Flow models to interpret population-based deep-sequence pathogen data

Oliver Ratmann (Imperial College London)

Mélodie Monod[*], Andrea Brizzi[*], Ronald M Galiwango[*], Robert Ssekubugu, Yu Chen, Xiaoyue Xi[*], Edward Nelson Kankaka[*], Victor Ssempijja[*], Lucie Abeler Dörner, Adam Akullian, Stella Alamo, Alexandra Blenkinsop, David Bonsall, Larry W Chang, Shozen Dan, Christophe Fraser, Tanya Golubchik, Ronald J Gray, Mathew Hall, Jade Jackson, Godfrey Kigozi, Oliver Laeyendecker, Lisa Mills, Lisa Nelson, Thomas C Quinn, Steven J Reynolds, John Santelli, Nelson Sewankambo, Simon Spencer, Joseph Ssekasanvu, Laura Thompson, Maria J Wawer, David Serwadda, Peter Godfrey-Fausset[*♦], Joseph Kagaayi, Kate Grabowski[*♦] on behalf of the PANGEA-HIV consortium

Imperial College London

PANGEA HIV

Bill & Melinda Gates foundation

NIH National Institute of Allergy and Infectious Diseases

CDC

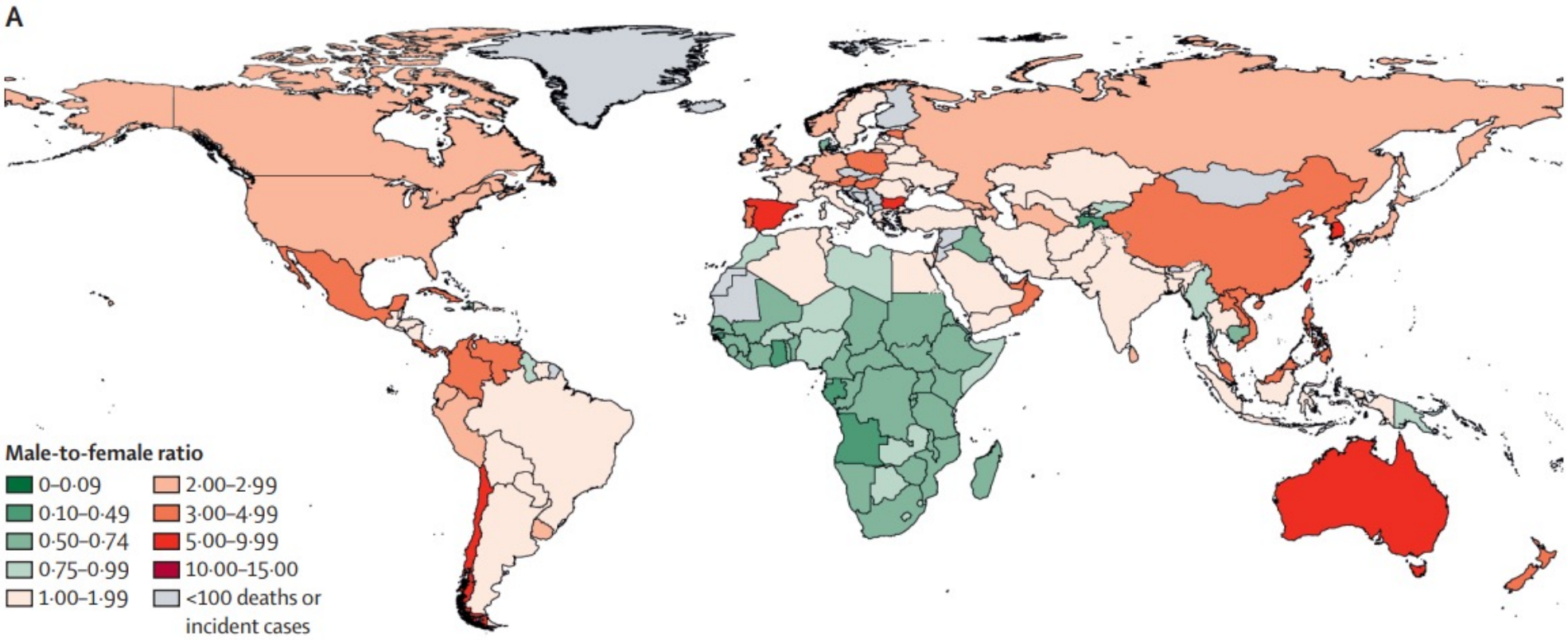
Rakai Health Sciences Program
Improved Health Through Research

Johns Hopkins School of Medicine

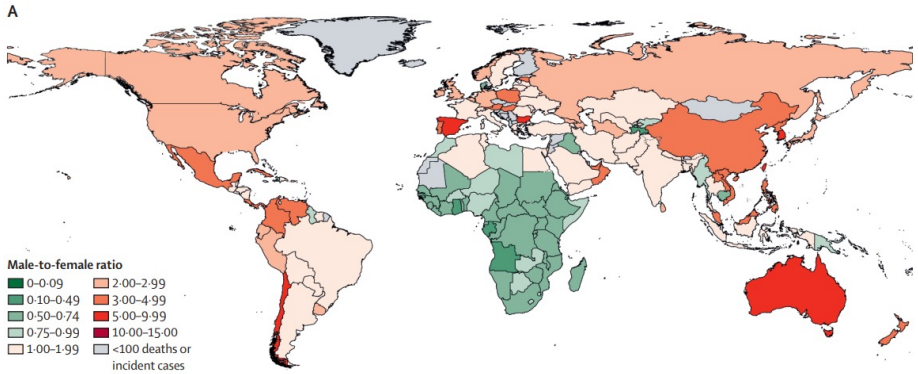
Makerere University

Big Data Institute

University of Oxford



Historically, the African HIV epidemic has been female.

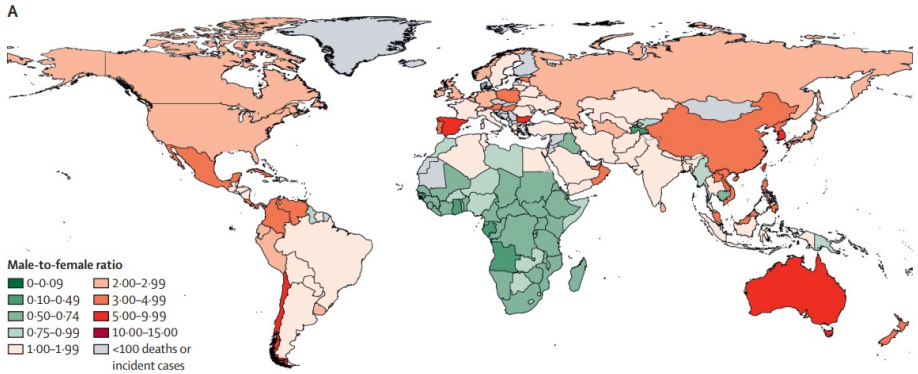


1. What are the recent trends in HIV incidence in women?

2. Are disparities between men and women closing or widening?

3. Which male populations drive incidence in women, and vice versa?

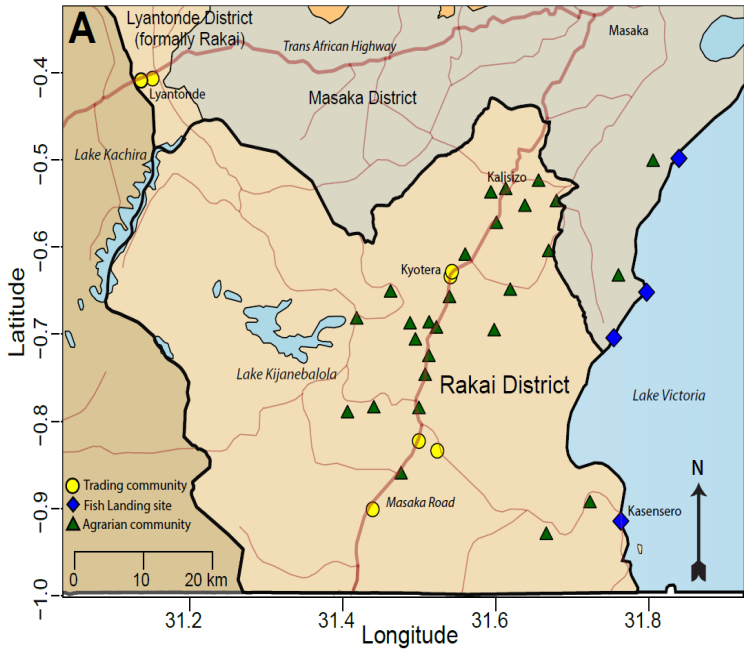
4. What are the best strategies to close gaps and improve population health?

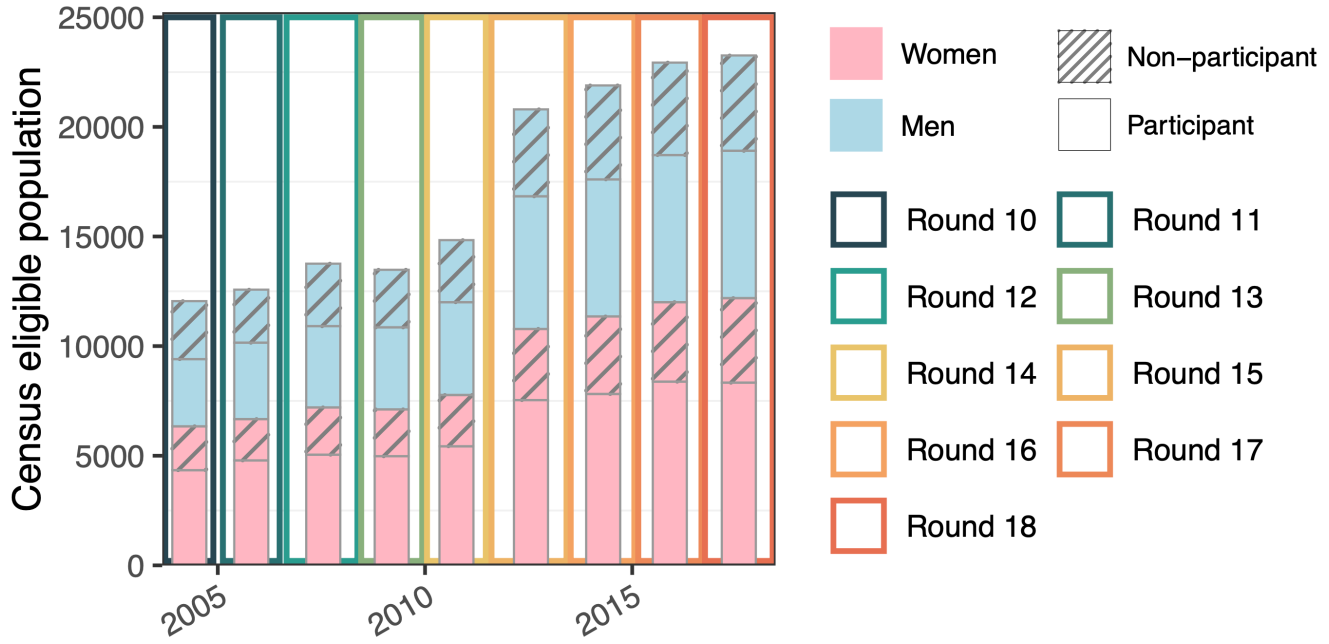


- Data from the Rakai Community Cohort Study
- Longitudinal surveillance of HIV incidence and transmission sources, 2008-2018
- Population-based cohort
- Lower-risk inland communities and high-risk fishing communities; here focus on inland

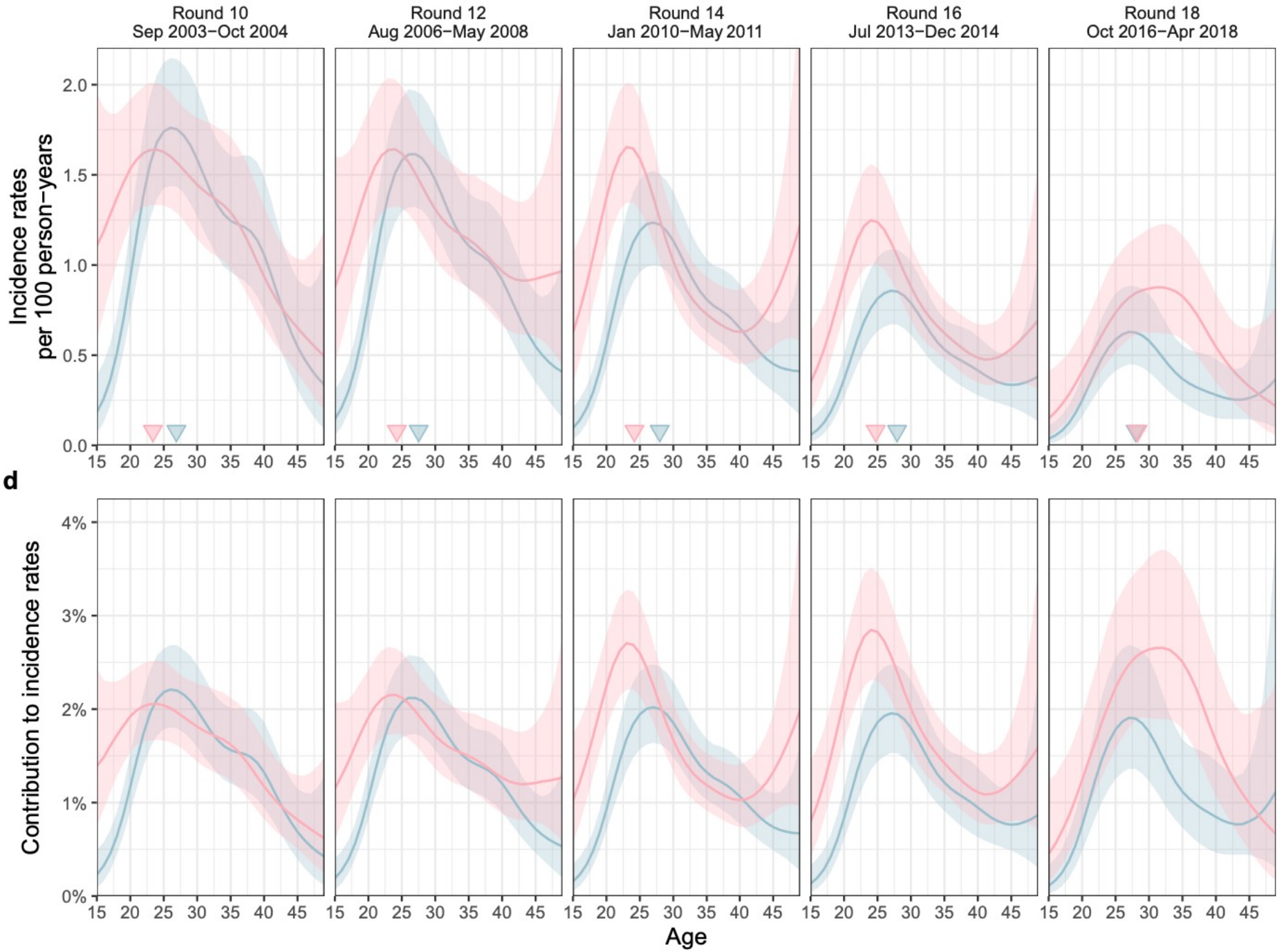
Trends in HIV incidence, 2010 - 2018

- **Rakai Community Cohort Study**





- **1100 incident cases observed over 127k PY, 2003-2018**
- **Faster declines in HIV incidence in men than women, ages 25 and above.**



Monod et al – almost submitted

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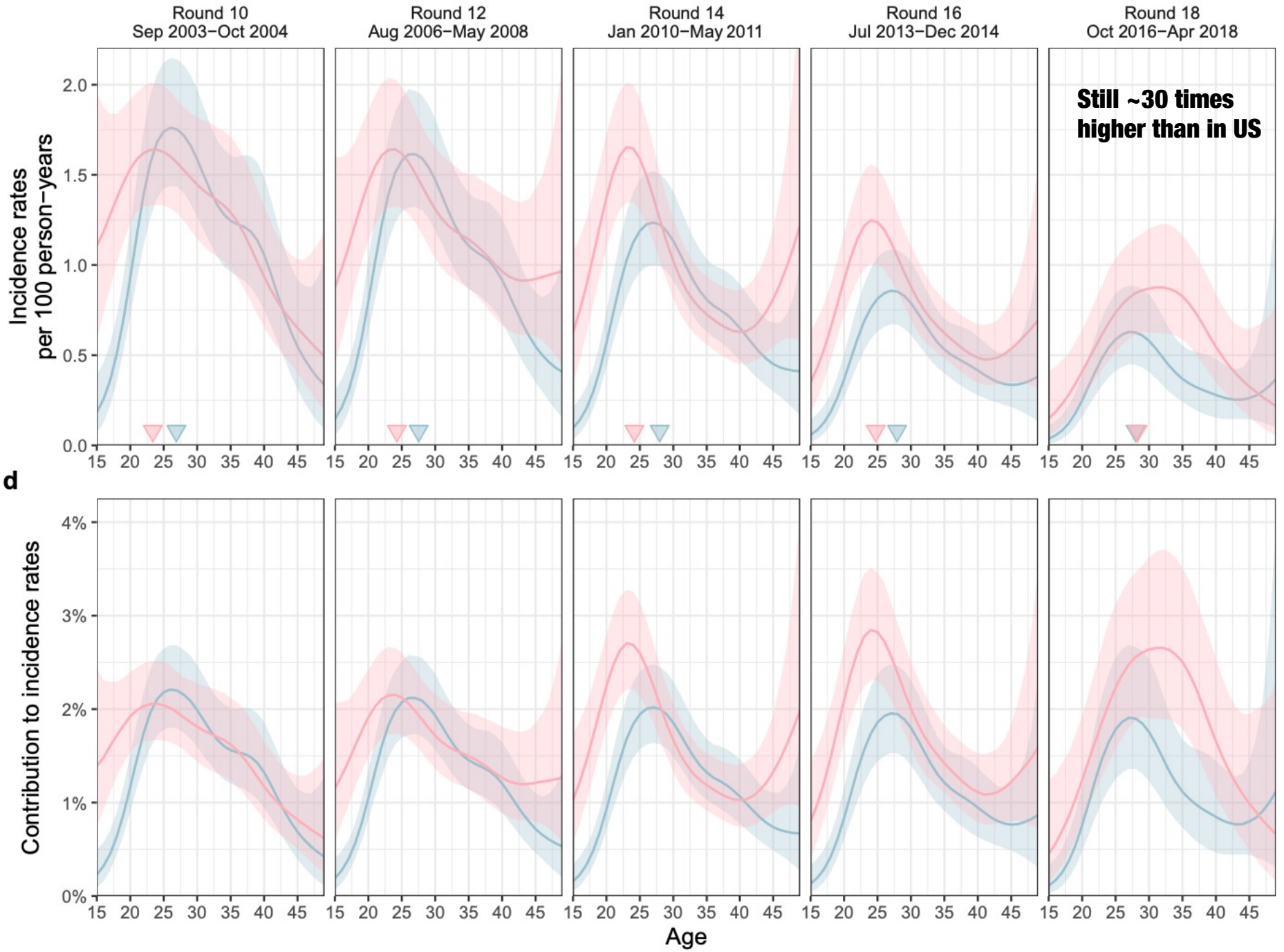

Monod et al – almost submitted

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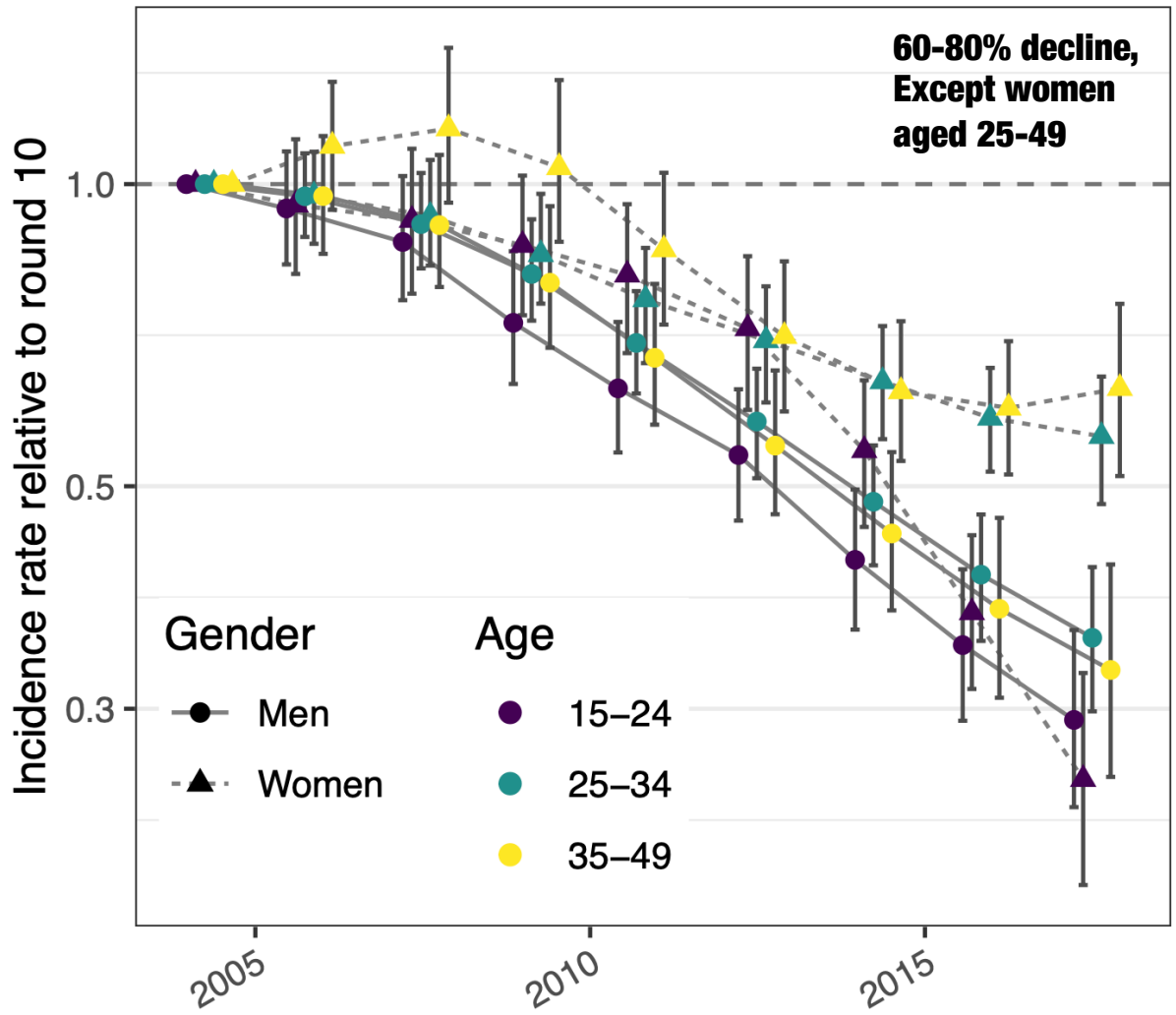
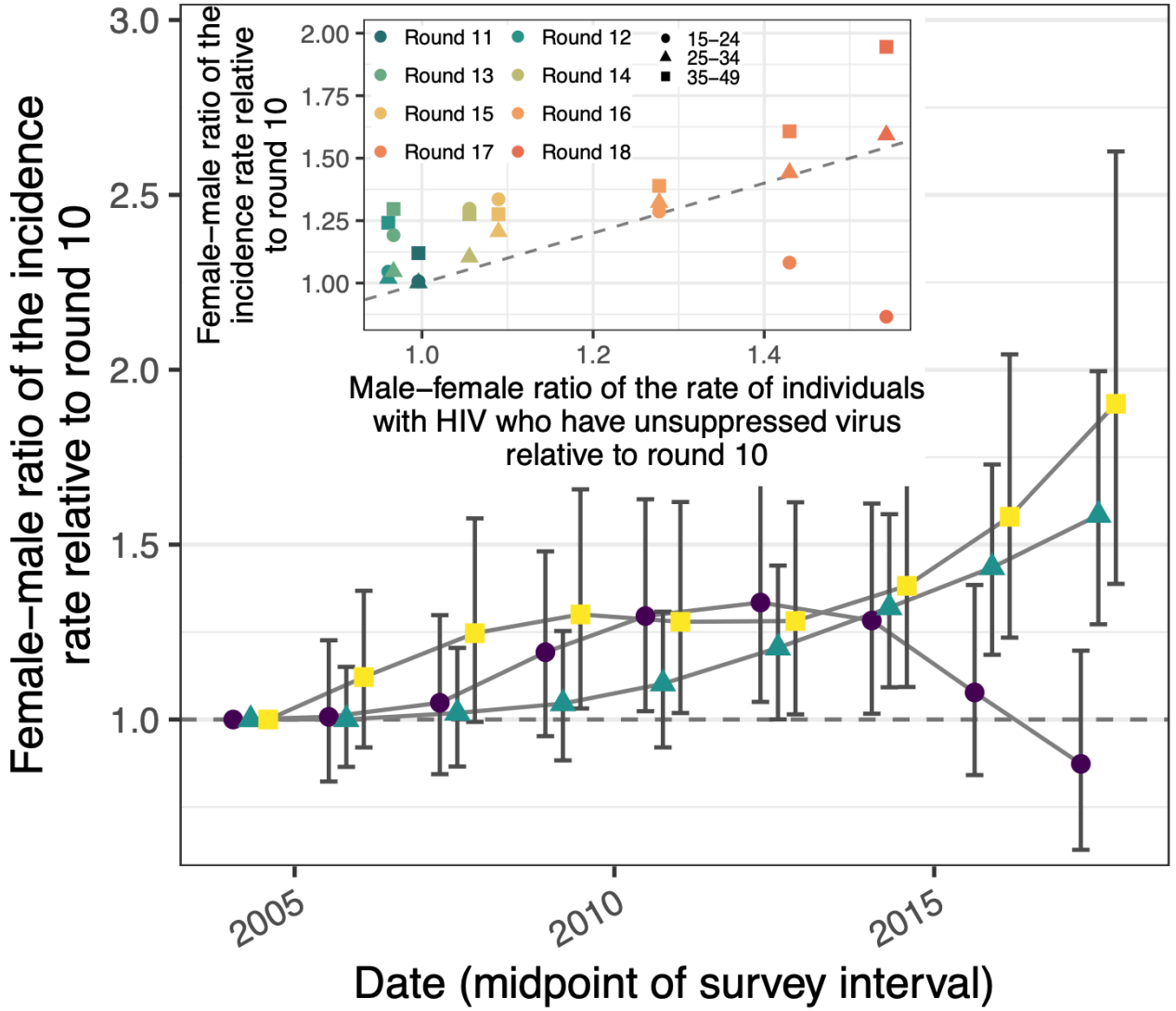

60-80% decline,
Except women
aged 25-49
Incidence rate relative to round 10
1.0
0.5
0.3
Gender
Men
Women
Age
15–24
25–34
35–49
2005
2010
2015

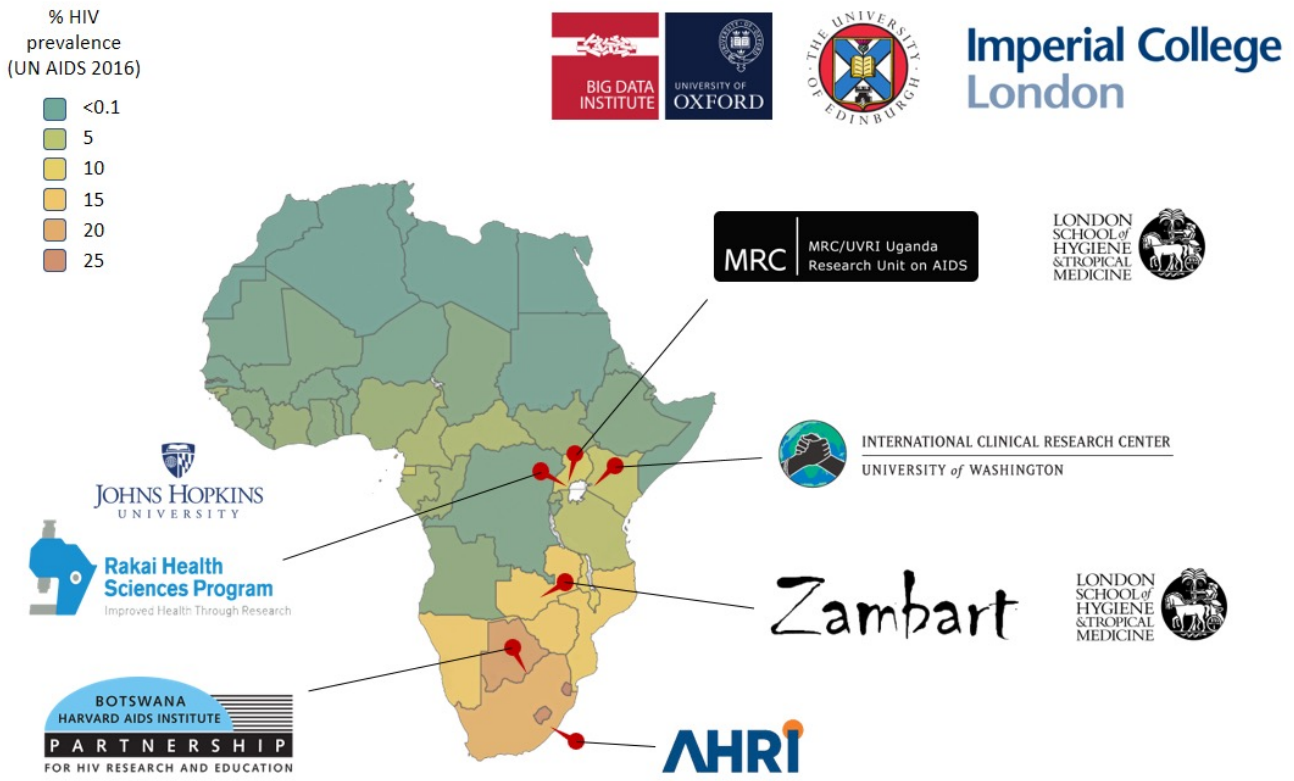

Female–male ratio of the incidence rate relative to round 10
3.0
2.5
2.0
1.5
1.0
Round 11
Round 12
Round 13
Round 14
Round 15
Round 16
Round 17
Round 18
15–24
25–34
35–49
2.00
1.75
1.50
1.25
1.00
1.0
1.2
1.4
Male–female ratio of the rate of individuals with HIV who have unsuppressed virus relative to round 10
2005
2010
2015
Date (midpoint of survey interval)

Understanding the changing sources

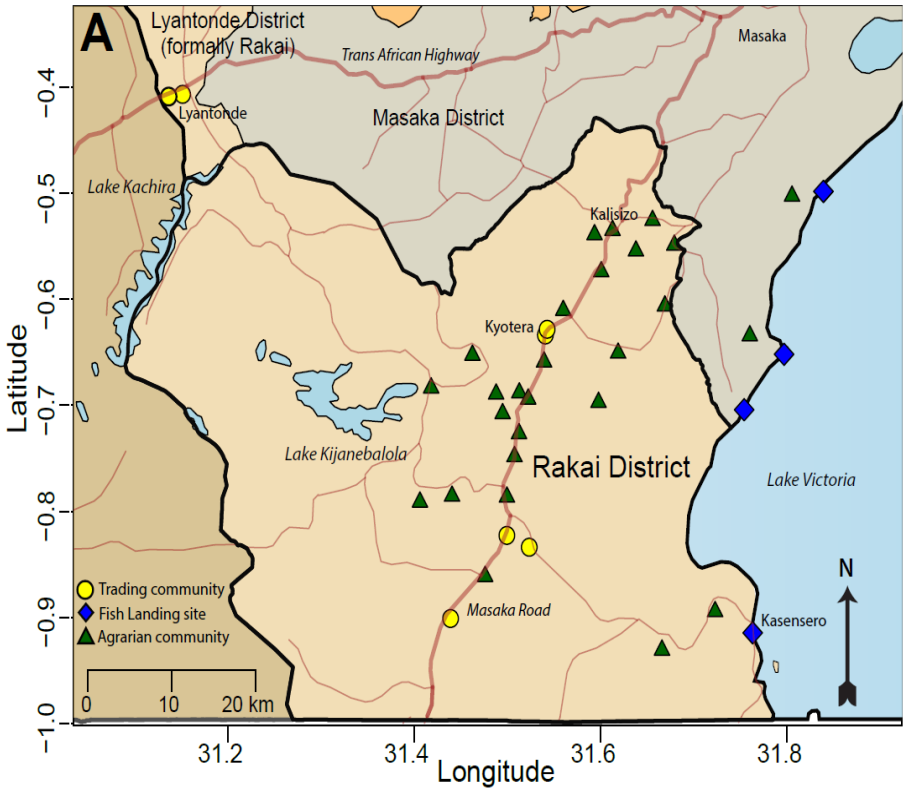
of these infections,

2010 - 2018

- **PANGEA-HIV: pan-African HIV pathogen genomics program integrated with population surveillance and clinical care**



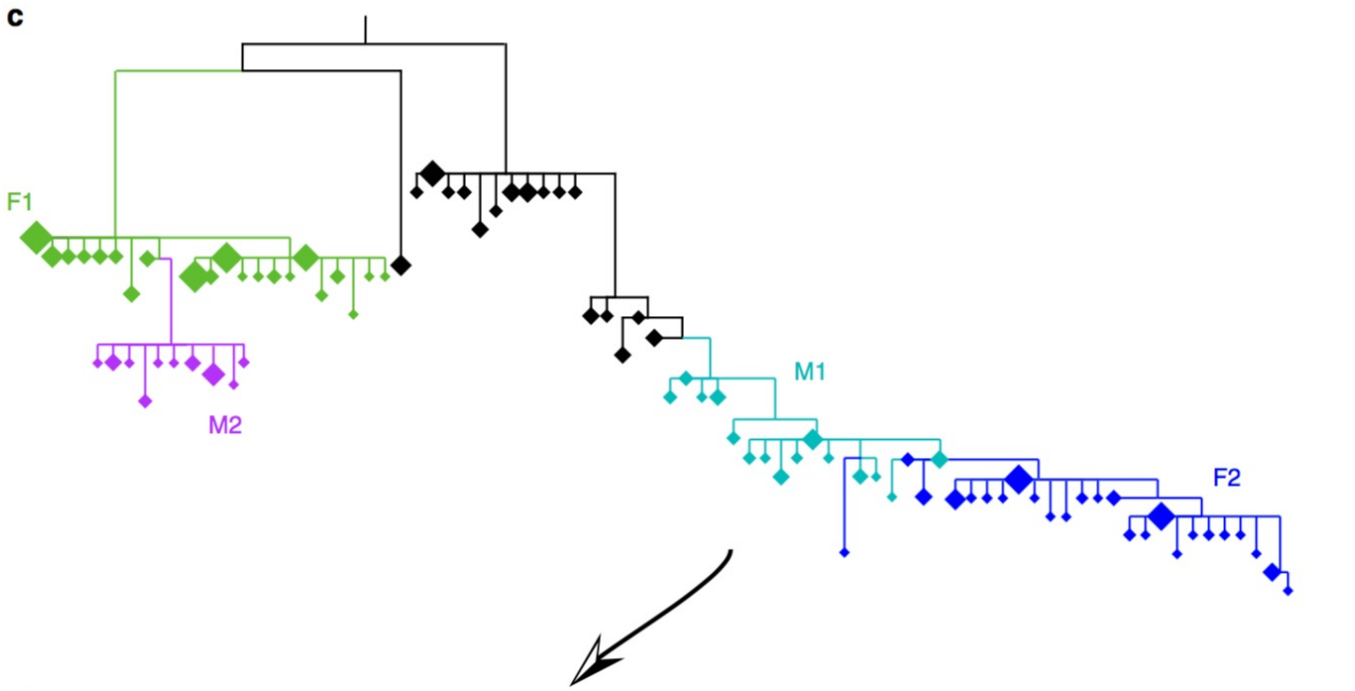
- **PANGEA-HIV: pan-African HIV pathogen genomics program integrated with population surveillance and clinical care**

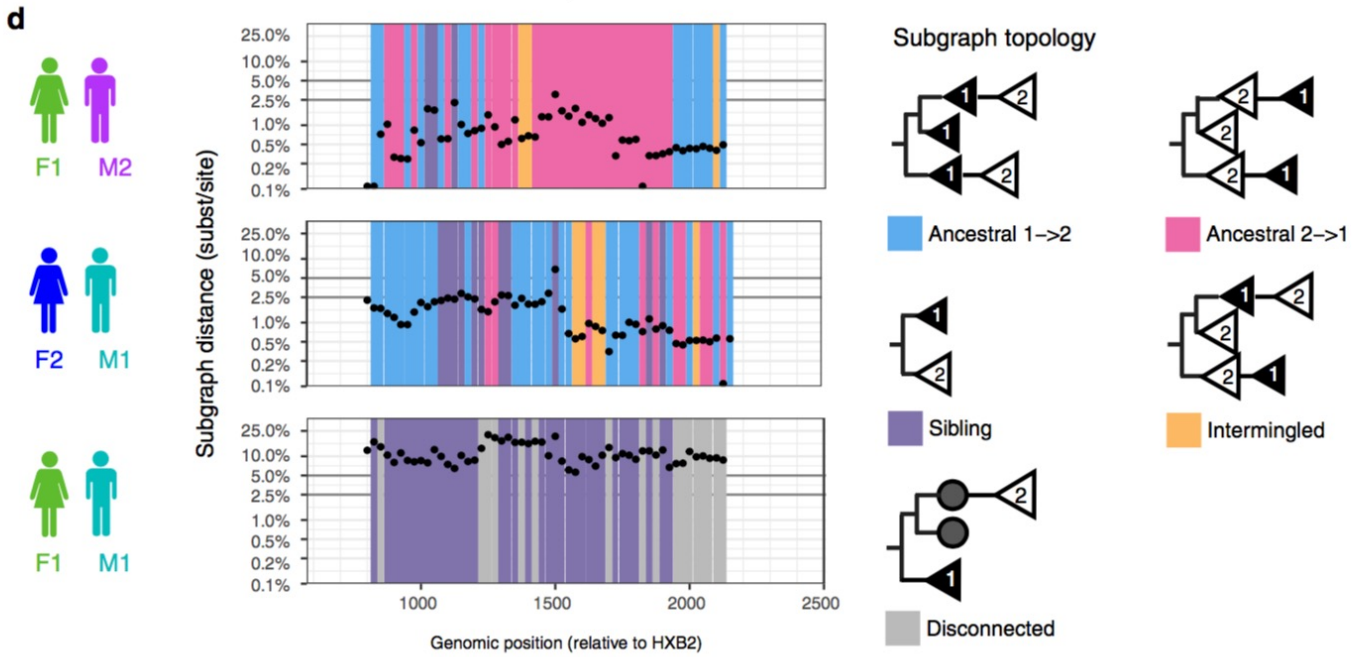


	Participants with HIV (n)	Participants with HIV reporting no ART use at first visit (n)	(n)	Participants with HIV and with virus ever deep-sequenced † (%)
Total	5682	4341	2174	38 %
Female (Total)	3817	2836	1291	34 %
Age				
15-24	1066	817	424	40 %
25-34	2074	1488	740	36 %
35-49	1446	826	411	28 %
Male (Total)	1865	1506	883	47 %
Age				
15-24	272	220	157	58 %
25-34	955	782	499	52 %
35-49	984	670	436	44 %
Round‡				
10	884	–	115	13 %
11	1002	884	176	18 %
12	1105	912	234	21 %
13	1160	900	368	32 %
14	1741	1392	820	47 %
15	1944	1331	1085	56 %
16	1875	868	892	48 %
17	2015	646	933	46 %
18	1860	432	848	46 %

† Individuals with virus ever deep-sequenced were defined as HIV-positive individuals with deep-sequence output meeting minimum quality criteria, see Methods. ‡ Totals by round include individuals seen in other rounds.

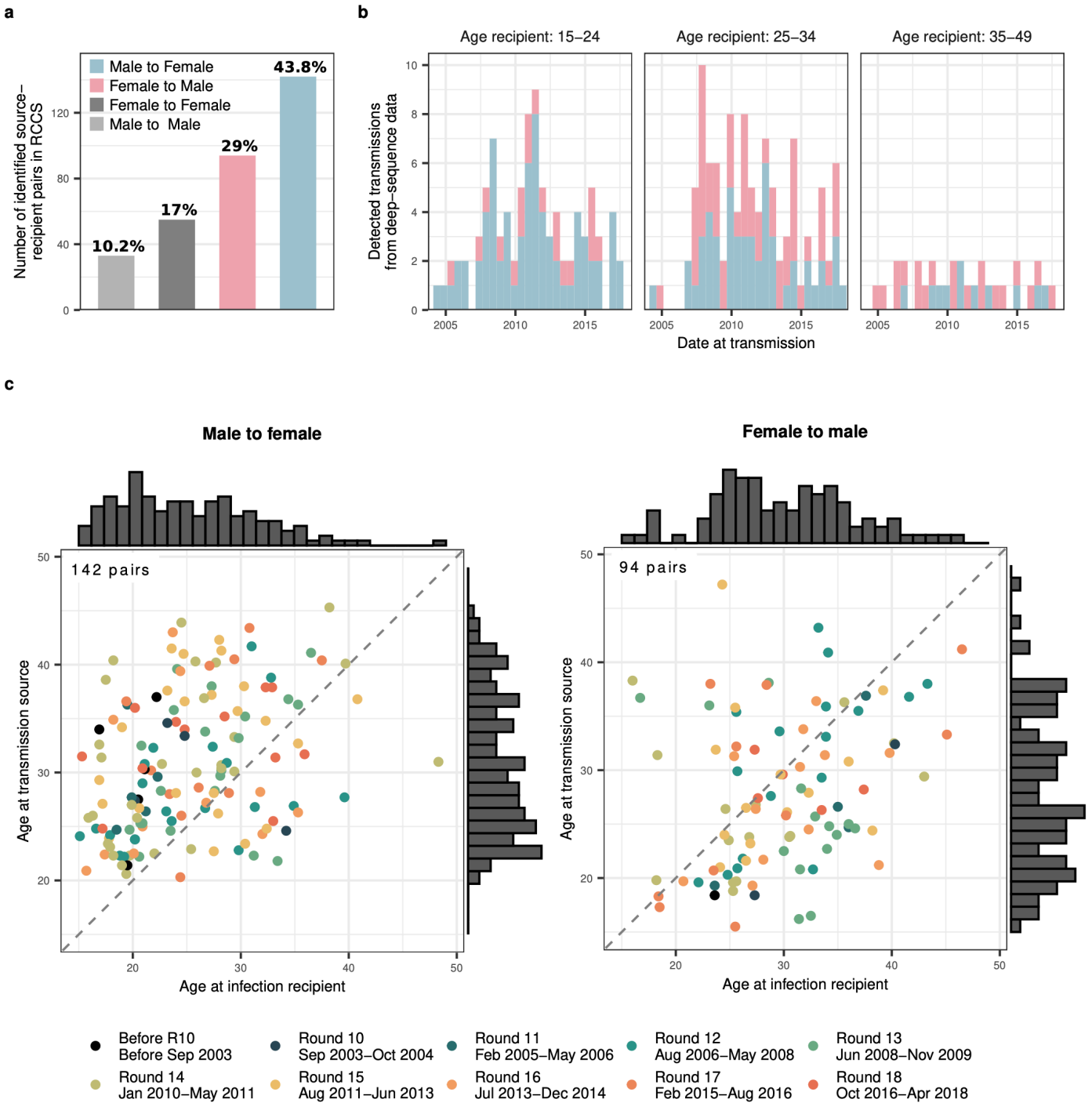
Key discovery of PANGEA-HIV





- HIV deep sequencing provides multiple sequence fragments per person
- Think: phylogeography between individuals
- Inference of transmission direction

Wymant et al. MBE 2017
Hall et al. Elife 2019
Ratmann et al. Nature Communications 2019
Ratmann et al. Lancet HIV 2020
Xi et al. JRSSC 2022



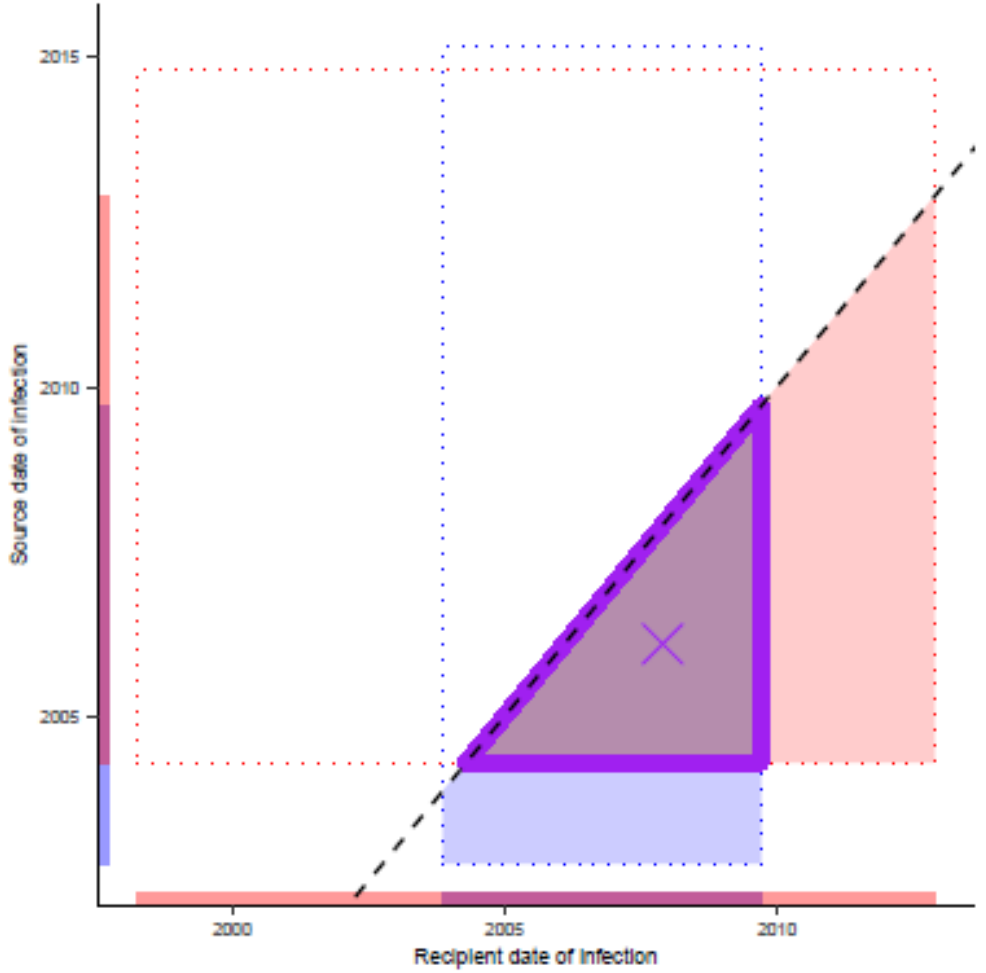
Transmission cohort, 2013-2018

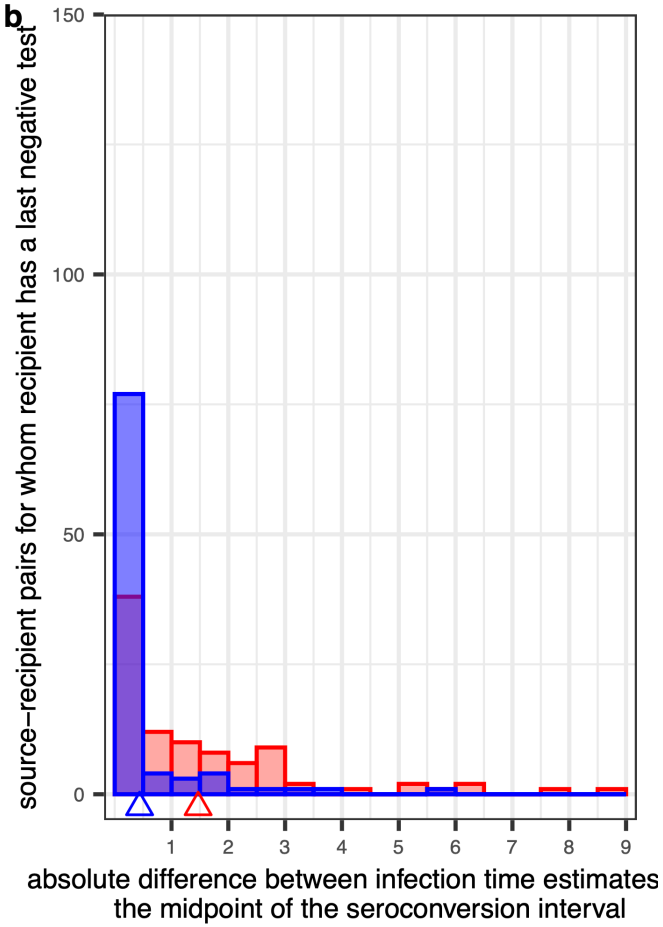
Identified 236 heterosexual source-recipient pairs

Retained 227 in whom transmission was estimated to have occurred during the study period.

Dating the likely infection time with deep-sequence data

- Used phyloTSI algorithm
- Augmented infection time estimates with epidemiologic data





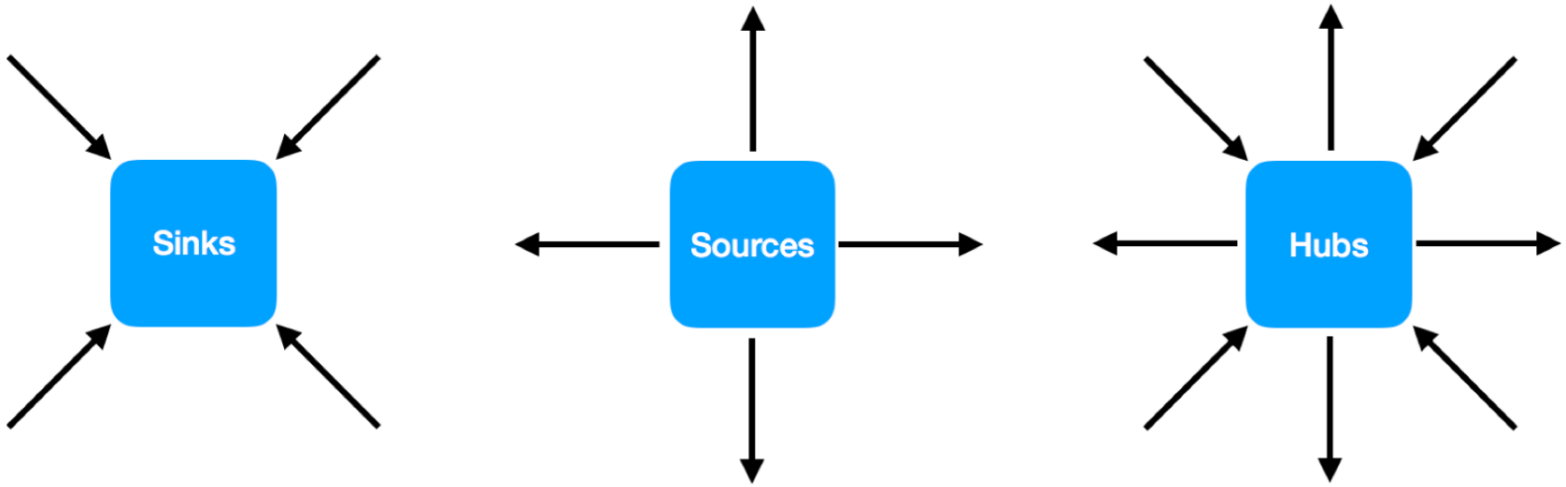
△ phyloTSI on deep sequence data

△ refined infection time estimates accounting further for serohistory and transmission direction

Golubchik et al. Medxriv. 2022

A statistical perspective on phylodynamics: regression models on observed flows

Concept: transmission sinks, sources, hubs



Groups at high risk of infection

Groups at high risk of infecting others

Groups of high risk of infection and of infecting others

Target quantities

- Directional transmission flows,
  e.g. from and to areas with high (h) and low (l) HIV prevalence

$$\boldsymbol{\pi} = \begin{pmatrix} \pi_{hh} & \pi_{hl} \\ \pi_{lh} & \pi_{ll} \end{pmatrix}, \quad \sum_{a,b} \pi_{a,b} = 1$$

Target quantities

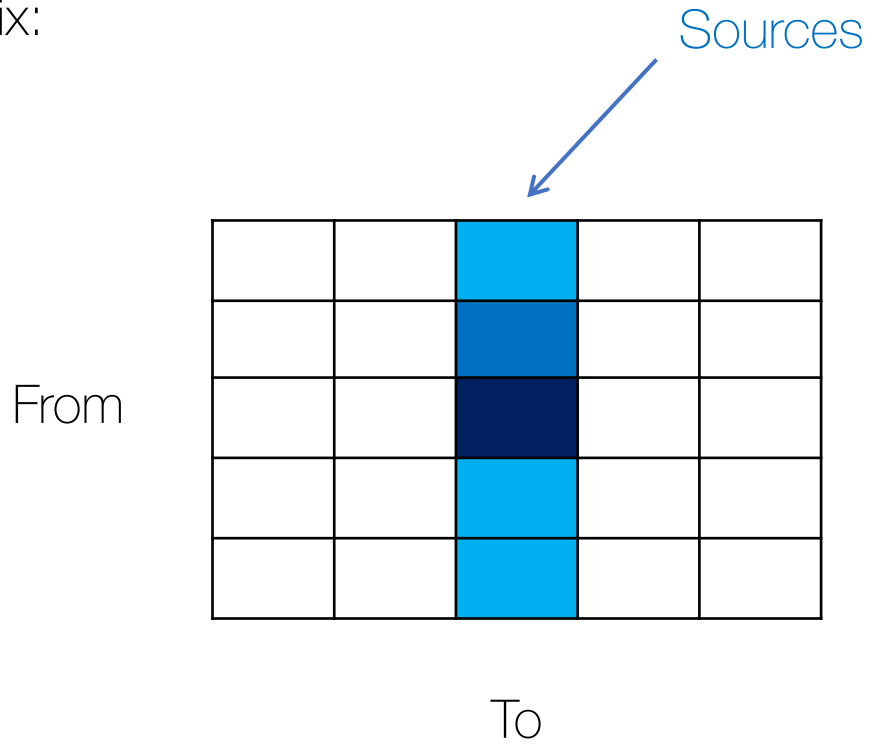
- Directional transmission flows,
  e.g. from and to different age bands:

$$\boldsymbol{\pi} = \begin{pmatrix} \boldsymbol{\pi}^{mf} & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\pi}^{fm} \end{pmatrix}, \quad \boldsymbol{\pi}^{mf} = \begin{pmatrix} \pi_{11}^{mf} & \cdots & \pi_{1K}^{mf} \\ \vdots & \ddots & \vdots \\ \pi_{K1}^{mf} & \cdots & \pi_{KK}^{mf} \end{pmatrix} \quad \boldsymbol{\pi}^{fm} = \begin{pmatrix} \pi_{11}^{fm} & \cdots & \pi_{1K}^{fm} \\ \vdots & \ddots & \vdots \\ \pi_{K1}^{fm} & \cdots & \pi_{KK}^{fm} \end{pmatrix}$$

male→female female→male

Target quantities

- Target quantities derived from the transmission flow matrix:



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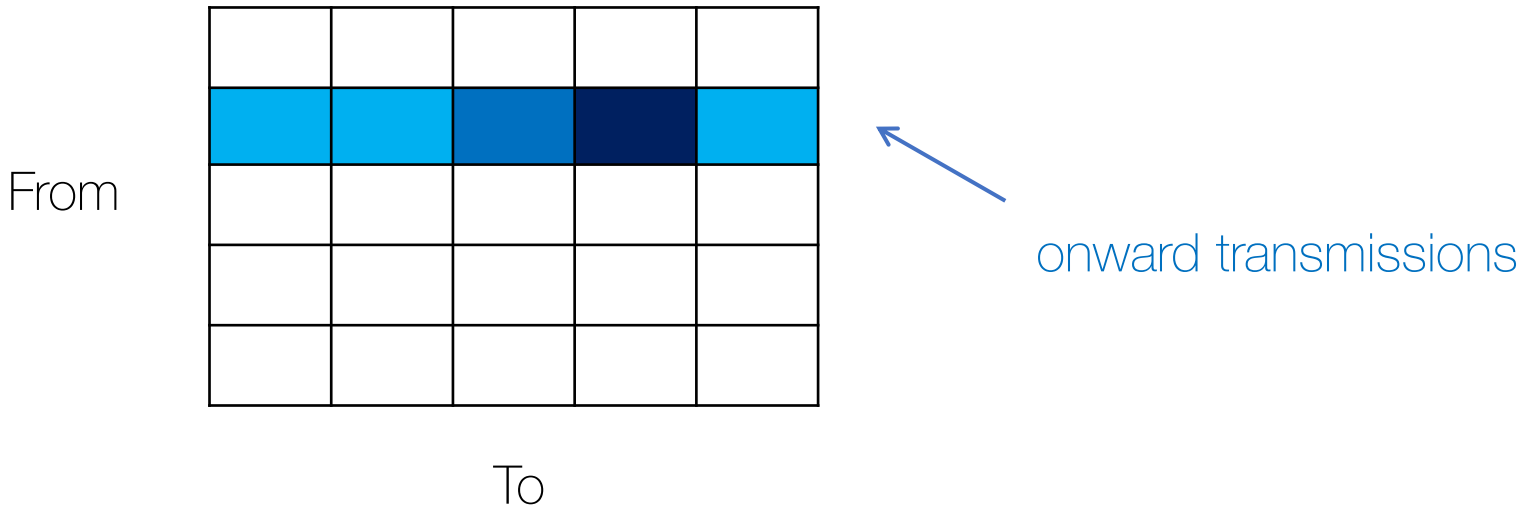


Regression-type source attribution analysis

ORIGINAL ARTICLE | Open Access

Inferring the sources of HIV infection in Africa from deep-sequence data with semi-parametric Bayesian Poisson flow models

Xiaoyue Xi, Simon E. F. Spencer, Matthew Hall, M. Kate Grabowski, Joseph Kagaayi, Oliver Ratmann, on behalf of Rakai Health Sciences Program and PANGEA-HIV

First published: 13 March 2022 | https://doi.org/10.1111/rssc.12544

Xi et al. JRSSC. 2022
Bu et al. – almost submitted.
Monod et al. – almost submitted.

Regression-type source attribution analysis

$$Y_{p,i,j}^{g\to h} \sim \text{Poisson}\left(\xi_{p,j}^{h} \sum_{r\in p} \lambda_{r,i,j}^{g\to h}\right) \tag{6a}$$

$$\lambda_{r,i,j}^{g\to h} = \beta_{r,i,j}^{g\to h} \times S_{r,j}^{h} \times I_{r,i}^{g} \times \left|\left(t_r^{\text{end}} - t_r^{\text{start}}\right)\right| \tag{6b}$$

$$\log \beta_{r,i,j}^{g\to h} = \hat{\boldsymbol{c}}^{g\to h}(i,j) + \gamma_0 + \gamma_g + \gamma_r + \gamma_{p(r)} + \boldsymbol{f}_0^{g\to h}(i,j) + \boldsymbol{f}_r^{g\to h}(j) + \boldsymbol{f}_{p(r)}^{g\to h}(i), \tag{6c}$$

$$\frac{\sum_i \lambda_{r,i,j}^{g\to h}}{S_{r,j}^{h} \times \left|\left(t_r^{\text{end}} - t_r^{\text{start}}\right)\right|} \sim \text{LogNormal}$$

Xi et al. JRSSC. 2022
Fan et al. – almost submitted.
Monod et al. – almost submitted.

Pros and cons

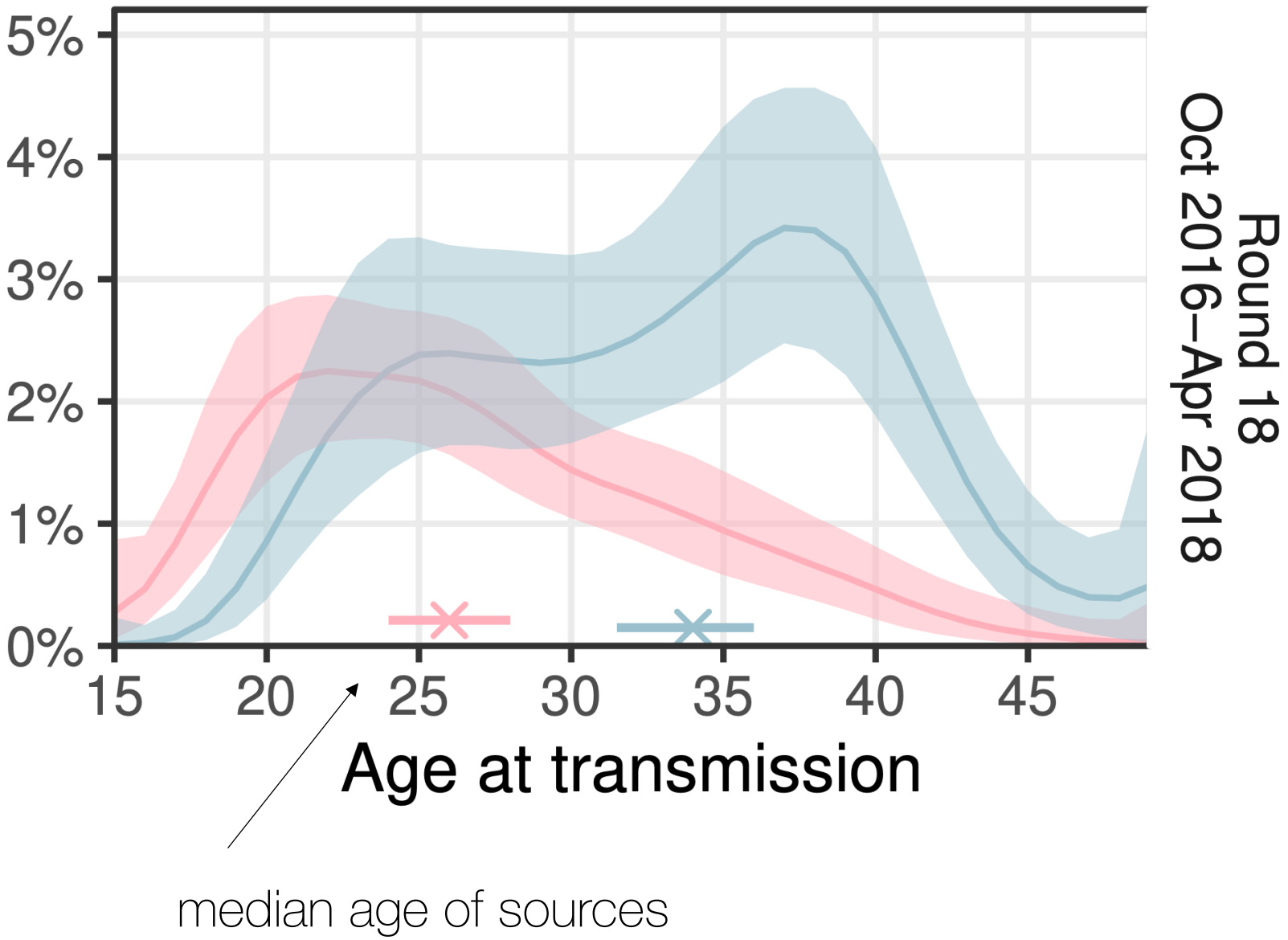
Advantages:

- estimation of transmission flows computationally tractable (runtime several hours to 2-3 days)
- can be implemented in Stan
- can adjust flow estimates for observed sampling heterogeneity
- Gaussian process smoothing can be used to regularize inferences in highly-stratified populations

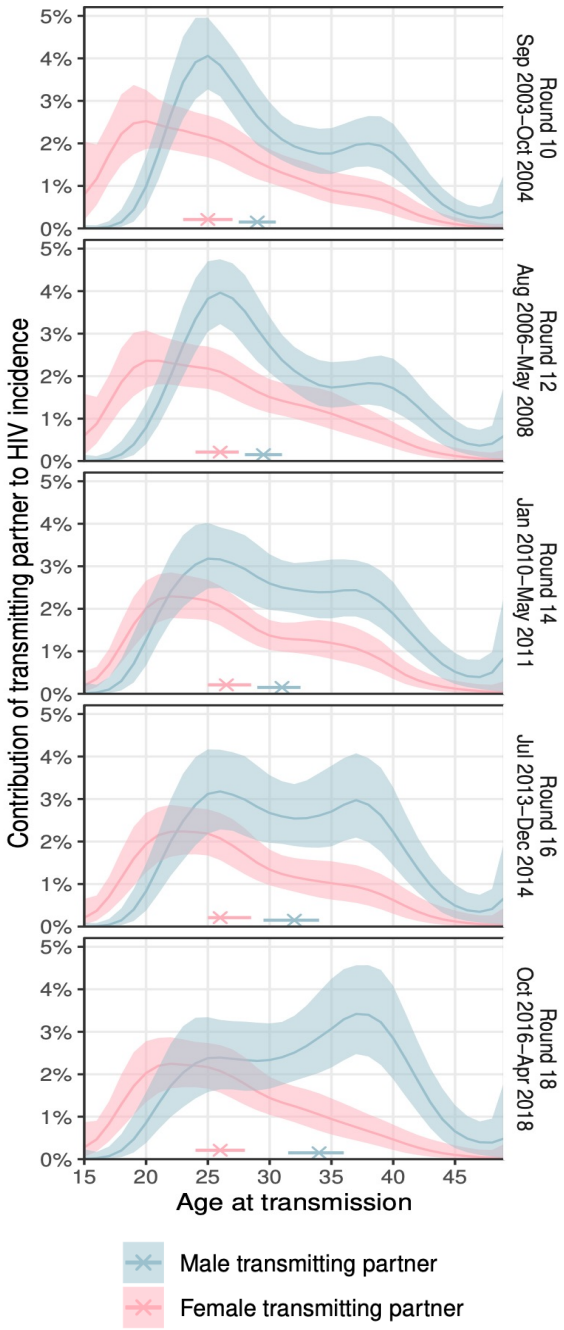
Disadvantages:

- requires deep-sequence data
- does not use all available sequence data, only phylogenetically strongly supported source-recipient pairs

- **Age profile of male sources (blue), and female sources (pink)**
- **Blue + red = 100%**



%transmission from men
57.9% [56.1-59.6]
61.9% [60.2-63.7]
62.8% [60.2-65.2]



- **Proportion of transmissions from men is increasing**
- **Transmissions from men are shifting to older ages**
- **Disparities are widening, not closing**

Changes in age/gender transmission flows

Transmission direction	Male-female difference in age at transmission	Infected partner by age at transmission			
		15-24 years (%)†	25-34 years (%)†	35-49 years (%)†	Total (%)†
Round 10, September 26, 2003 - November 23, 2004; 28 communities surveyed					
Male to female	Total	31.9% [30.2-33.6]	18.6% [17.7-19.6]	7.3% [6.7-7.9]	57.9% [56.1-59.6]
	<0 years	0.4% [0.2-0.7]	4.5% [3.0-6.3]	4.1% [2.7-5.5]	9.0% [6.8-11.5]
	0-6 years	16.0% [12.8-19.3]	8.5% [7.0-10.2]	3.0% [1.8-4.2]	27.5% [23.5-31.5]
	>6 years	15.5% [12.2-18.8]	5.6% [4.1-7.3]	0.2% [0.0-0.5]	21.3% [17.2-25.2]
Female to male	Total	14.8% [13.9-15.8]	20.7% [19.7-21.7]	6.6% [6.2-7.1]	42.1% [40.4-43.9]
	<0 years	6.8% [5.2-8.7]	4.3% [2.9-6.0]	0.4% [0.2-0.8]	11.6% [8.8-14.8]
	0-6 years	7.9% [5.9-9.9]	12.3% [10.5-13.9]	2.5% [1.7-3.3]	22.7% [19.7-25.7]
	>6 years	0.1% [0.0-0.2]	4.0% [2.7-5.8]	3.7% [2.7-4.7]	7.8% [5.8-10.1]
Total		46.7% [45.3-48.2]	39.3% [38.2-40.5]	13.9% [13.2-14.7]	100%
Round 15, August 10, 2011 - July 05, 2013; 33 communities surveyed					
Male to female	Total	32.2% [30.1-34.3]	22.0% [20.7-23.4]	7.7% [7.0-8.5]	61.9% [60.2-63.7]
	<0 years	0.5% [0.3-1.0]	4.8% [3.2-6.9]	3.9% [2.4-5.5]	9.3% [6.8-12.2]
	0-6 years	16.0% [12.7-19.4]	10.0% [8.1-12.0]	3.5% [2.1-4.9]	29.6% [25.3-33.9]
	>6 years	15.6% [12.2-19.1]	7.1% [5.3-9.1]	0.2% [0.1-0.7]	23.1% [18.6-27.3]
Female to male	Total	11.5% [10.6-12.4]	18.8% [17.8-19.9]	7.7% [7.1-8.4]	38.1% [36.3-39.8]
	<0 years	6.4% [4.9-7.8]	4.2% [2.9-5.9]	0.6% [0.2-1.2]	11.2% [8.7-14.0]
	0-6 years	5.1% [3.8-6.5]	11.8% [10.1-13.2]	3.2% [2.2-4.2]	20.0% [17.3-22.7]
	>6 years	0.0% [0.0-0.0]	2.8% [1.9-3.9]	3.9% [2.8-5.1]	6.8% [5.1-8.6]
Total		43.7% [41.9-45.6]	40.8% [39.3-42.4]	15.4% [14.6-16.4]	100%
Round 18, October 03, 2016 - May 22, 2018; 35 communities surveyed					
Male to female	Total	20.6% [18.2-23.4]	27.3% [25.3-29.4]	14.7% [13.3-16.3]	62.8% [60.2-65.2]
	<0 years	0.3% [0.1-0.7]	5.3% [3.2-8.4]	7.2% [4.8-9.7]	12.9% [9.2-17.4]
	0-6 years	8.7% [6.2-11.7]	13.2% [10.5-16.0]	7.0% [4.8-9.3]	29.0% [25.0-33.2]
	>6 years	11.5% [8.6-14.7]	8.6% [6.0-11.7]	0.5% [0.1-1.4]	20.7% [16.1-25.5]
Female to male	Total	11.2% [9.9-12.6]	17.3% [15.8-18.9]	8.7% [7.7-9.9]	37.2% [34.8-39.8]
	<0 years	5.8% [4.2-7.7]	3.5% [2.4-5.2]	0.4% [0.2-1.1]	9.8% [7.3-13.0]
	0-6 years	5.4% [3.6-7.1]	11.0% [9.3-12.6]	3.2% [2.1-4.5]	19.6% [16.7-22.4]
	>6 years	0.0% [0.0-0.1]	2.8% [1.8-4.0]	5.0% [3.5-6.4]	7.8% [5.8-9.9]
Total		31.9% [29.4-34.5]	44.7% [42.5-46.8]	23.4% [21.7-25.3]	100%

† Posterior median flow estimates and 95% credible intervals in each survey round.

Monod et al. – almost submitted.

Transmission versus contacts

Monod et al. – almost submitted.
Chen et al. – in preparation.
Dan et al. arxiv 2022 https://arxiv.org/pdf/2210.11358.pdf

Basic notations and definitions

Participant's, contact's age / gender

$a, b \in \{0, 1, \ldots, 83, 84\}$

$g, h \in \{M, F\}$

Observed contact counts

Y_{ab}^{gh}

$(Y_{ab}^{MF}, Y_{ab}^{FM}, Y_{ab}^{MM}, Y_{ab}^{FF})$

Age-gender-specific sample size

N_a^g

(N_a^M, N_a^F)

Age-gender-specific pop. size

P_b^h

(P_b^M, P_b^F)

Dan et al. arxiv 2022 https://arxiv.org/pdf/2210.11358.pdf

Basic notations and definitions

Participant's, contact's age / gender
$a, b \in \{0, 1, \ldots, 83, 84\}$
$g, h \in \{M, F\}$

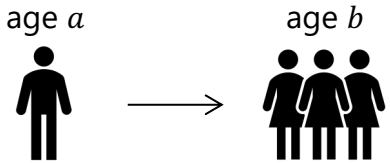
Observed contact counts
Y_{ab}^{gh}
$(Y_{ab}^{MF}, Y_{ab}^{FM}, Y_{ab}^{MM}, Y_{ab}^{FF})$

Age-gender-specific sample size
N_a^g
(N_a^M, N_a^F)

Age-gender-specific pop. size
P_b^h
(P_b^M, P_b^F)

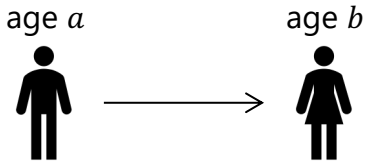
Contact intensity

$$m_{ab}^{MF} = \frac{\mathbb{E}[Y_{ab}^{MF}]}{N_a^M} = \frac{\mu_{ab}^{MF}}{N_a^M}$$



Contact rate

$$\gamma_{ab}^{MF} = \frac{m_{ab}^{MF}}{P_b^F} = \frac{\mu_{ab}^{MF}}{N_a^M P_b^F}$$

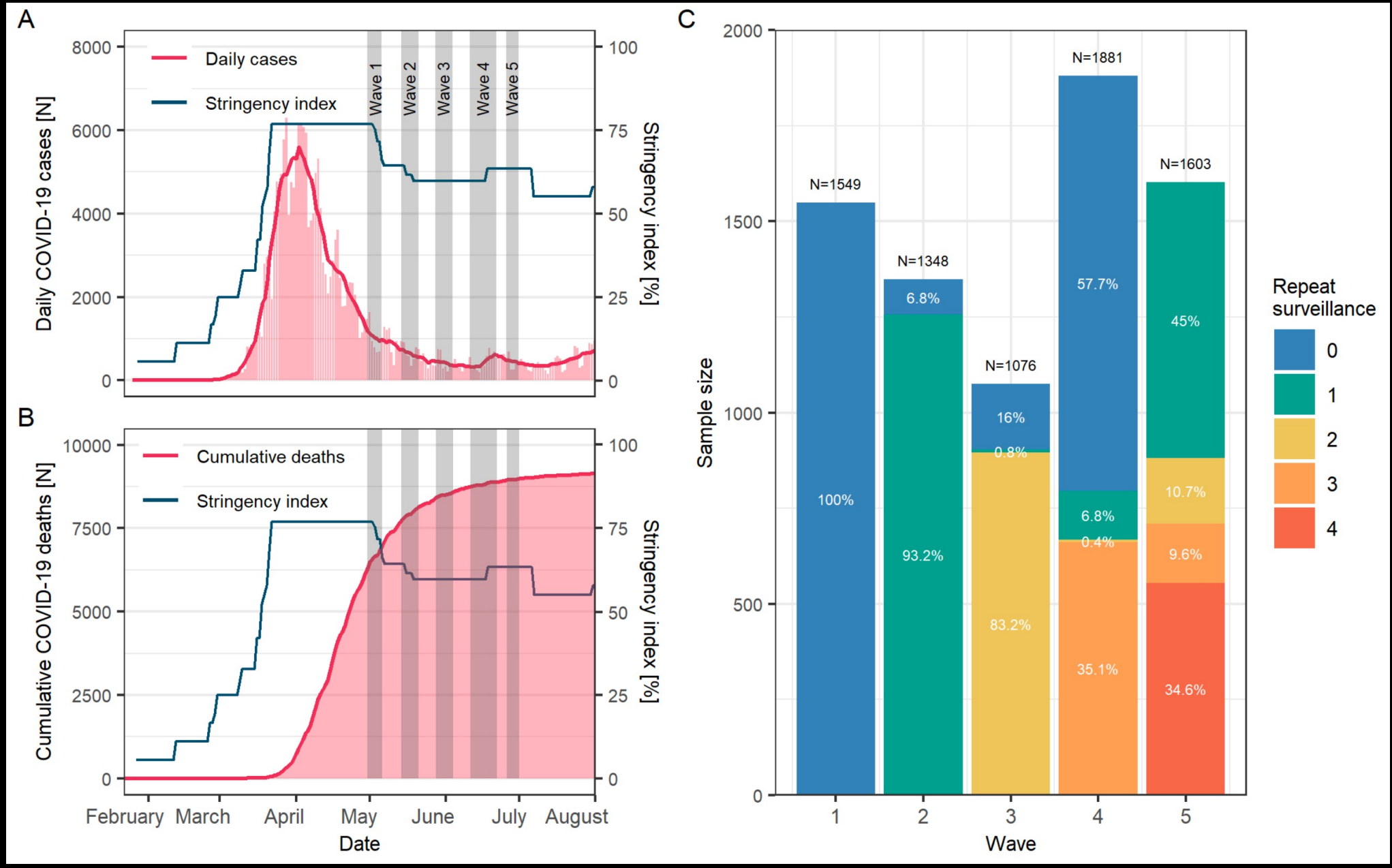


$$\gamma_{ab}^{MF} N_b^F P_a^M = \gamma_{ba}^{FM} N_a^F P_b^M$$

$$\gamma_{ab}^{MF} = \gamma_{ba}^{FM}$$
$$\gamma_{ab}^{MM} = \gamma_{ba}^{MM} \text{ for } a < b$$

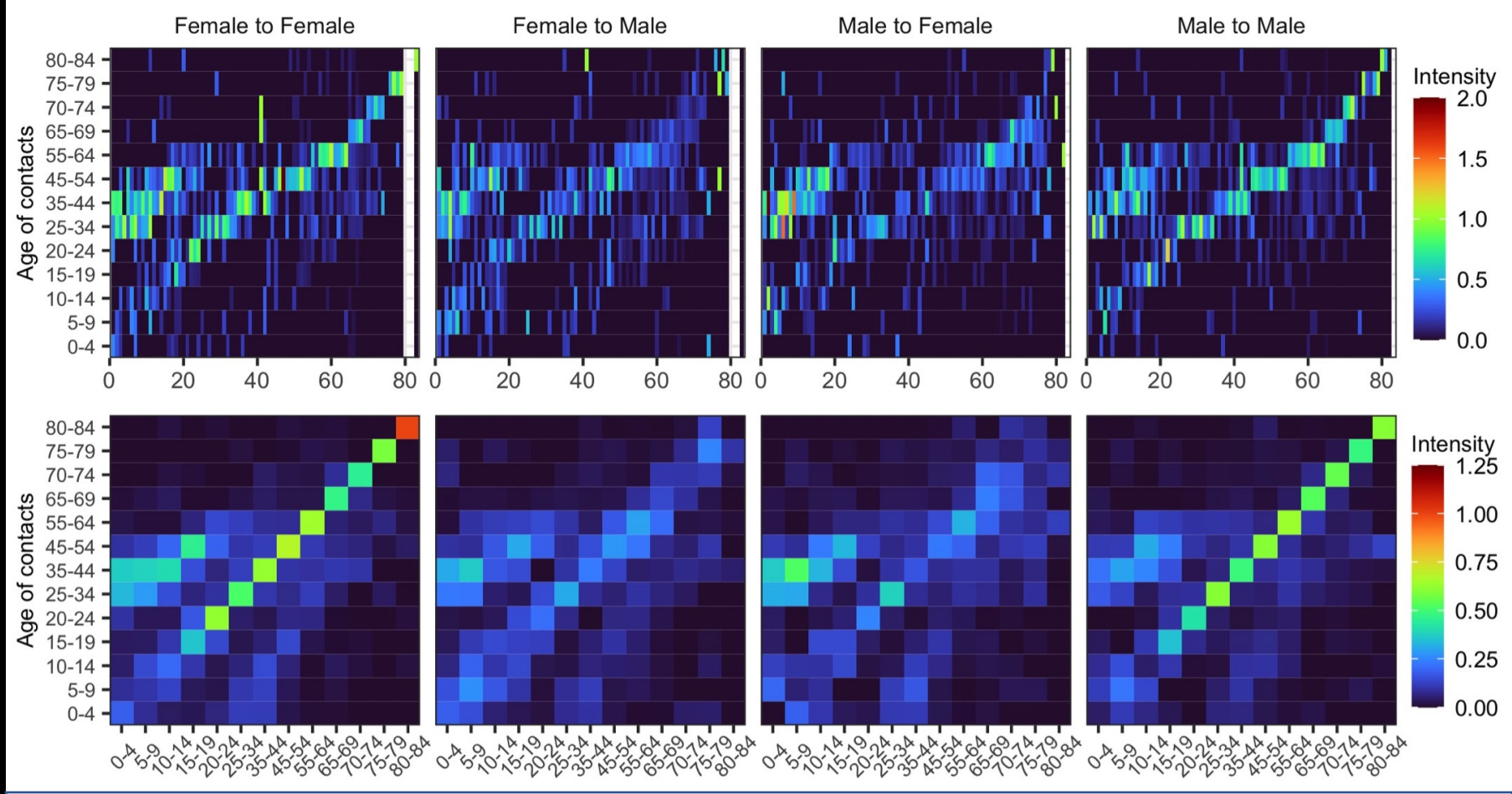
Dan et al. arxiv 2022 https://arxiv.org/pdf/2210.11358.pdf

COVIMOD study, first 5 waves



Dan et al. https://arxiv.org/pdf/2210.11358.pdf

Data for wave 1, Germany



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Probabilistic modelling of contact patterns

Model age-gender-specific contact counts with negative binomial

$$Y_{ab}^{gh} \sim \text{NegBinomial}\left(\alpha_{ab}^{gh}, \frac{1-\nu}{\nu}\right)$$

$$\mu_{ab}^{gh} = \alpha_{ab}^{gh} \frac{\nu}{1-\nu}$$

$$\log \mu_{ab}^{gh} = \log m_{ab}^{gh} + \log N_a^g$$

Gender specific 2D offsets associated with 2D GP priors

$$\log m_{ab}^{gh} = \beta_0 + f^{gh}(a,b) + \log P_b^h$$

Exploit symmetry

$$f^{MF}(a,b) = f^{FM}(b,a) \quad \forall\, a,b$$
$$f^{MM}(a,b) = f^{MM}(b,a) \quad a \le b$$
$$f^{FF}(a,b) = f^{FF}(b,a) \quad a \le b$$

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Recovering fine age structure from coarse age data

Contacts' age is reported in discrete coarse age categories

$$c \in \{0-4, 5-9, 10-14, \ldots, 20-24, 25-34, 35-44, \ldots, 65-69, 70-74, 80-84, \}$$

Link our fine-age model to the coarse-age data by summing the shape parameter

$$Y_{ac}^{gh} = \sum_{b \in c} Y_{ab}^{gh} \sim \text{NegBinomial}\left(\sum_{b \in c} \alpha_{ab}^{gh}, \frac{1-\nu}{\nu}\right)$$

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Non-parametric modelling of contact rates

Input is a 2D grid $\mathbf{x_1} = (\mathbf{a_1}, \mathbf{b_1}), \ldots, \mathbf{x_{AB}} = (\mathbf{a_A}, \mathbf{b_B})$. A zero-mean multivariate Gaussian prior will have covariance matrix $\mathbf{K} \in \mathbb{R}^{\mathbf{AB}\times\mathbf{AB}}$ with elements $\mathbf{k}(\mathbf{x_i}, \mathbf{x_j})$.

$$k\big((a,b),(a',b')\big) = k^1(a,a')k^2(b,b')$$

$$k^1(a,a') = \alpha^2 \exp\left(-\frac{(a-a')^2}{2\ell_a^2}\right)$$

$$k^2(b,b') = \alpha^2 \exp\left(-\frac{(b-b')^2}{2\ell_b^2}\right)$$

Decompose.

Kronecker product.

$$K = K^2 \otimes K^1 = (L^2 \otimes L^1)(L^2 \otimes L^1)^{\mathrm{T}}$$

Linear transformation of standard i.i.d. Gaussians.

$$f(x) = (L^2 \otimes L^1)z = \mathrm{vec}\left(\left(L^2\left(L^1 \mathrm{reshape}(z, A, B)\right)^T\right)^T\right)$$

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Gaussian process approximations to alleviate computational bottleneck

Cost of evaluating log-posterior for GP is $\mathcal{O}(\mathbf{n}^3)$. Approximate the covariance kernel to reduce cost to $\mathcal{O}(\mathbf{mn} + \mathbf{m})$ where $\mathbf{m} \ll \mathbf{n}$.

Spectral density function of the covariance kernel + theory of pseudo-differential operators on compact space

$$k^1(a, a') \approx \sum_{j=1}^{M^1} S^1\left(\sqrt{\lambda_j^1}\right) \phi_j^1(a) \phi_j^1(a')$$

$$S^1(\omega) = \alpha^2 (2\pi \ell_a) \exp\left(-\frac{\ell_a^2 \omega}{2}\right)$$

$$\sqrt{\lambda_j^1} = \frac{j\pi}{2L^1}$$

$$\phi_j^1(x) = \sqrt{1/L^1} \sin\left(\sqrt{\lambda_j^1}(x + L^1)\right)$$

$$L^1 \approx \tilde{L}^1 = \Phi^1 \sqrt{\Delta^1}$$

$$f(x) = \left(\tilde{L}^2 \otimes \tilde{L}^1\right) \tilde{z}$$

Difference in age parameterization

Human contact concentrate among individuals of similar age and individuals with similar age gaps

Parameterize contact rate surface on a difference-in-age by age space as opposed to an age-by-age space

$$\boldsymbol{f} = \begin{bmatrix} f_{11} & f_{12} & f_{13} & \cdots & f_{1A} \\ f_{21} & f_{22} & f_{23} & & \\ f_{31} & f_{32} & f_{33} & & \\ \vdots & & & \ddots & \\ f_{A1} & & & & f_{AA} \end{bmatrix} \quad \hat{\boldsymbol{f}} = \begin{bmatrix} & & & & f_{A1} \\ & & & \iddots & \vdots \\ & & f_{31} & \cdots & f_{A,A-2} \\ & f_{21} & f_{32} & \cdots & f_{A,A-1} \\ f_{11} & f_{22} & f_{33} & \cdots & f_{AA} \\ f_{12} & f_{23} & \cdots & \iddots & \\ f_{13} & \cdots & \iddots & & \\ \vdots & \iddots & & & \\ f_{1A} & & & & \end{bmatrix}$$

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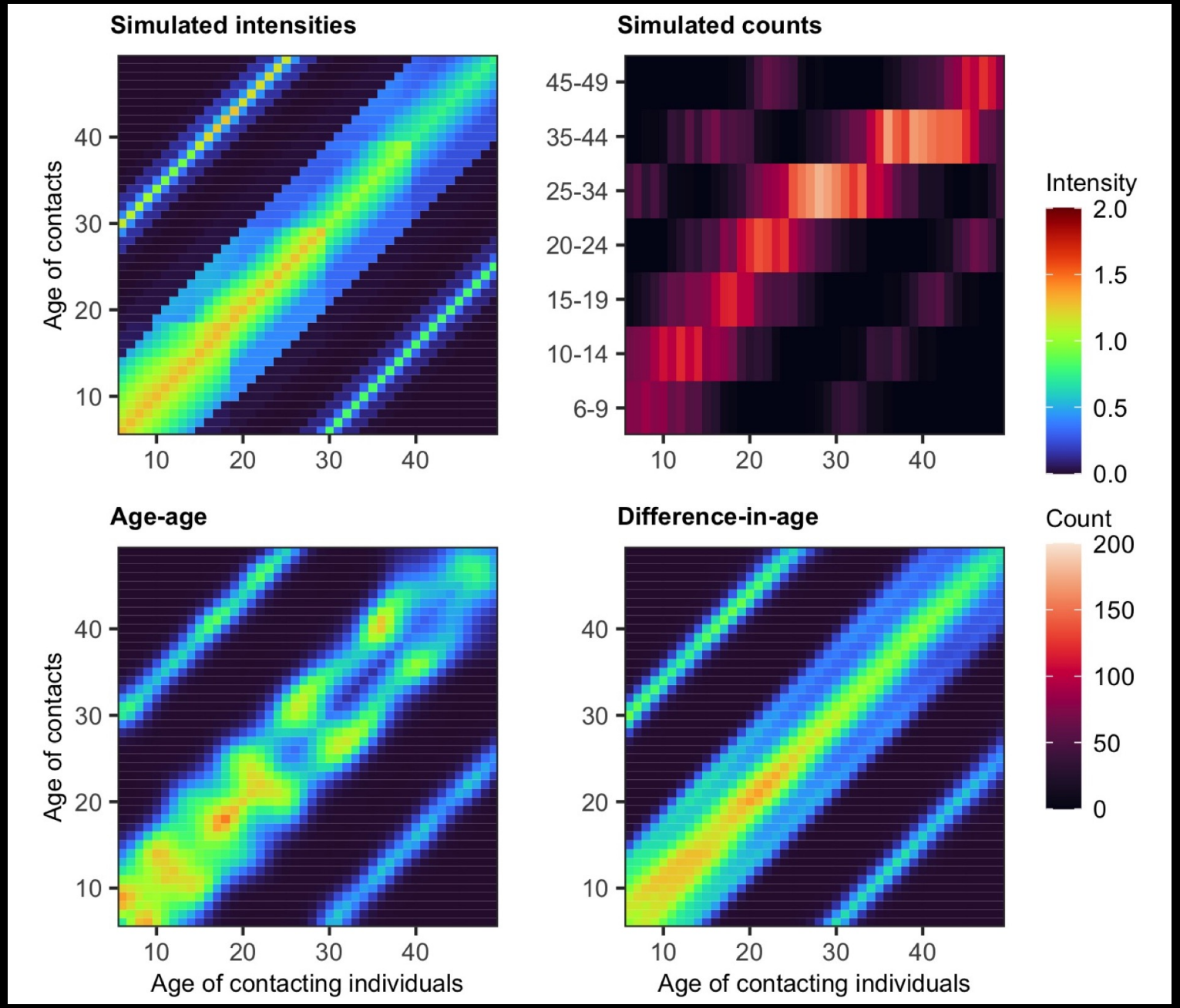
Accuracy on simulated data mimicking pre-COVID19 contact patterns



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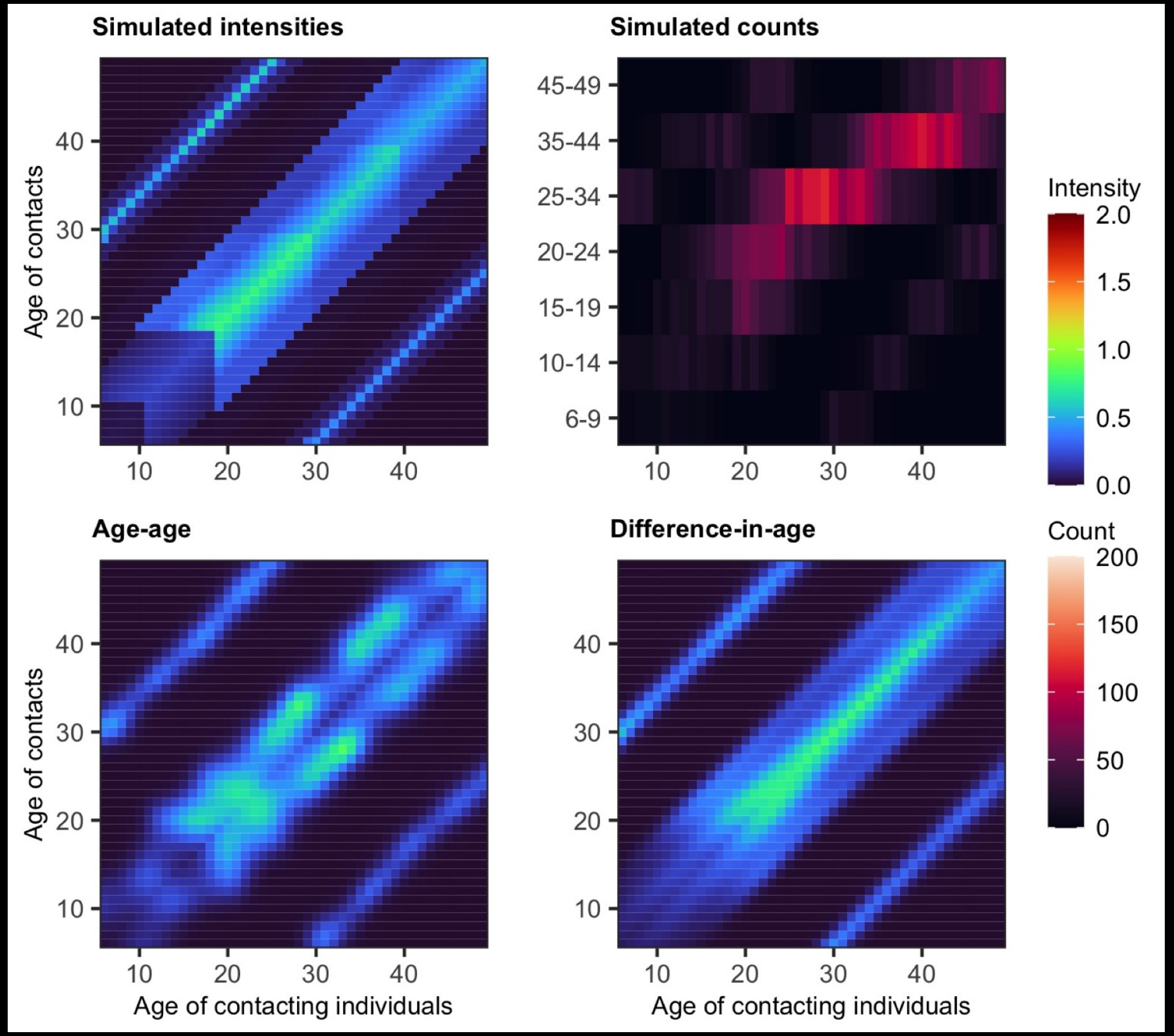
Accuracy on simulated data mimicking in-COVID19 contact patterns



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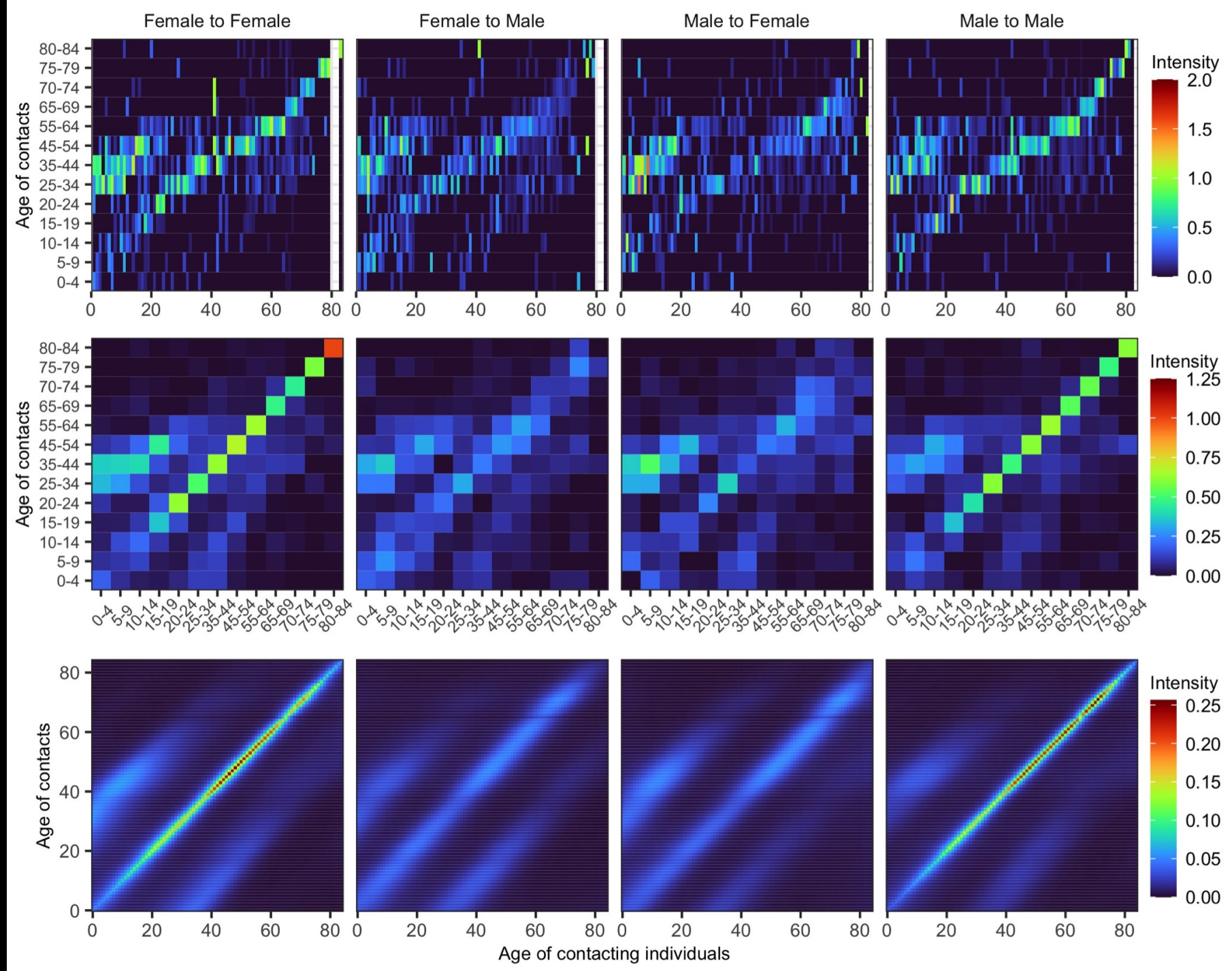
Estimates for wave 1, Germany



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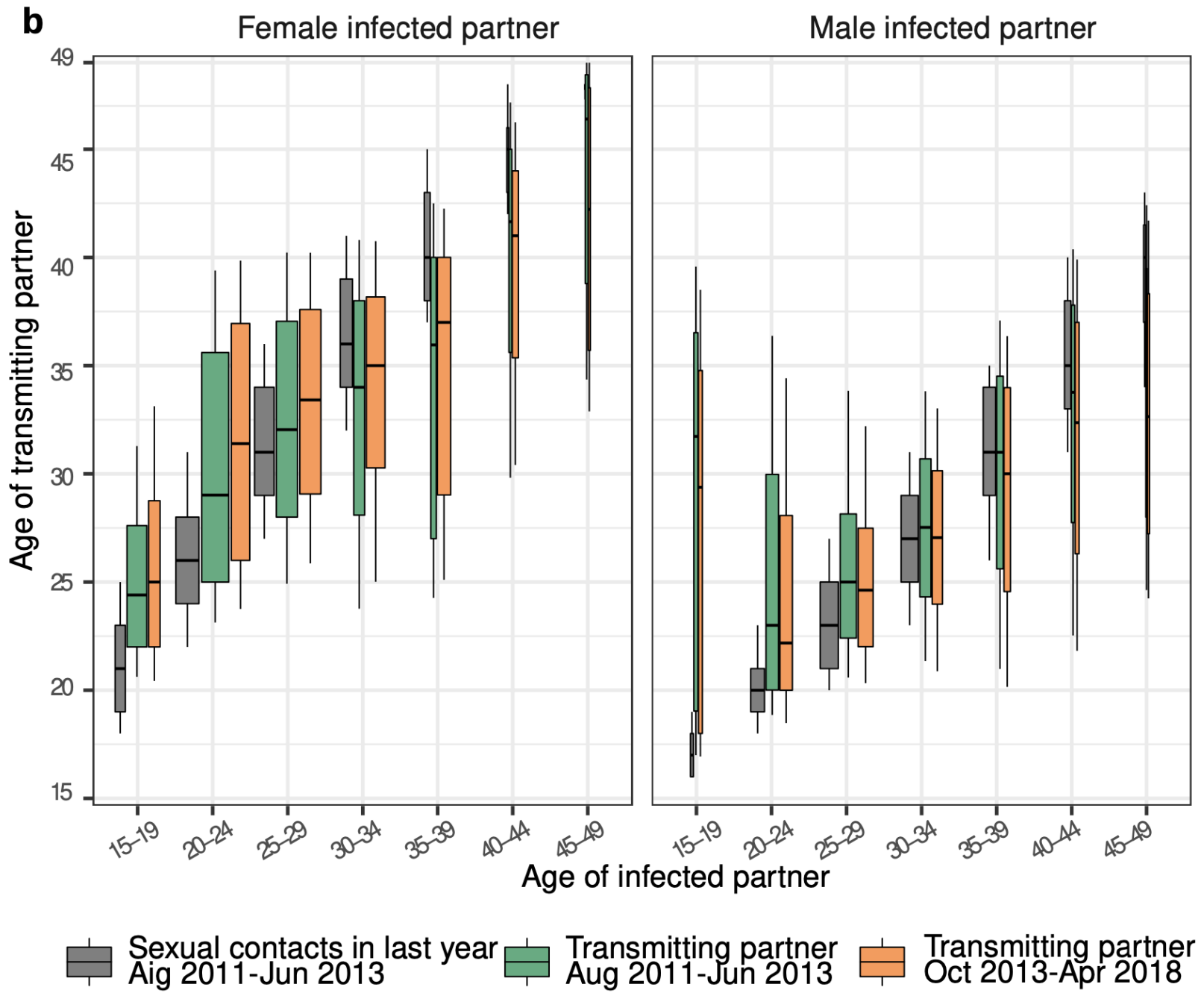
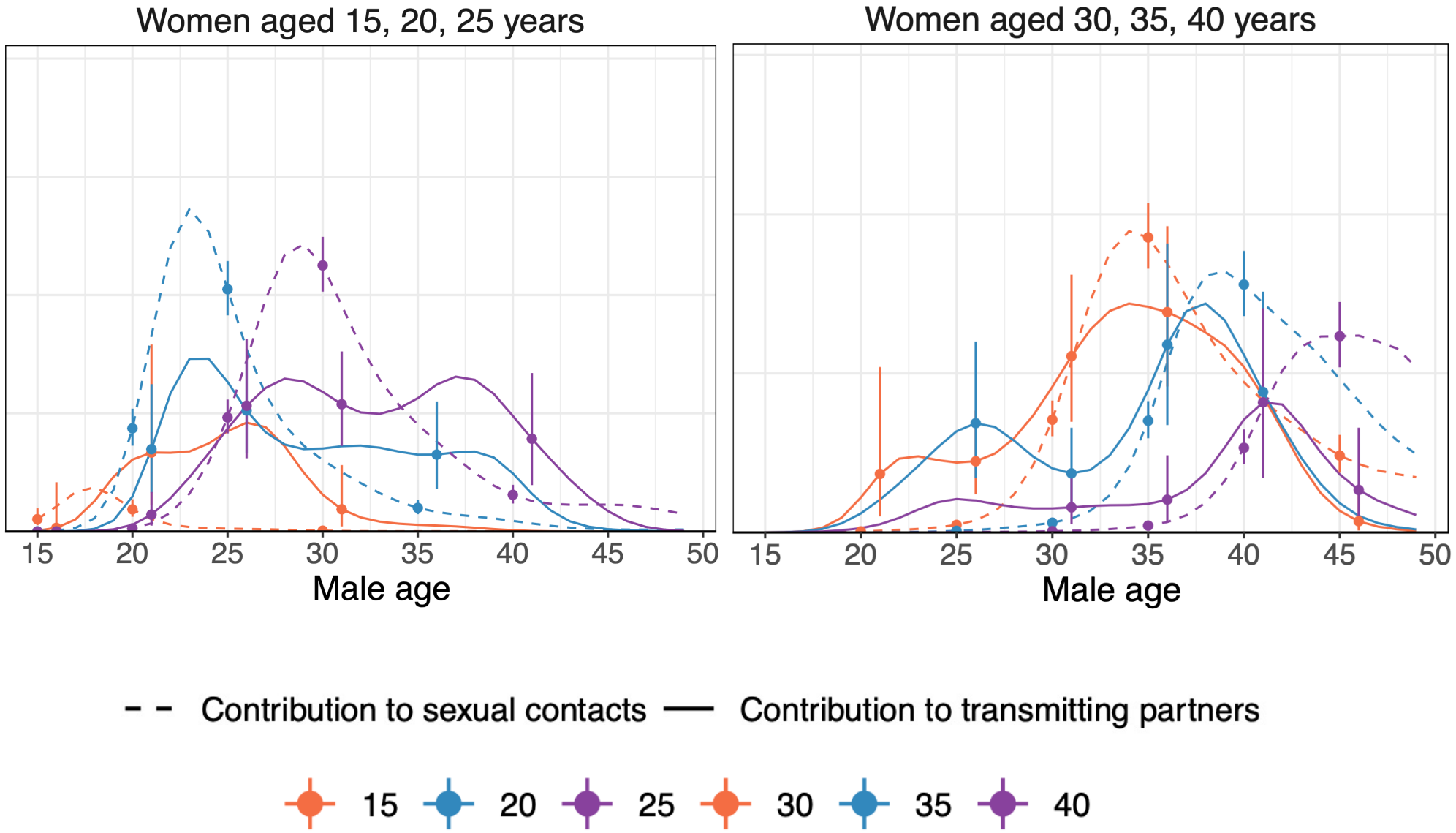
- **Adolescent girls and young women are infected by unusually older male partners.**
- **As women age, age difference between woman and infecting partner decreases.**



Monod et al. – almost submitted.

Transmission flows vs. sexual contact patterns



Monod et al. – almost submitted.

- HIV incidence has declined faster among men than women.
- Average age of infection is increasing among women; and avg. age of transmission is increasing among men.
- While viral load suppression has increased in both genders, the viral load suppression gap has increased between men and women.
- Men are accounting for an increasing proportion of transmissions.
- Having closed the viral load suppression gap between men in women, would have reduced female HIV incidence by 50%.

Thank you

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Steven J Reynolds
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Simon Spencer

Rakai Health Science Program Staff and Study participants

Johns Hopkins School of Medicine

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CDC

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PANGEA HIV

Rakai Health Sciences Program
Improved Health Through Research

NIH National Institute of Allergy and Infectious Diseases

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