Challenges and opportunities with interpretation of results from recency assays used within HIV testing services

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1 Background

What are recency assays?

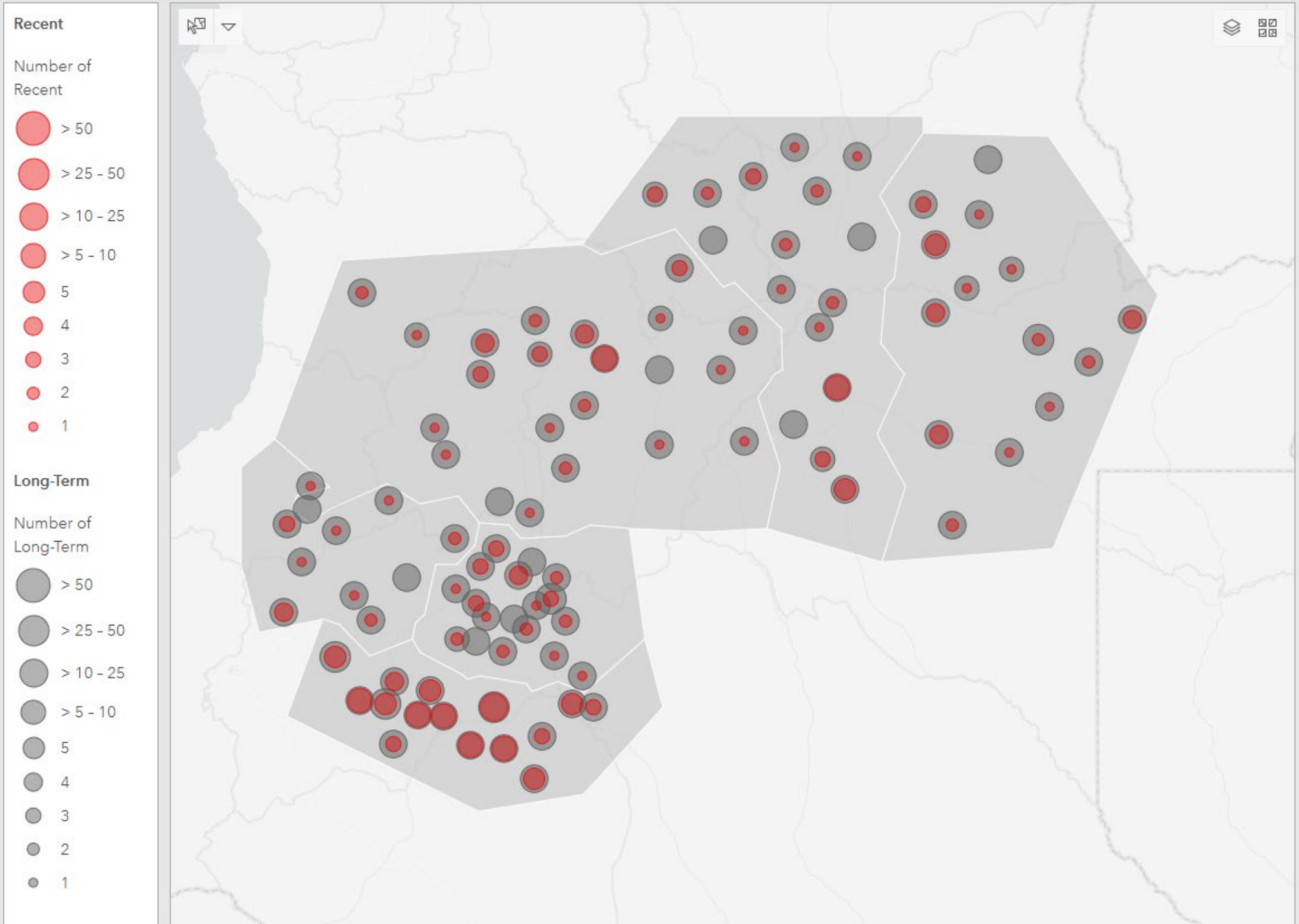
- An HIV “recency assay” is either a serological laboratory-based assay or a rapid test for recent infection (RTRI), which classifies an HIV infection as recent or long-standing.
  - Recency assays use one or more biomarkers to determine longevity of infection, typically by measuring the evolution of the immune response following initial infection.
- RTRIs are used after an individual is diagnosed with HIV and differentiates between recent and long-term infection in a single lateral flow test (as part of a recent infection algorithm).
- In contrast, laboratory-based assays generally produce a numeric result, for which a cut-off set by the assay manufacturer is used to determine whether the infection is classified as recent or not.

Asanté™ HIV-1 Rapid Recency® Assay (Sedia Biosciences)
Photo credit: trace-recency.org.

How are recency assays used?

- In many countries, HIV “recency assays” are now being run on all people newly diagnosed with HIV within HIV testing services (HTS) sites or as part of case surveillance programs
- Assay results are used to calculate an indicator of recency (e.g., number of recent results / number of people tested for HIV) to aid resource prioritization in the quest to eliminate HIV.
  - This indicator has been used to create maps of geographic “hotspots” or identify subpopulations that appear to have ongoing HIV transmission.
  - In these scenarios a high “proportion recent” is considered a red flag indicating that further intervention is needed.

SAMPLE (fictitious) dashboard created by ICAP and available on trace-recency.org/example-dashboard



Recent
234

Long-Term
1,645

Number Tested
1,889

Most Number of Recent Infections

Facility 20
Recent: 11
Long-Term: 26
Number Tested: 37

Facility 22
Recent: 8
Long-Term: 23
Number Tested: 31

Facility 15
Recent: 7
Long-Term: 19
Number Tested: 26

Facility 23
Recent: 7
Long-Term: 17

2 Challenges with Interpretation

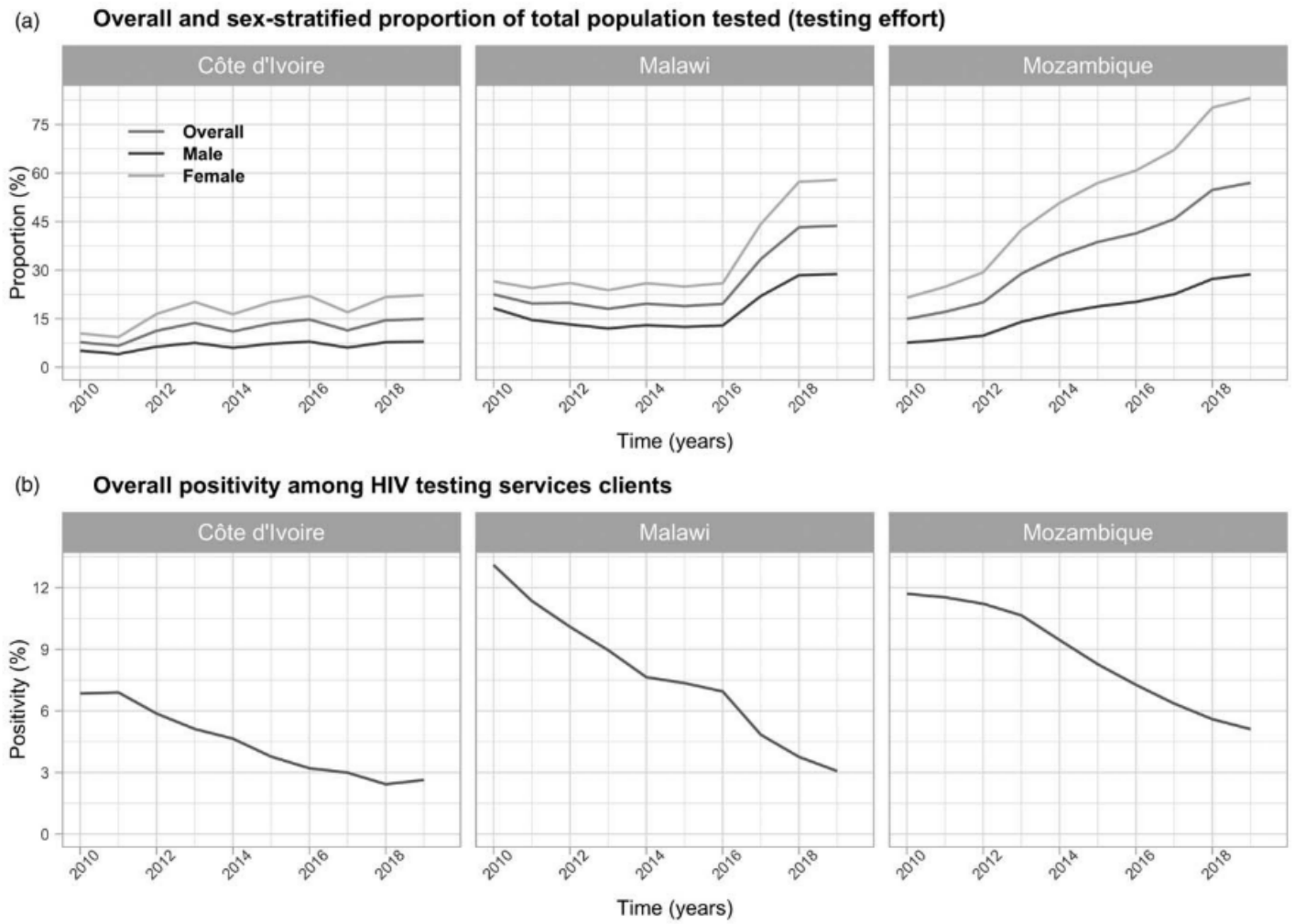
Why is interpretation challenging?

- Trends are affected by changes in testing patterns and coverage
- Differences in different regions may be about selection bias (who comes to the sites in those regions), not real differences
- Geographic clustering is affected by mobility

Godin, *et al*. 2021

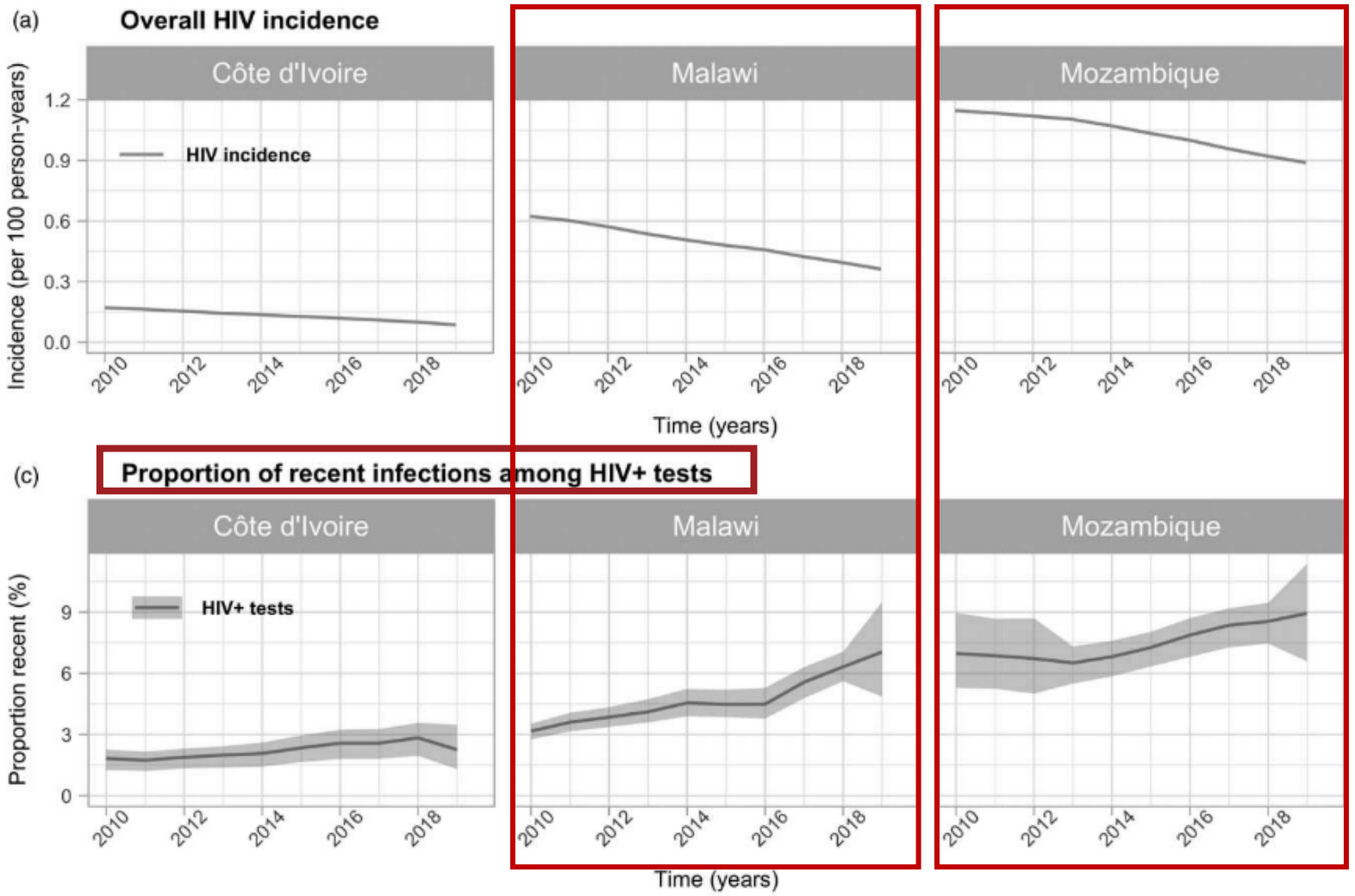
AIDS, 35(14):2383-8.

Used a mathematical model to compare different denominators for recency indicators, to measure indicator trends compared to “true” incidence over time



Godin, *et al*. 2021

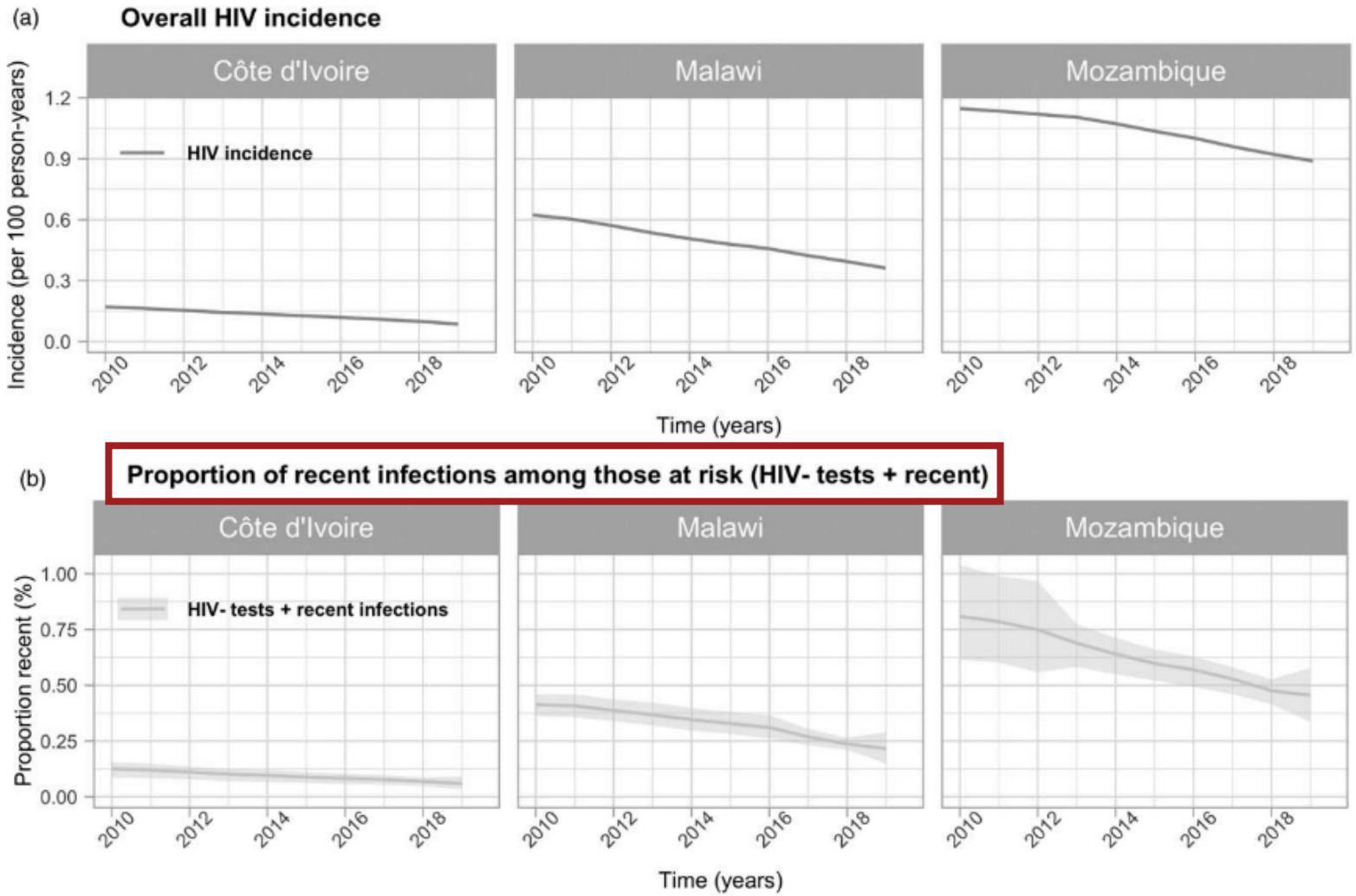
AIDS, 35(14):2383-8.



In some cases, trends in the recency indicator differed substantially from incidence trends.

Godin, *et al*. 2021

AIDS, 35(14):2383-8.



Godin, *et al*. 2021

AIDS, 35(14):2383-8.

- Bottom line: use of the total number of people newly diagnosed with HIV as a denominator may be very inaccurate, and may even have a trend in the opposite direction to HIV incidence.

Best Practice 3.3. When calculating a proportion-based indicator of recency from case surveillance or HIV testing services, the "proportion recent" should be calculated as the number of recent infections divided by the total number of people at risk for HIV (those testing recent + those testing HIV-negative, *not* the total number of people newly diagnosed).

Mitchell, *et al*. 2020

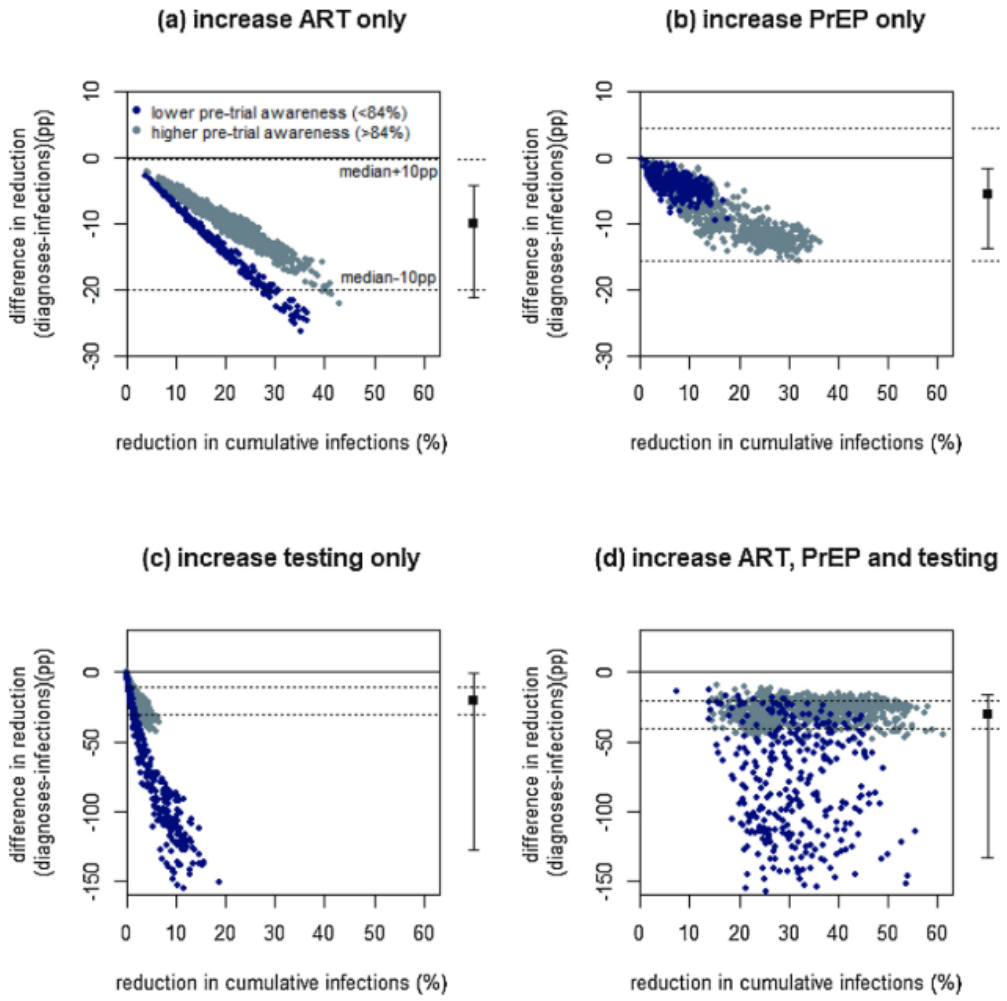
Epidemics, 33:100423.

- Used an HIV transmission model fitted to an MSM epidemic in Baltimore to determine whether routinely collected data could be used in place of an HIV incidence cohort to track changes in HIV incidence
  - Simulated a cluster-randomized controlled trial of HIV prevention strategies
- Looked at the bias (differences in reduction in diagnoses) due to expanded ART, PrEP, and HIV testing, and combo over a 2-year trial (with 6-month scale-up period)

Mitchell, *et al*. 2020

Epidemics, 33:100423.

- Found that when interventions only expanded ART or PrEP, reductions in acute/early infection sufficiently mirrored reductions in HIV incidence
- However, if HIV testing was being expanded as part of the intervention, none of the investigated measures derived from routine surveillance data adequately reflected reductions in HIV incidence well enough to be used

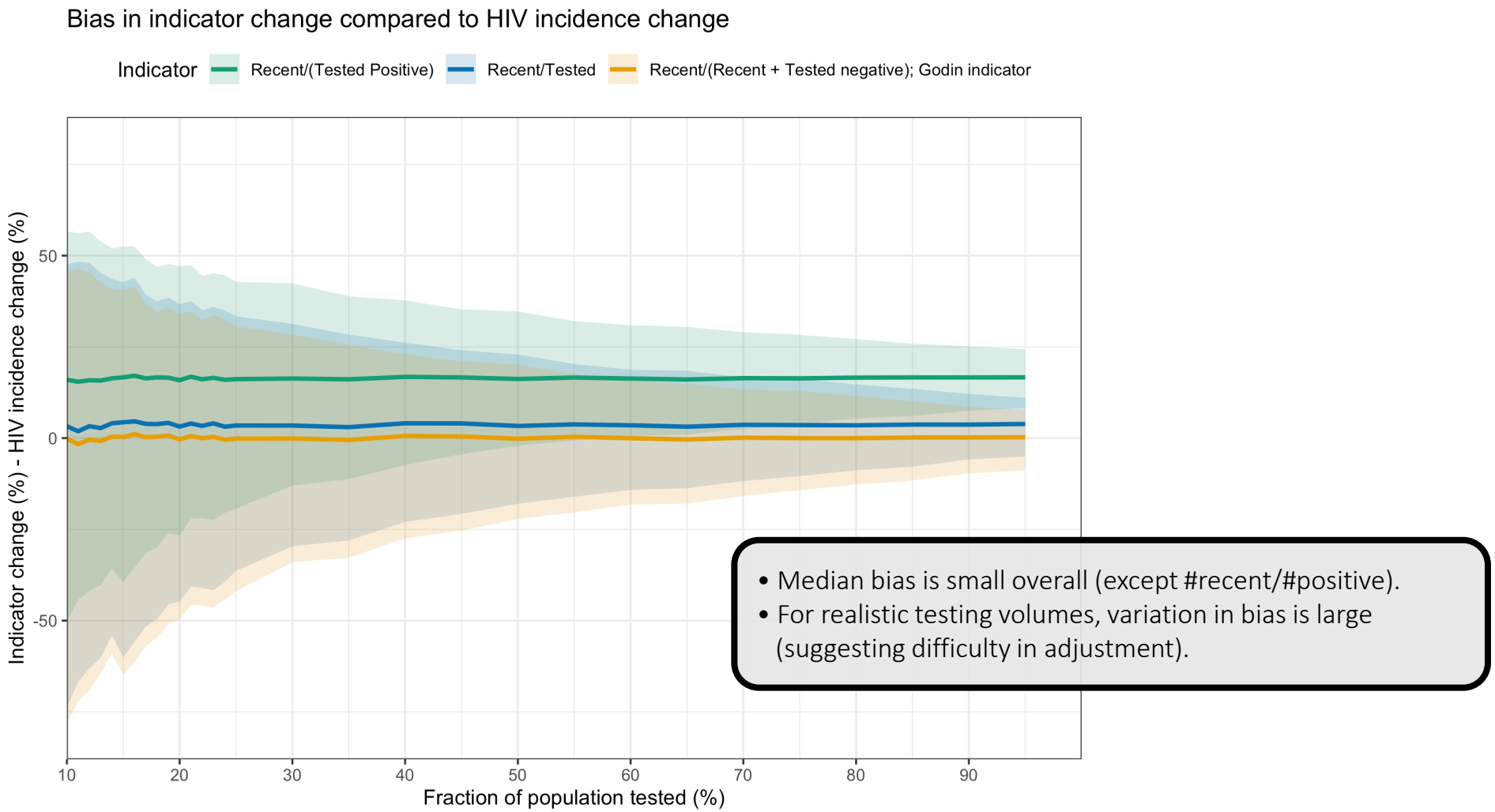


3 Our analysis

Methods

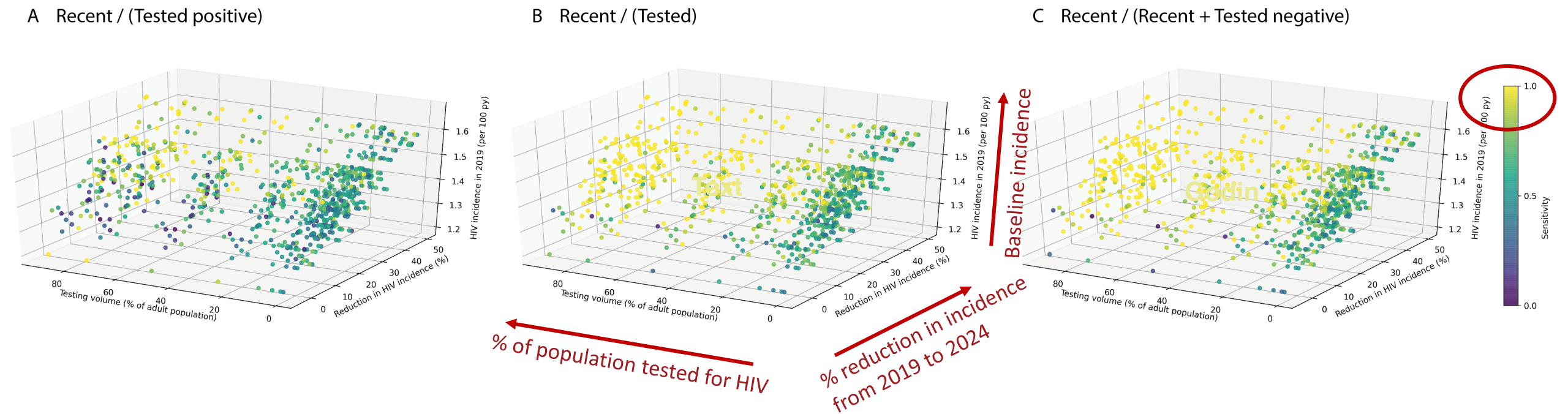
- We used an individual-based model calibrated to a hypothetical community setting to quantify various recency indicators and their sensitivity to contextual factors (the underlying HIV care cascade, HIV prevalence, testing coverage, and recruitment strategies of targeted HTS programs).
  - Population of 50,000 people, with 15-20% prevalence
- We simulated a variety of scenarios to better understand when recency indicators are accurate proxies for rates of ongoing transmission, and when contextual factors result in the indicator providing a skewed sense of epidemic trends.
  - True incidence rate over 6 months was calculated for 2019 and 2024

Results



- Median bias is small overall (except #recent/#positive).
- For realistic testing volumes, variation in bias is large (suggesting difficulty in adjustment).

Results


A Recent / (Tested positive)
B Recent / (Tested)
C Recent / (Recent + Tested negative)
Testing volume (% of adult population)
Reduction in HIV incidence (%)
HIV incidence in 2019 (per 100 py)
Sensitivity
Baseline incidence
% of population tested for HIV
% reduction in incidence from 2019 to 2024

Results

Sensitivity

Indicator	Indicator sensitivity (%)							
	HIV incidence change <20%				HIV incidence change ≥20%			
	Fraction tested (% of population)				Fraction tested (% of population)			
	10%	20%	50%	90%	10%	20%	50%	90%
Number recent/Number tested HIV-positive	48	49	45	40	68	74	89	99
Number recent/Number tested for HIV	64	70	83	89	83	90	99	100
Number recent/(Number tested HIV-negative + Number tested recent)	68	75	88	93	85	94	100	100

4 Conclusions

Conclusions

- Recency indicators using direct proportions may vary considerably based on the underlying HIV testing and care cascade and therefore may not correlate well with HIV incidence.
- The closer programs are to achieving 100% of people diagnosed during early infection – an explicit goal of most targeted HTS programs – the less meaningful these recency indicators become.
  - Is a recency indicator approaching 100% the goal? Or a sign of needed intervention?
- The use of recency assays to calculate indicators on proportion recent (as opposed to true incidence calculations) should be interpreted with caution.
  - If used, "proportion recent" should be calculated as the number of recent infections divided by (number testing HIV-negative + number testing recent), not the total number of people newly diagnosed. *Godin 2021*

So, how can we use recency assays *well*?

1. When you have a representative sample (in a region or sub-population) large enough to estimate HIV incidence directly
2. When you have two populations (geographic, demographic, or time) and want to compare recency rates between them, IF:
    - You are able to minimize selection bias (x2) and have a generalizable sample
    - You use the appropriate denominator for your recency indicator
    - The two populations have comparable:
        - PrEP coverage (including long-acting injectables, which will complicate)
        - HIV testing coverage/behavior (including re-testing)
        - ART coverage