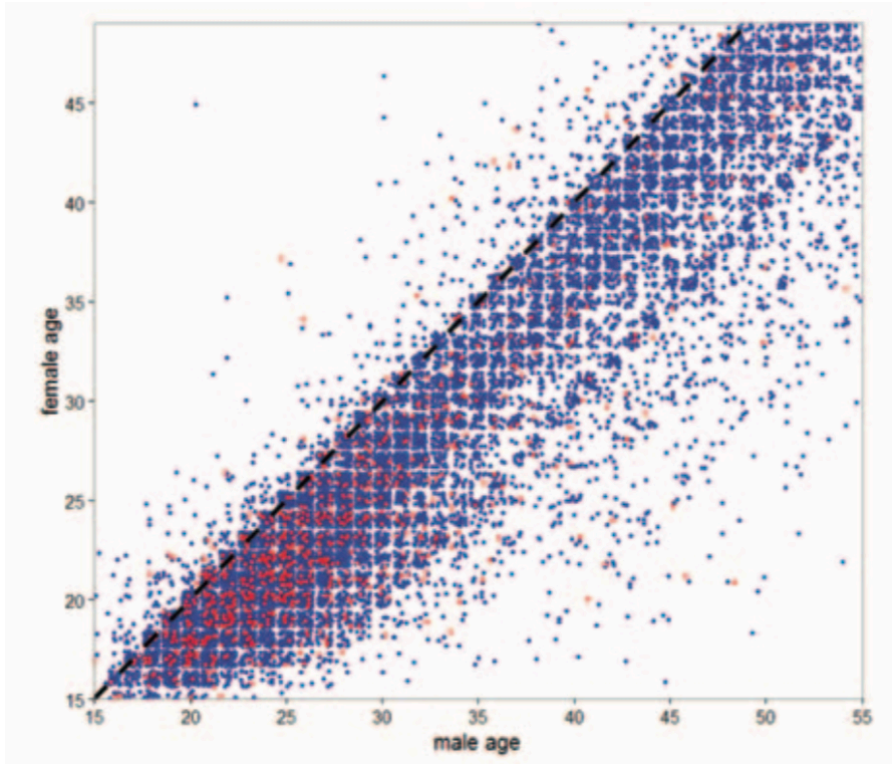
- Africa Centre DSS, 2004-2015

- Considering 7251women reporting age of most recent partner

Figures from: Akullian et al. AIDS 2017

Study objective

- Estimate proportion of infections among women that are attributable to older men using deep-sequence data

- South-eastern Uganda, MRC/UVRI and Rakai

Convenience sample, MRC/UVRI, 2014-2017

Figure from: Dwyer Lindgren et al. Nature 2019

Figure from: Bbosa et al. Viruses 2020

Convenience sample, MRC/UVRI, 2014-2017

- 72 source-recipient pairs between men and women

- 22 pairs involving female recipient <25 at enrollment

	Estimated sources of infection among study participants, based on data excluding same-sex pairs* (mean, 95% credibility interval of posterior density)			
	Men 18–24 years	Men 25–59 years	Women 18–24 years	Women 25–59 years
Recipient				
Women 18–24 years	34.7% (17.1%–55.9%	65.3% (44.1%–82.9%)	--	--
Women 25–59 years	27.7% (14.1%–45.7%)	72.3% (54.3%–85.9%)	--	--

Rakai study area

Figure from: Dwyer Lindgren et al. Nature 2019

Figure from: Ratmann et al. Lancet HIV 2020

Population-based deep-sequence data, Rakai, 2011/08/10-2015/01/30
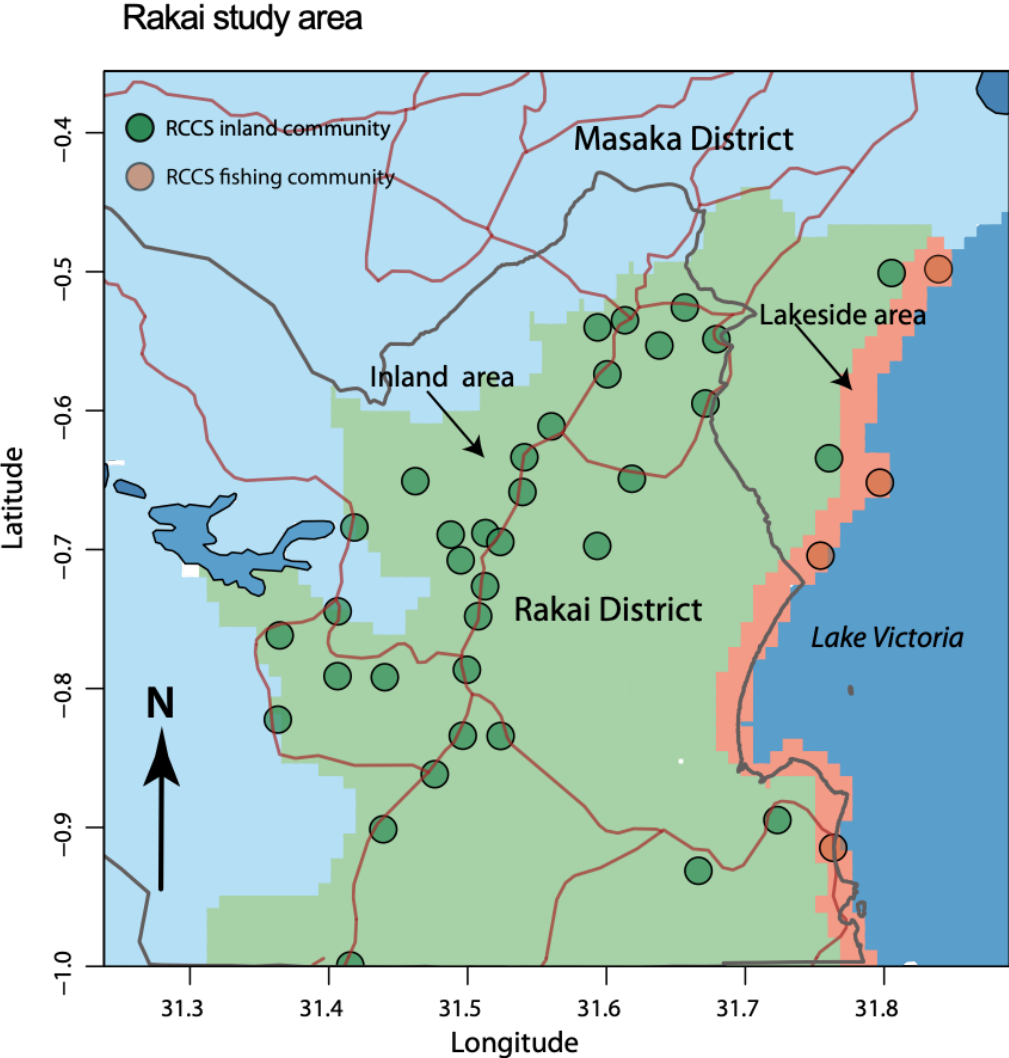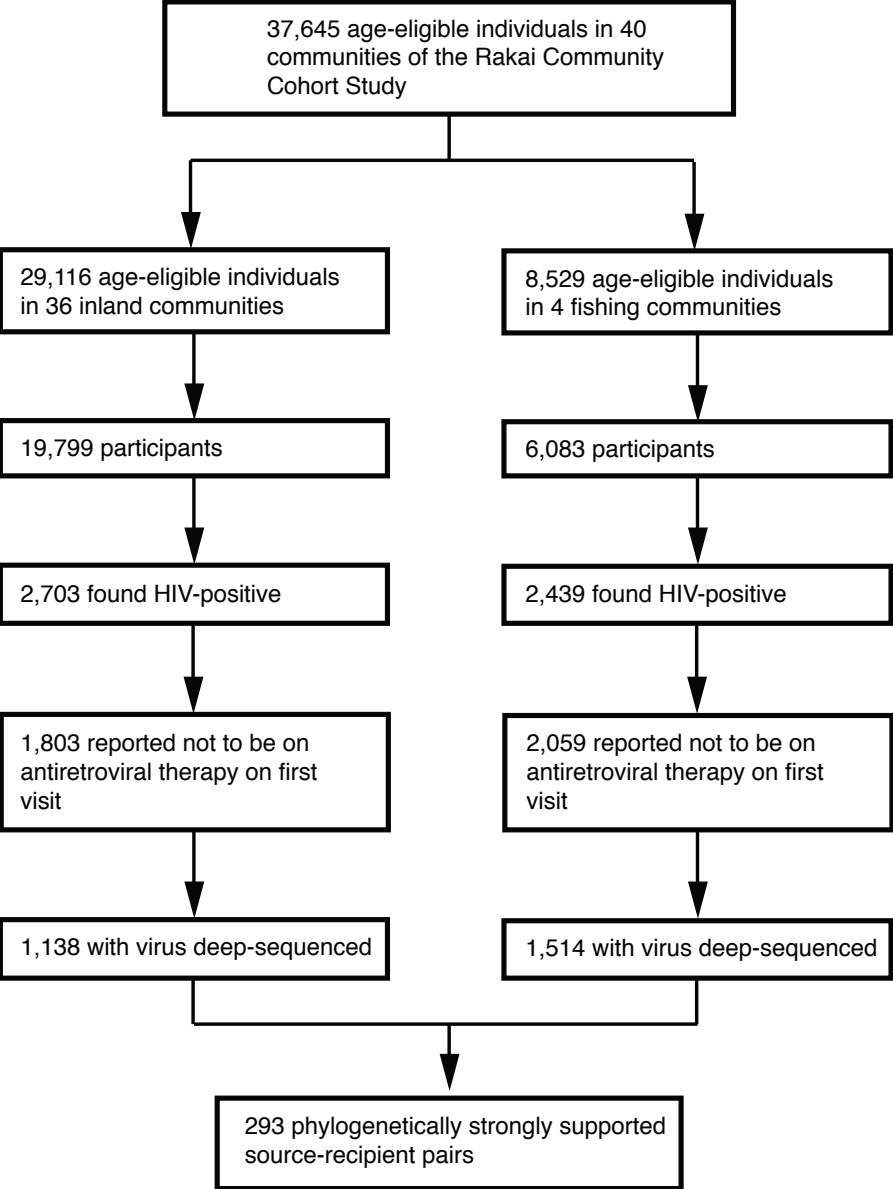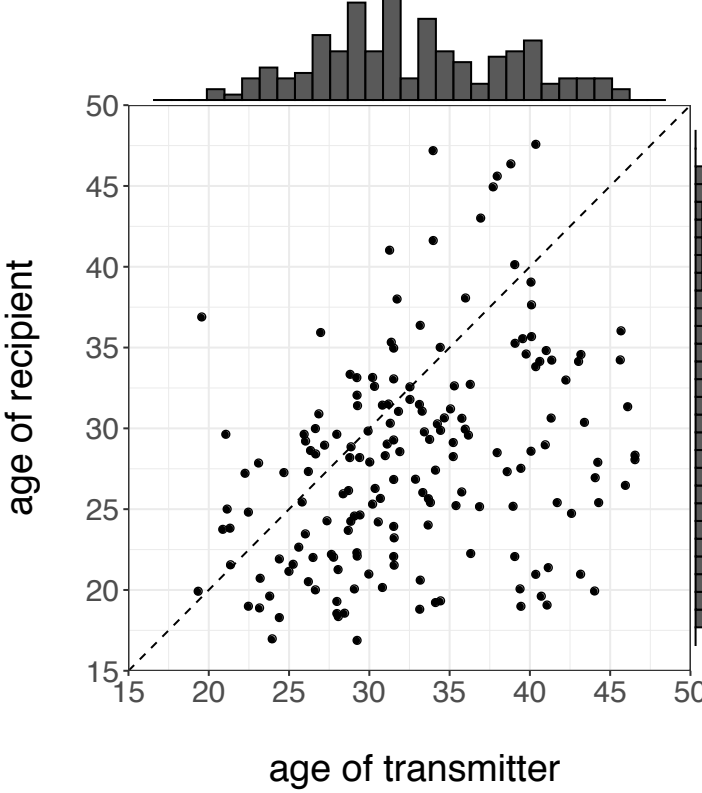

Figure from: Ratmann et al. Lancet HIV 2020

Source-recipient pairs by age

from female to male

age of recipient

age of transmitter

n=120

from male to female

age of recipient

age of transmitter
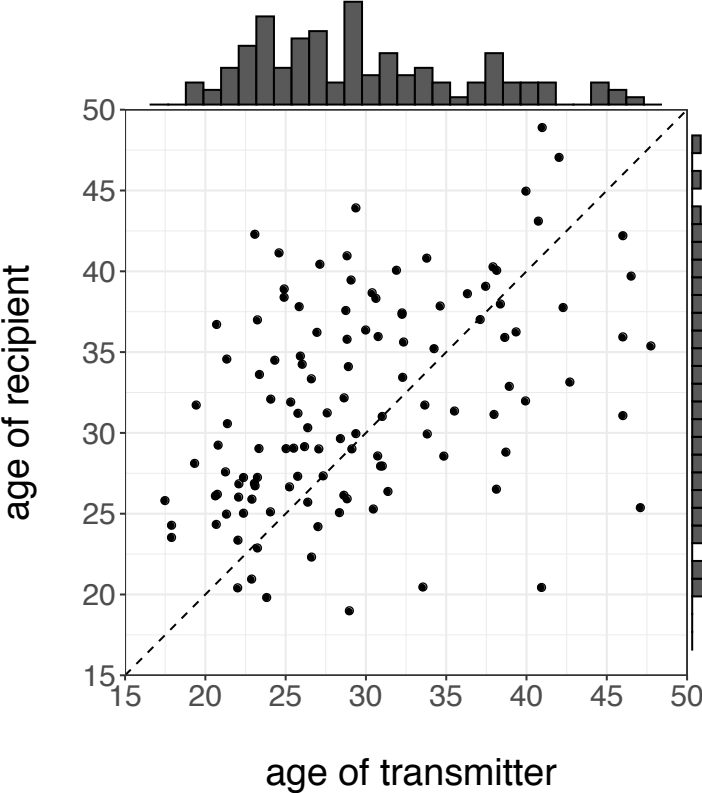
n=173

- 96 source-recipient pairs involving women <25

- 57 source-recipient pairs with female recipient <25

Xi et al. in preparation

Adjusting for sampling cascade
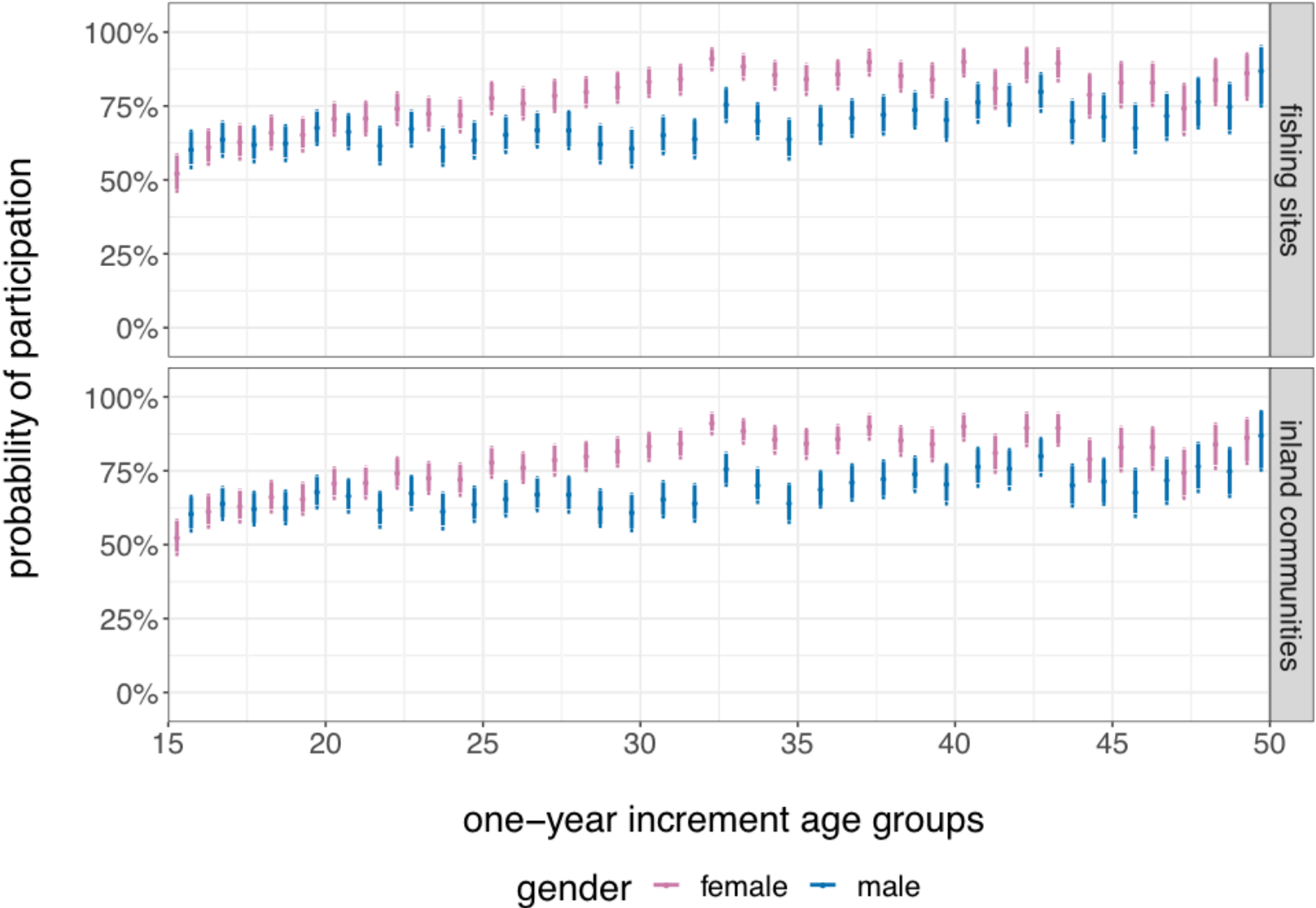
Fit of statistical flow model

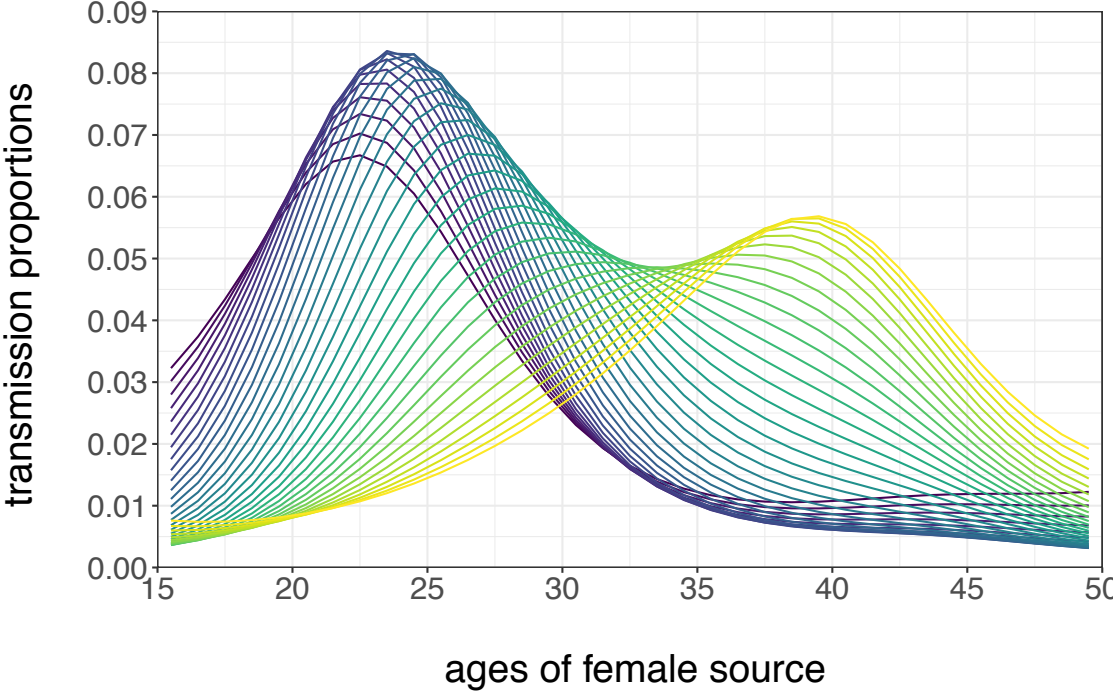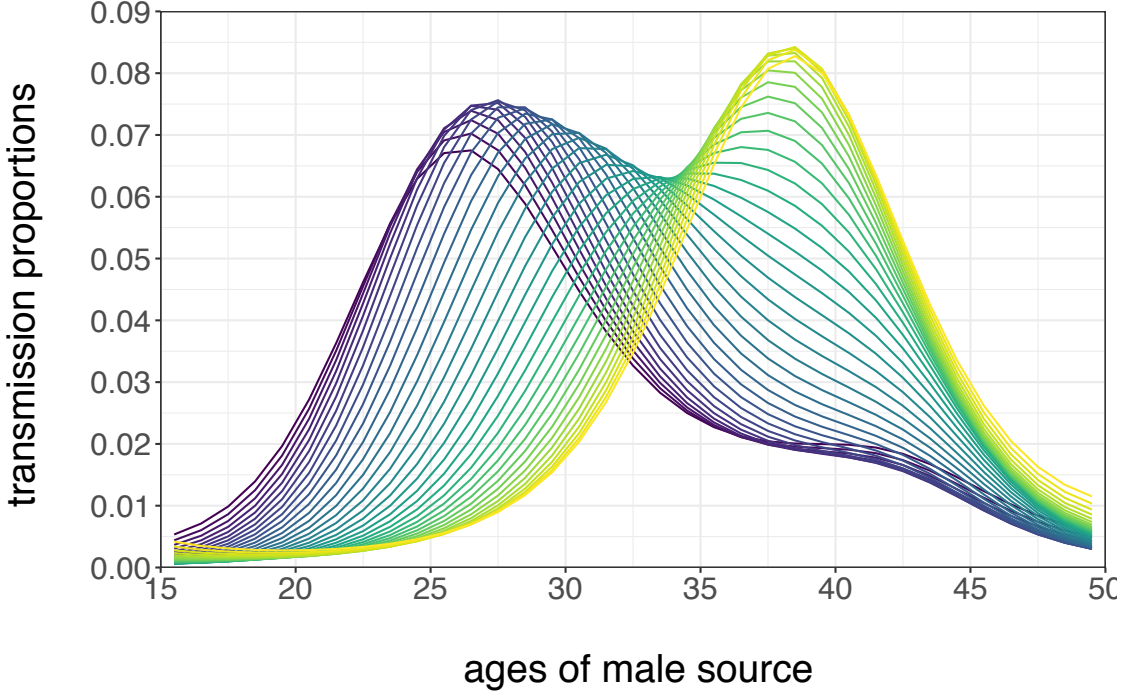from female to male
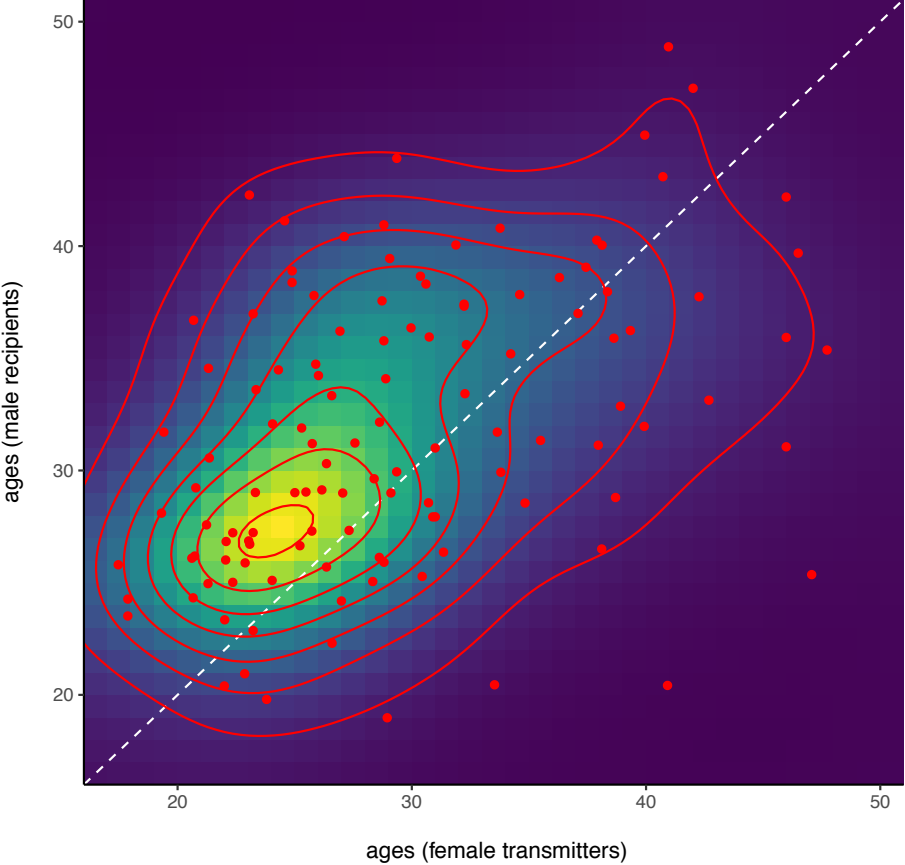
from male to female

n=120
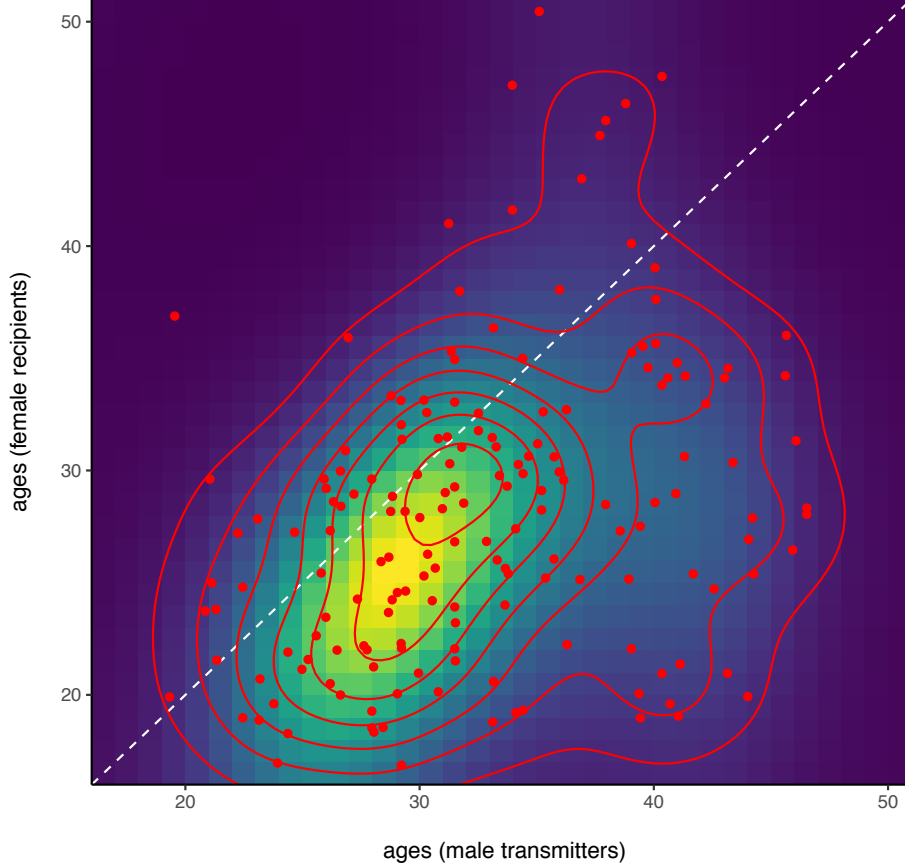
n=173

Age of sources
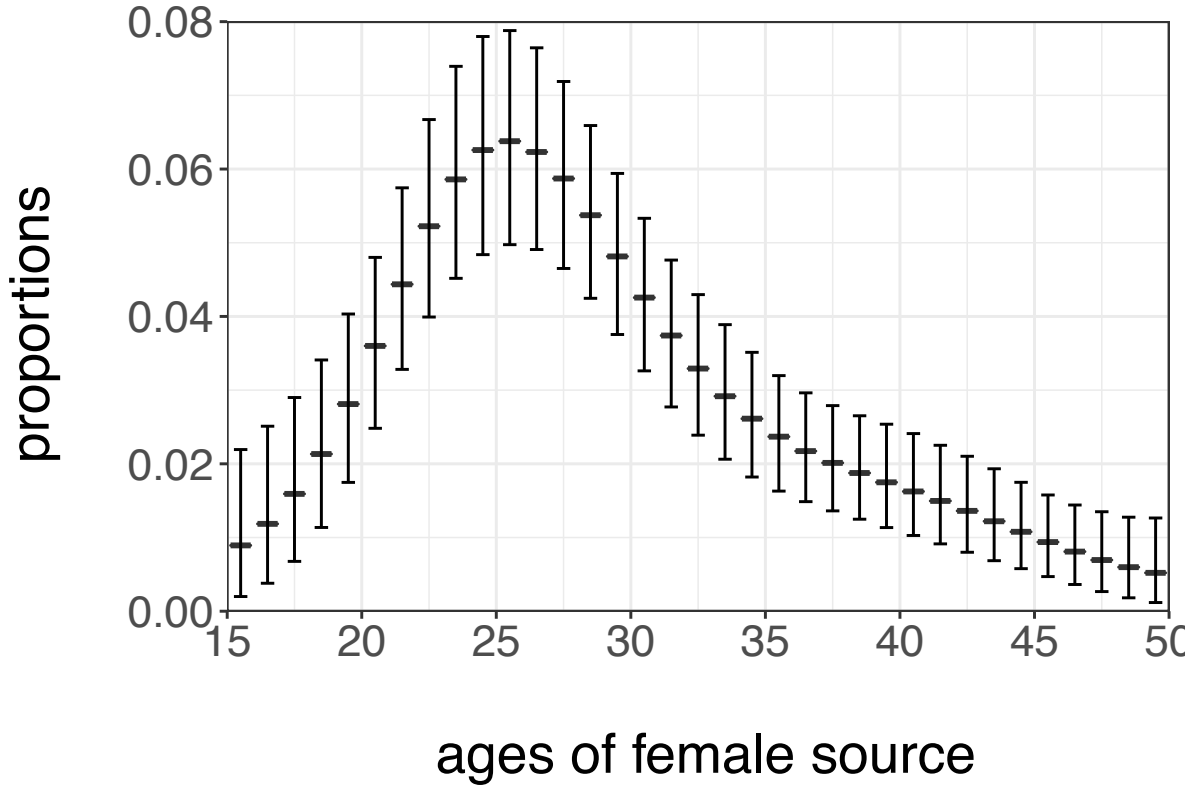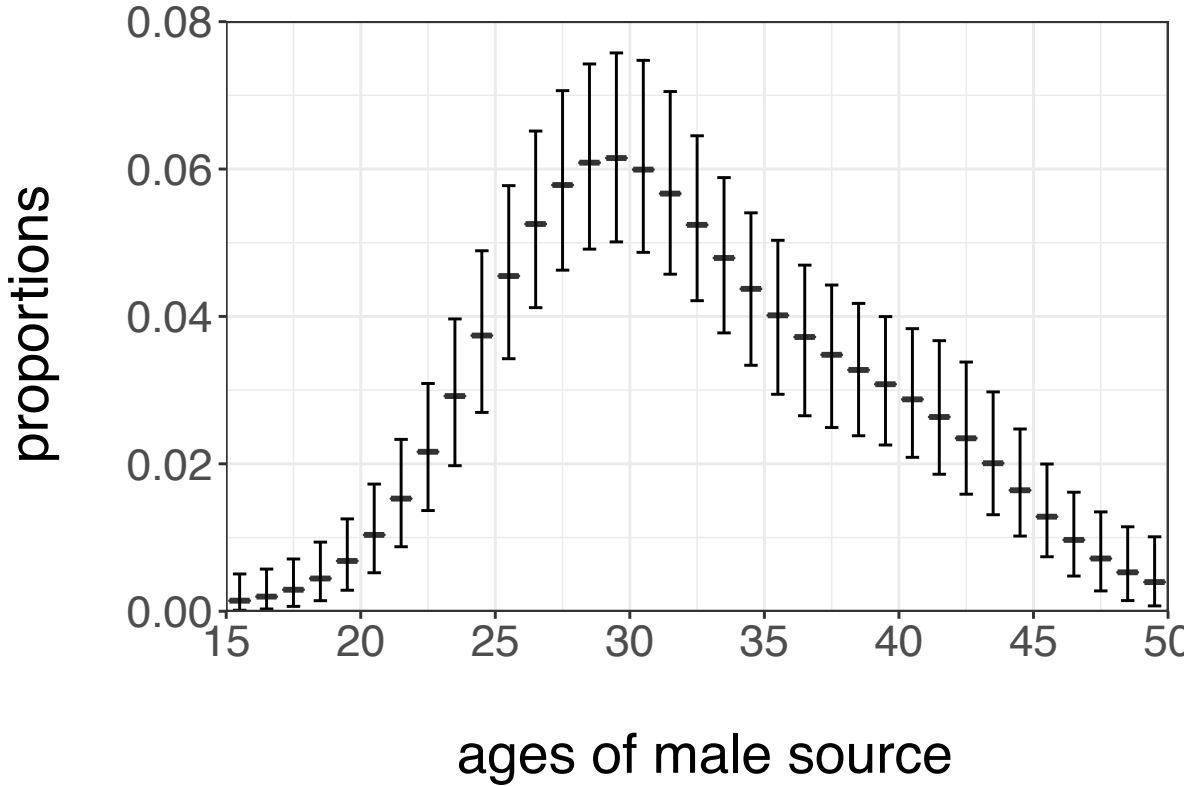
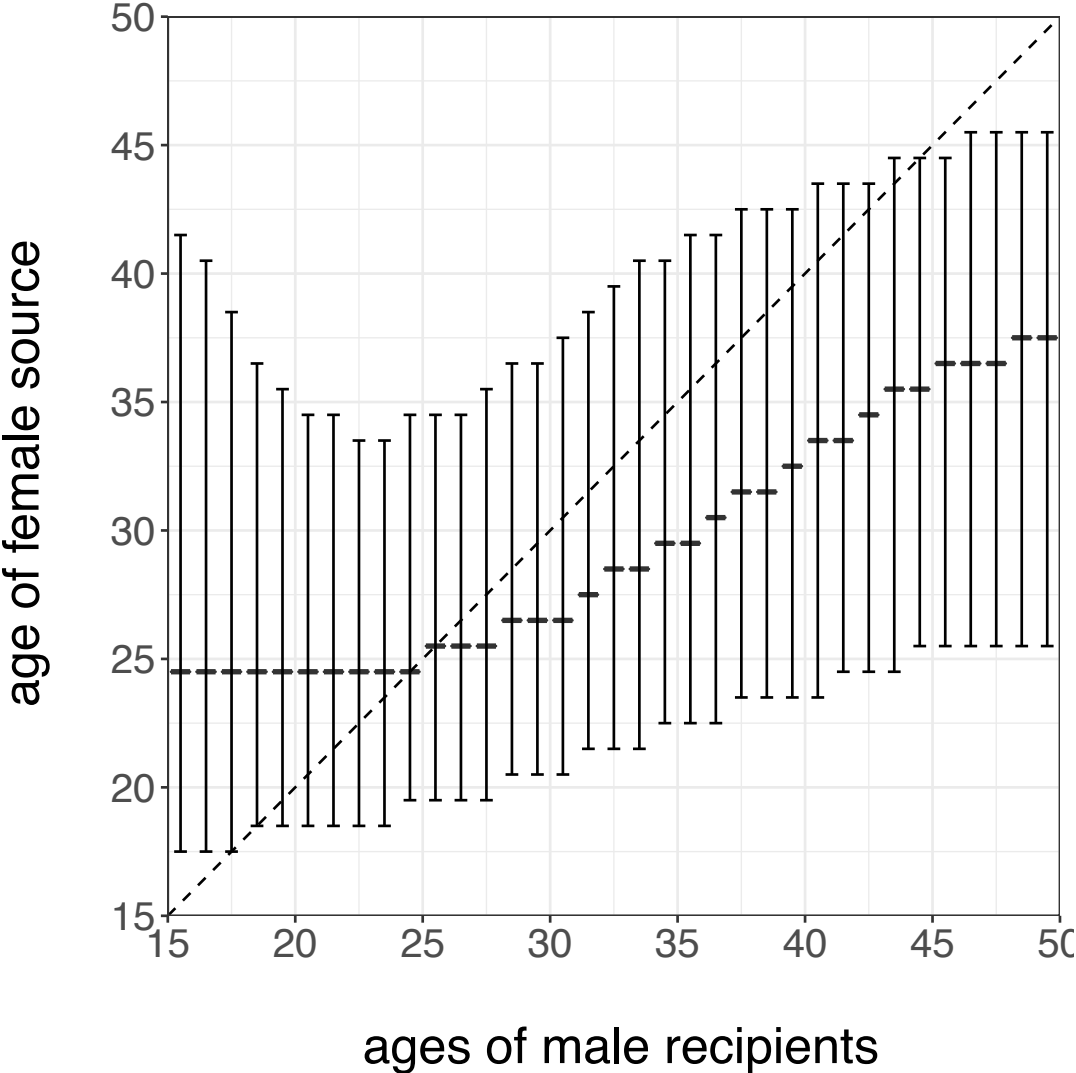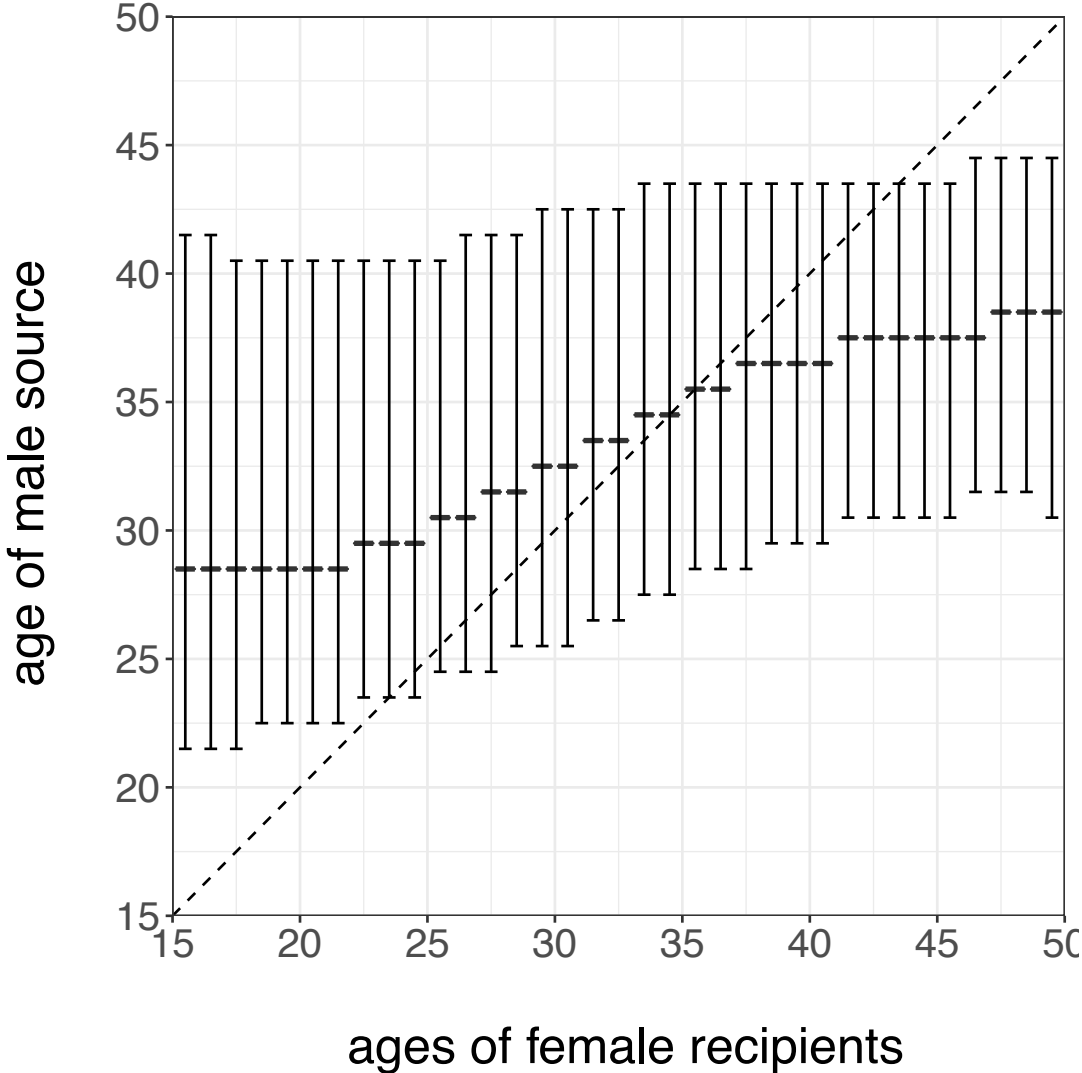50% of infections in women attributed to men aged 26-37
50% of infections in men attributed to women aged 23-34

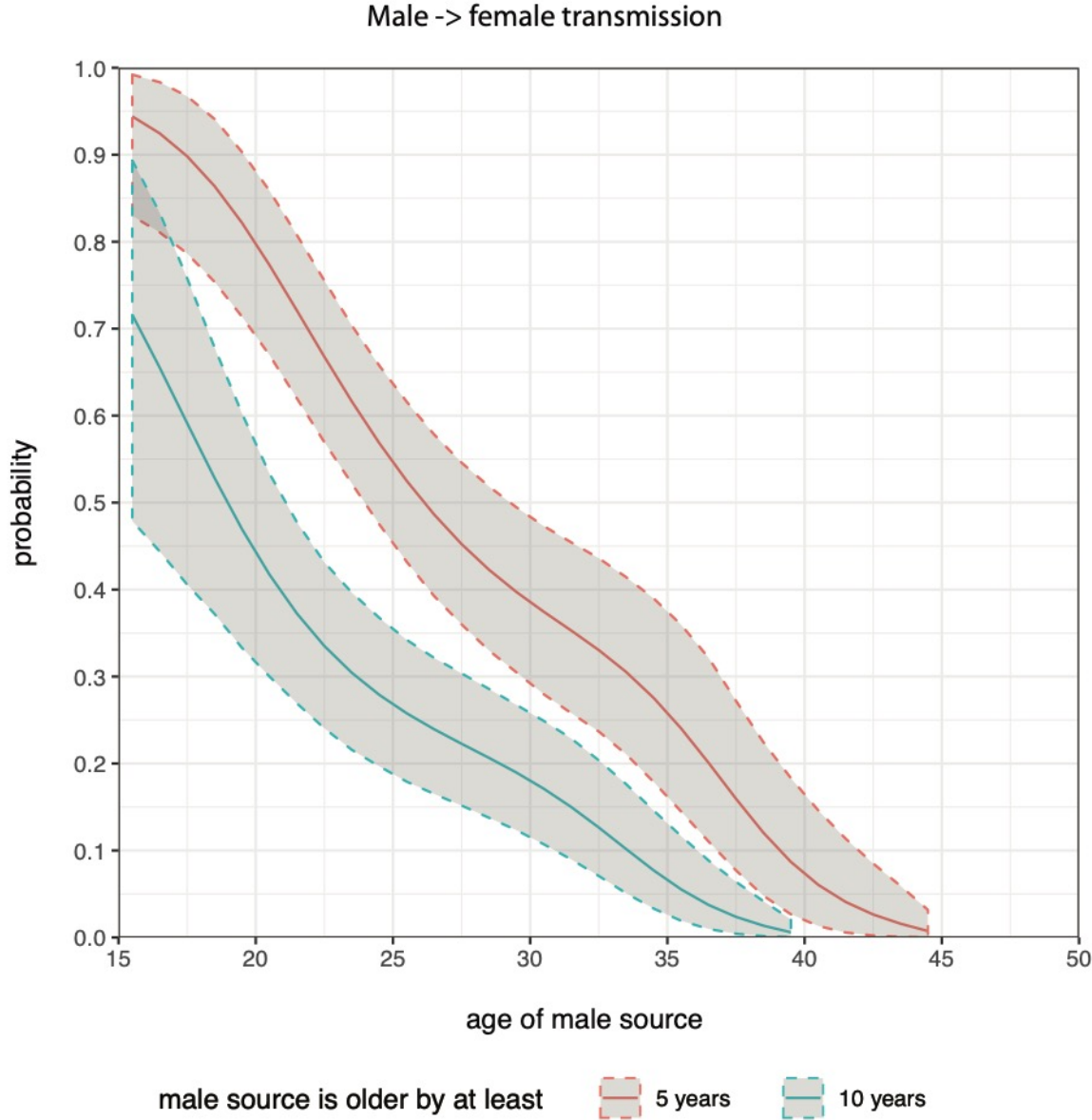# Age of sources by age of recipient

Xi et al. in preparation

Age difference between source and recipient

Xi et al. in preparation

Contribution of age-discordant relationships, male -> female

Male -> female transmission

Xi et al. in preparation

Summary of findings

- Overall, half of all infections among women were attributed to men aged 26-37, whereas half of all infection among men were attributed to women aged 23-34.

- However the mean age of the source case depended on the age of the recipient, and on gender. Women aged >35 were typically infected by younger men. Men aged >25 were typically infected by younger women.

- Most young women (aged 15-24) were infected by men who are >5 years older. An estimated 91% of women aged 15 were infected by men >5 years older, which declined to 73% at age 20, and 51% at age 25.

Youth bulge + rapid increases in prevalence among men and women
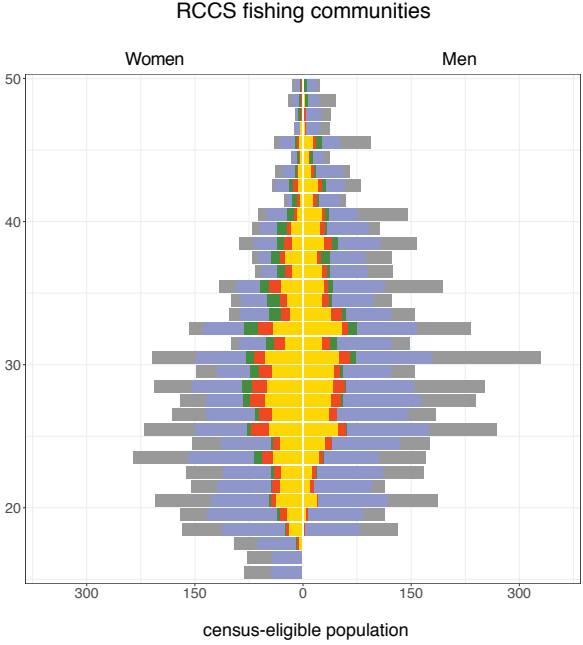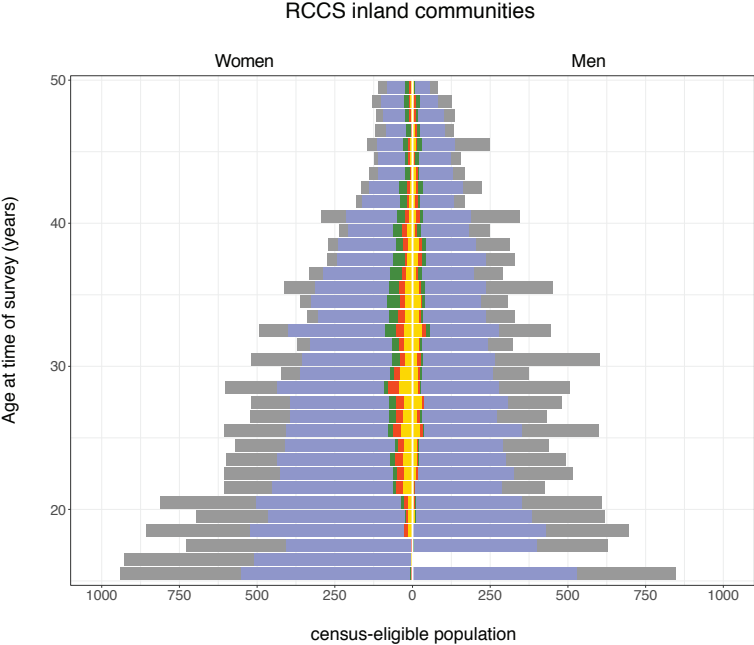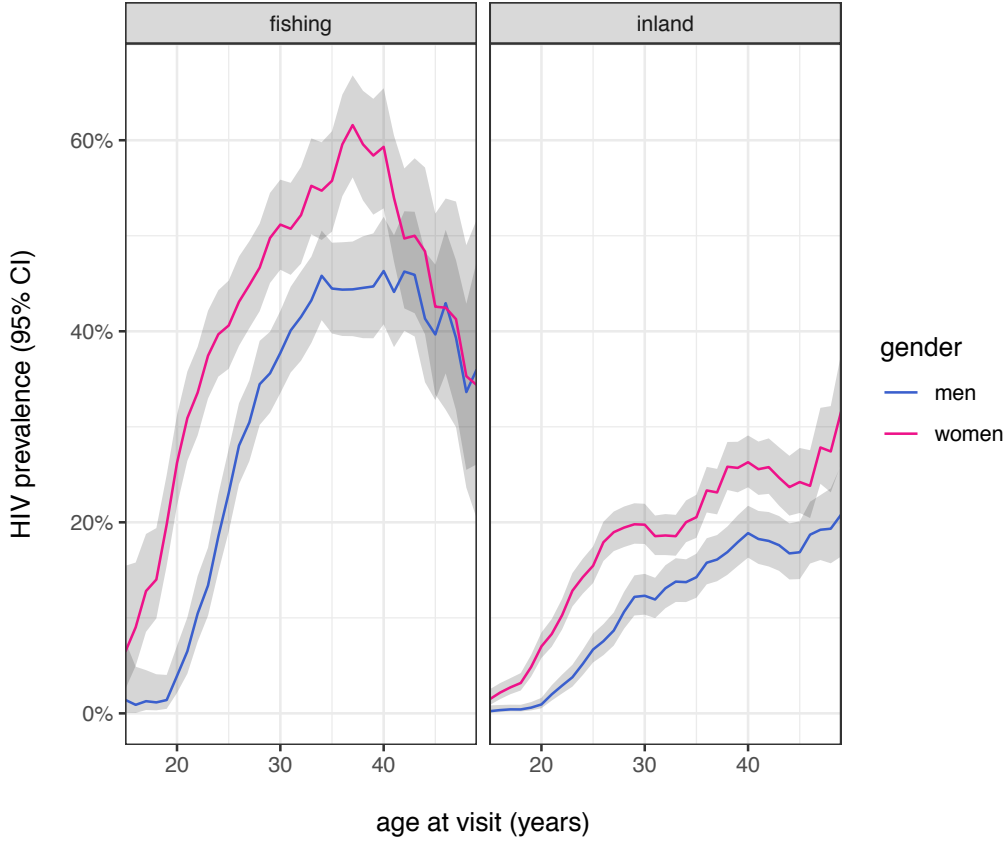
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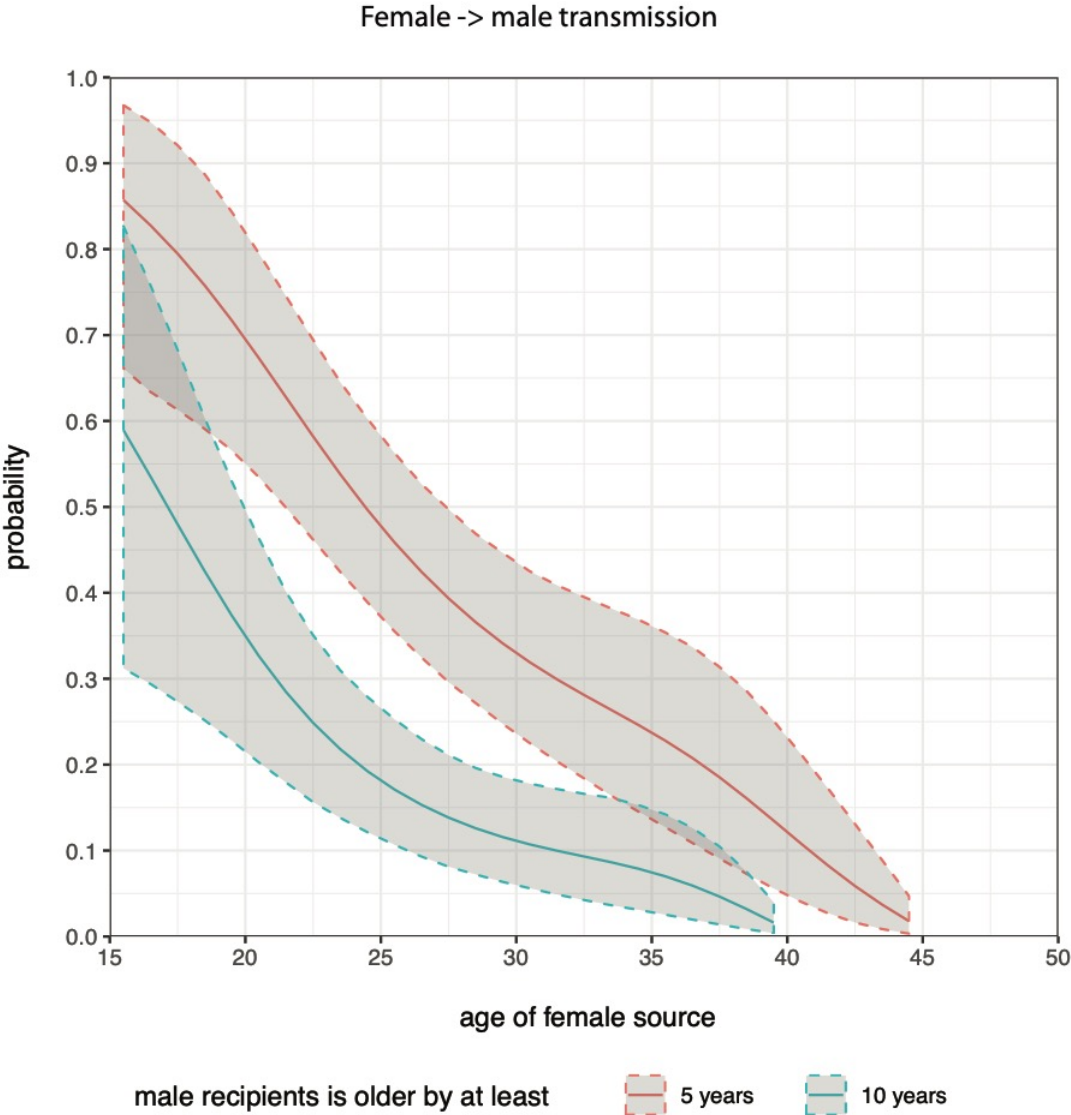High performance computing center

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Rakai Health Science Program Staff and Study participants

MRC/UVRI Program Staff and Study participants

Thank you

Contribution of age-discordant relationships, female -> male

Female -> male transmission

Xi et al. in preparation

An intuitive example (1)

actual transmissions

observed transmissions

to

1   2

from 1 | 50 | 10 |
from 2 | 20 | 20 |

sampling

1   2

| 60% | 100% |

to

1   2

from 1 | 18 | 6 |
from 2 | 12 | 20 |

An intuitive example (2)

actual transmissions

observed transmissions

to

1   2

sampling

1   2

to

1   2

from 1 | 50 | 10

from 2 | 20 | 20

| 60% | 100% |

from 1 | 18 | 6

from 2 | 12 | 20

true
flows

| 50% | 10% |
| 20% | 20% |

estimated
flows

| 32.1%
[21.4%-45.1%] | 10.7%
[5.0%-21.4%] |
| 21.4%
[12.7%-33.8%] | 35.7%
[24.5%-48.8%] |