

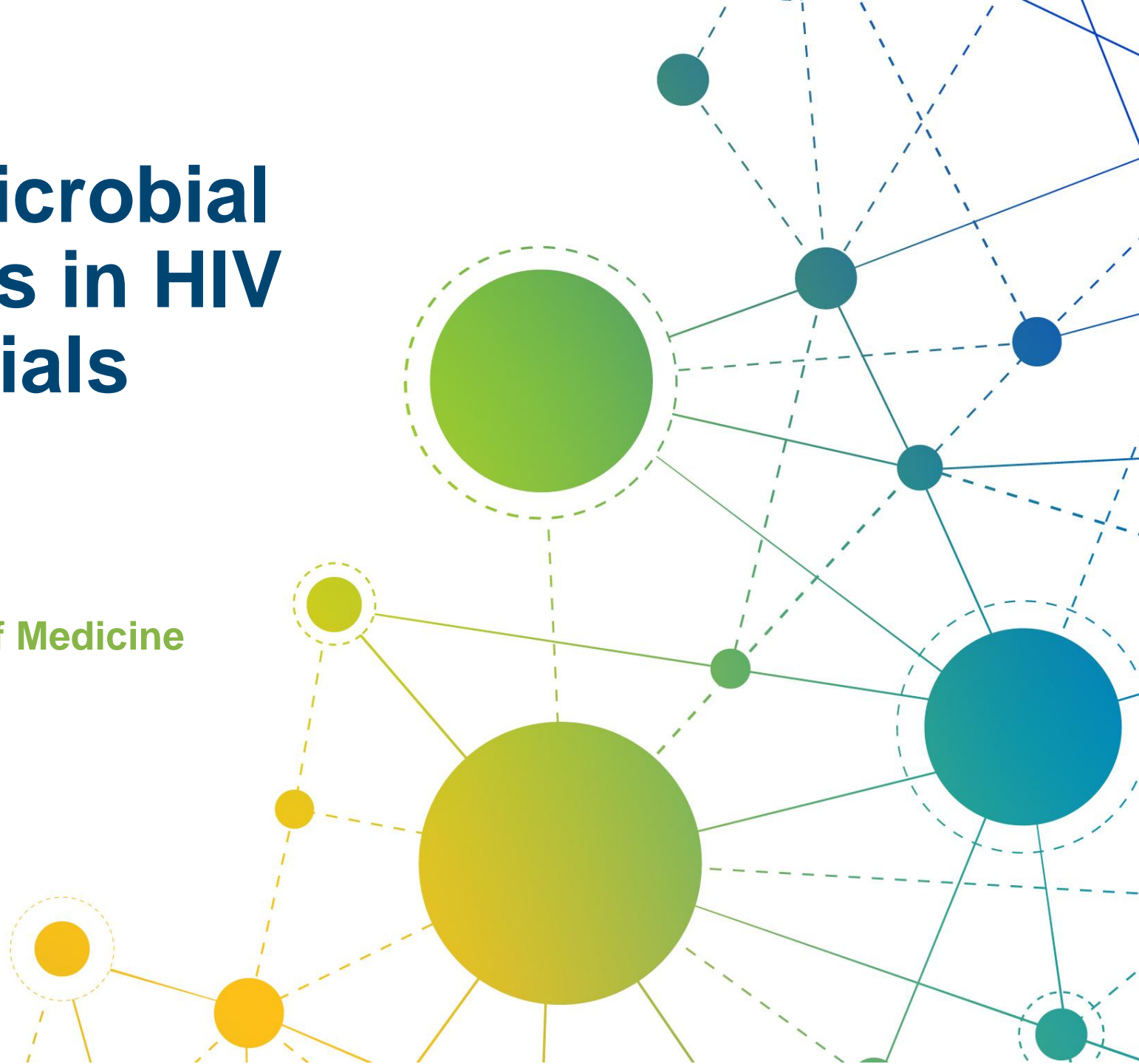
# Assessing Antimicrobial Resistance in STIs in HIV Prevention Trials

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HPTN LC

June 18, 2024



# Key Findings and Takeaways

- Urgent need for POC diagnostics to combat STI epidemic
- Limited data on antimicrobial resistance (AMR) in STIs
- Assessment of AMR in NG is challenging, especially in LMICs
- STI research/prevention is HIV prevention

# High rates of STIs and the need for affordable POC diagnostics

# Global Curable STIs

## Incident cases of four curable STIs among adults (15–49 years old), by WHO region, 2020

Syphilis (*Treponema pallidum*), gonorrhoea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*) and trichomoniasis (*Trichomonas vaginalis*)

### GLOBAL

**374 million**  
[286 million–481 million]

### REGION OF THE AMERICAS

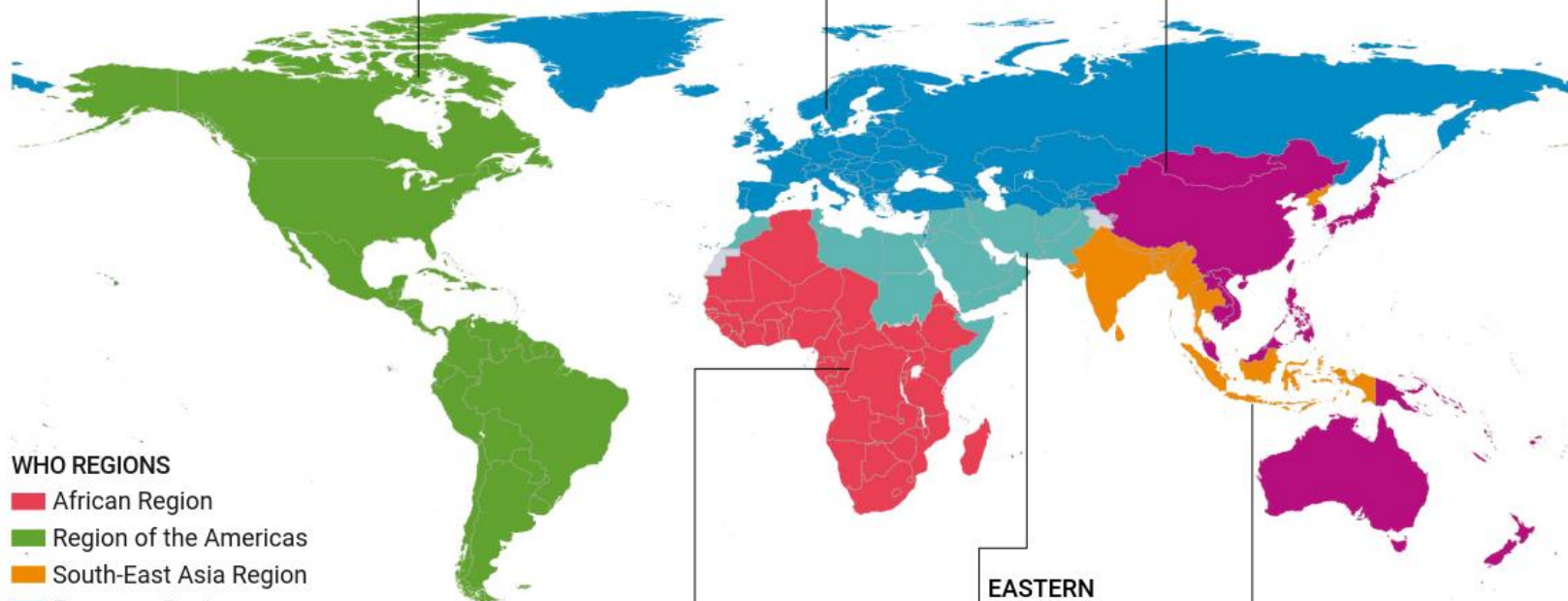
**74 million**  
[53 million–104 million]

### EUROPEAN REGION

**23 million**  
[16 million–31 million]

### WESTERN PACIFIC REGION

**86 million**  
[61 million–117 million]



### WHO REGIONS

- African Region
- Region of the Americas
- South-East Asia Region
- European Region
- Eastern Mediterranean Region
- Western Pacific Region
- Not applicable

**Chlamydia - 129 million**

**Gonorrhoea - 82 million**

**Syphilis - 7.1 million**

**Trichomoniasis - 156 million**

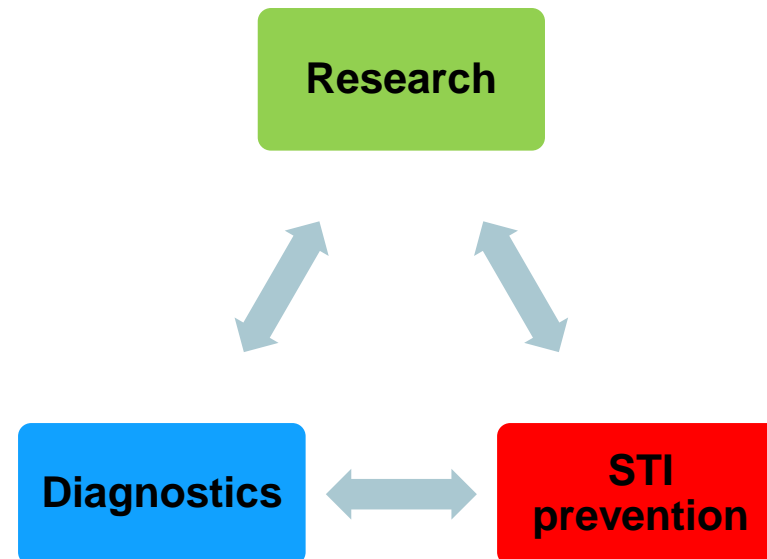
Source: WHO, 2021.

# Commercially Available POCT for STIs

Company Product	Cepheid Xpert	Binx io®	Visby	Osom	Quidel Solana
<b>Description</b>	<b>NG, CT, TV</b> NAAT with molecular beacon detection	<b>NG, CT</b> NAAT with electrochemical detection	<b>NG, CT, TV</b> Single-use deviceless NAAT	<b>TV</b> Immunochromatographic lateral flow assay	<b>TV</b> Helicase-dependent nucleic acid amplification
<b>Sensitivity (%)</b>	<b>Vaginal</b> – CT (98.7); NG (100) <b>Male urine</b> – CT (97.5); NG (98)	<b>Vaginal</b> – CT (96.1); NG (100) <b>Male urine</b> – CT (92.5); NG (97.3)	CT – 97.6 NG – 97.4 TV – 99.2	83-90%	<b>Vaginal</b> – 89.7 <b>Urine</b> – 100
<b>Specificity (%)</b>	<b>Vaginal</b> – CT (99.); NG (99.9) <b>Male urine</b> – CT (99.9); NG (99.9)	<b>Vaginal</b> – CT (99.1); NG (99.9) <b>Male urine</b> – CT (99.3); NG (100)	CT – 98.3 NG – 99.4 TV – 96.9	100%	<b>Vaginal</b> – 98.0 <b>Urine</b> – 99.9
<b>Turnaround time</b>	<b>CT/NG – 90 min; TV – 42 min</b>	<b>30 min</b>	<b>30 min</b>	<b>15 min</b>	<b>40 min</b>
<b>FDA cleared, CLIA waived</b>	Yes, No	Yes, Yes	510 (K) clearance, Yes	Yes, Yes	Yes, No
<b>Use Cases</b>	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic	Symptomatic, asymptomatic
<b>Specimen types</b>	Vaginal (self); Cervical (clinician); Urine; Rectal (self); Pharyngeal (self)	Vaginal (self); Urine	Vaginal (self)	Vaginal (self)	Vaginal (self); urine

**Molecular tests – expensive, require sophisticated instrumentation, and not suitable for LMICs**

# Assessment of a new diagnostic test for gonorrhoea in a LMIC





# Rapid Diagnostics for Gonorrhea

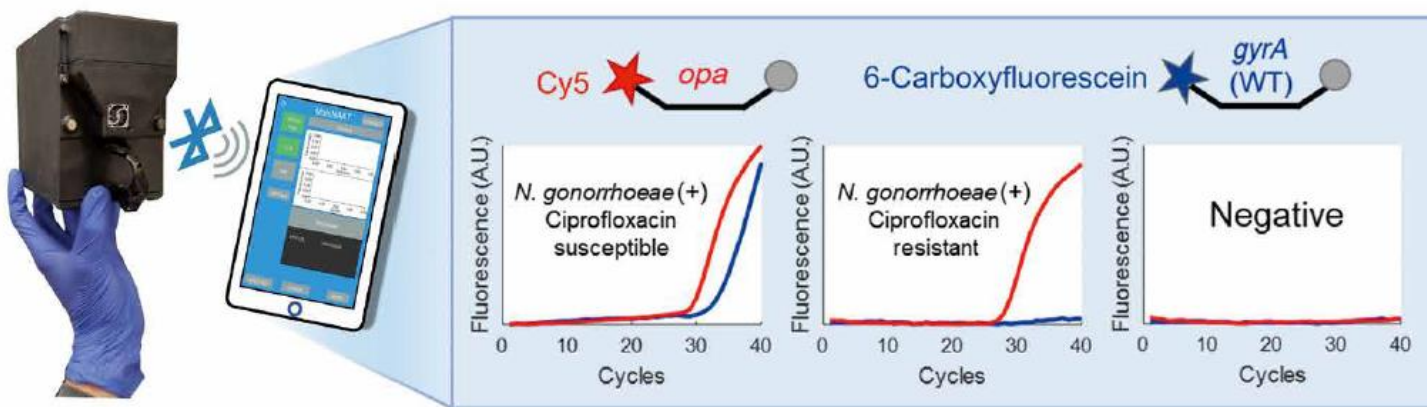
SCIENCE TRANSLATIONAL MEDICINE | REPORT

INFECTIOUS DISEASE

April 2021

## A portable magnetofluidic platform for detecting sexually transmitted infections and antimicrobial susceptibility

Alexander Y. Trick<sup>1</sup>, Johan H. Melendez<sup>2</sup>, Fan-En Chen<sup>1</sup>, Liben Chen<sup>3</sup>, Annet Onzia<sup>4</sup>, Aidah Zawedde<sup>4</sup>, Edith Nakku-Joloba<sup>5</sup>, Peter Kyambadde<sup>6</sup>, Emmanuel Mande<sup>4</sup>, Joshua Matovu<sup>4</sup>, Maxine Atuheirwe<sup>4</sup>, Richard Kwizera<sup>4</sup>, Elizabeth A. Gilliams<sup>2,7</sup>, Yu-Hsiang Hsieh<sup>8</sup>, Charlotte A. Gaydos<sup>2</sup>, Yukari C. Manabe<sup>2,4</sup>, Matthew M. Hamill<sup>2,7</sup>, Tza-Huei Wang<sup>1,2,3,9\*</sup>



- 15 min assay
- Detection of *N. gonorrhoeae* and *GyrA* genotype (ciprofloxacin susceptibility)
- Penile samples – Ugandan men
- Sensitivity and specificity
  - 97.7% (95% CI, 94.7 to 100%)
  - 97.6% (95% CI, 94.1 to 100%)
- US\$2 per cartridge
- Portable 5-V power bank

Additional specimens and data collected for follow-up analyses

# STIs in Ugandan Men

BMC Infectious Diseases

May 2022

RESEARCH

Open Access

High burden of untreated syphilis, drug resistant *Neisseria gonorrhoeae*, and other sexually transmitted infections in men with urethral discharge syndrome in Kampala, Uganda



Matthew M. Hamill<sup>1\*</sup>, Annet Onzia<sup>2</sup>, Tza-Huei Wang<sup>3</sup>, Agnes N. Kiragga<sup>2</sup>, Yu-Hsiang Hsieh<sup>1</sup>, Rosalind Parkes-Ratanshi<sup>2</sup>, Ethan Gough<sup>4</sup>, Peter Kyambadde<sup>5</sup>, Johan H. Melendez<sup>1</sup> and Yukari C. Manabe<sup>1,2</sup>

- Gonorrhea (**66.4%**), chlamydia (**21.7%**), trichomoniasis (**2.0%**)
- NG -100% resistance to ciprofloxacin, penicillin, and tetracycline
- HIV – 20% (n=50)
- Syphilis – 10% (80% unaware of infection)



April 2022

Retrospective Analysis of Ugandan Men with Urethritis Reveals *Mycoplasma genitalium* and Associated Macrolide Resistance

Johan H. Melendez,<sup>a</sup> Justin Hardick,<sup>a</sup> Annet Onzia,<sup>b</sup> Tong Yu,<sup>a</sup> Peter Kyambadde,<sup>c</sup> Rosalind Parkes-Ratanshi,<sup>b</sup> Edith Nakku-Joloba,<sup>b</sup> Agnes Kiragga,<sup>b</sup> Yukari C. Manabe,<sup>a</sup> Matthew M. Hamill<sup>a</sup>

- 12.8% positivity rate (41% MG mono infection)
- 10.7% - macrolide resistance
- *M. genitalium* – more common without gonorrhea ( $p=0.001$ )

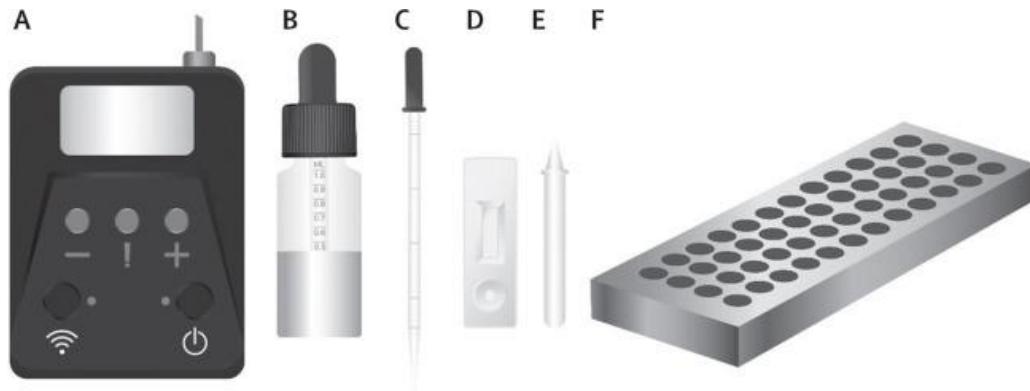
Assessment of molecular diagnostic supported additional research on STIs



# Non-Molecular NG Diagnostic for LMICs

## Novel lateral flow assay for point-of-care detection of *Neisseria gonorrhoeae* infection in syndromic management settings: a cross-sectional performance evaluation

Remco P H Peters, Jeffrey D Klausner, Laura Mazzola, Mandisa M Mdingi, Hyunsul Jung, Ranjana M S Gigi, Jeremie Piton, Joseph Daniels, Lindsey de Vos, Paul C Adamson, Birgitta Gleeson, Cecilia Ferreyra



### *Neisseria gonorrhoeae* lateral flow assay testing device

A) Automated reader, B) buffer bottle, C) pipette, D) test cassette, E) dropper, F) specimen block

Urine or eluted vaginal swab is mixed with buffer, 4 drops loaded onto the test cassette. After 20 min, the cassette is read using a handheld electronic fluorescence reader, which provides automated qualitative result (positive, negative, or invalid) for NG detection.

- Handheld reader – powered by an external battery (charge every 3–4 weeks); internet connectivity not required.
- One test at a time, few seconds per cassette; results can be downloaded from the reader.

## Participants – 5 health care facilities in South Africa

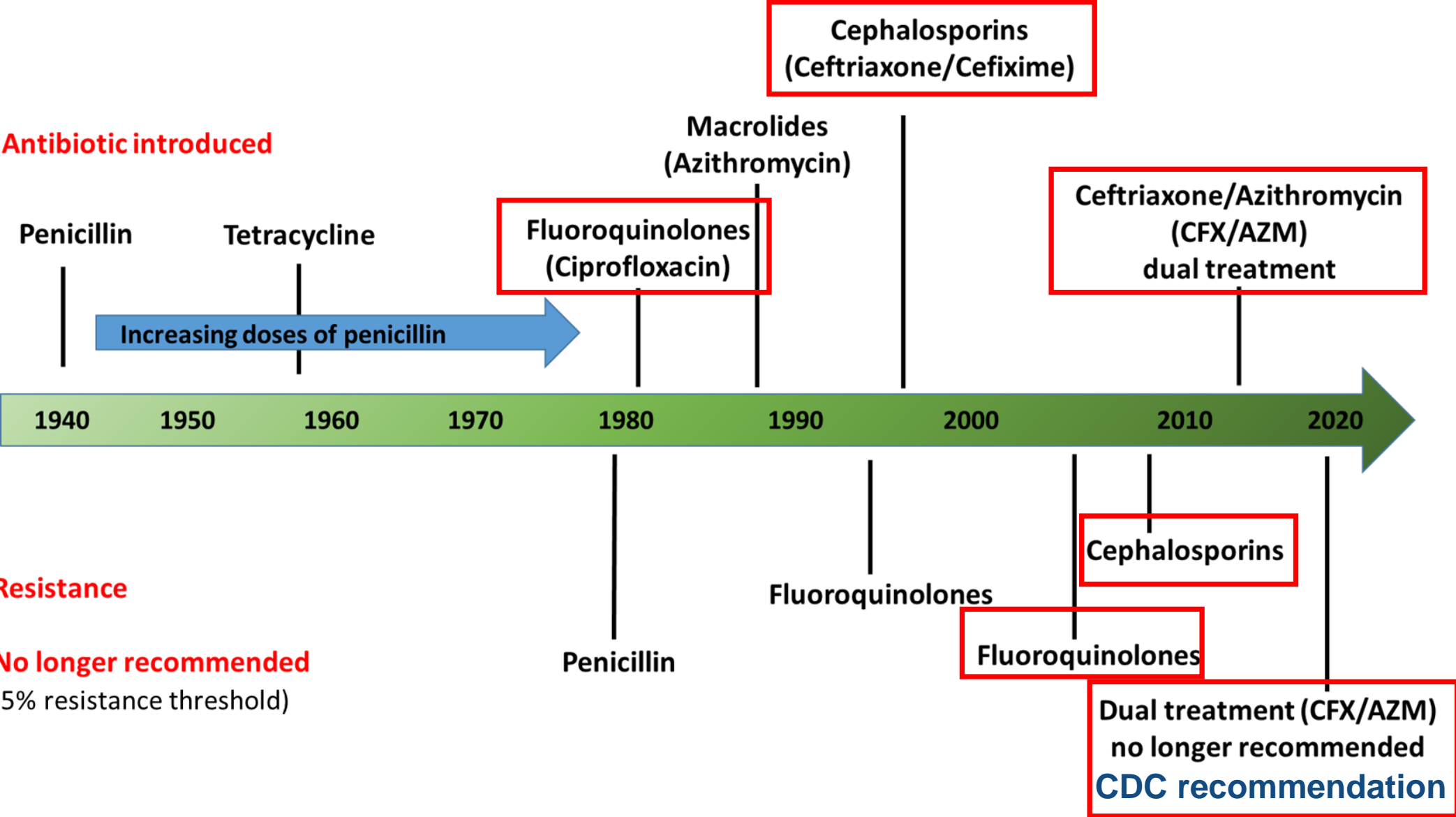
	Male patients (n=200)	Female patients (n=200)
<i>Neisseria gonorrhoeae</i> prevalence	128 (64%)	36 (18%)
Sensitivity	96.1% (91.2–98.3)	91.7% (78.2–97.1)
Specificity	97.2% (90.4–99.2)	96.3% (92.2–98.3)
Positive predictive value	98.4% (94.4–99.6)	84.6% (70.3–92.8)
Negative predictive value	93.3% (85.3–97.1)	98.1% (94.7–99.4)
Accuracy	96.5% (93.0–98.3)	95.5% (91.7–97.7)

Data n (%) or % (95% Wilson’s CI).

Table 3: Diagnostic performance characteristics of *Neisseria gonorrhoeae* lateral flow assay compared with Xpert for the detection of *N gonorrhoeae* in symptomatic male and female patients

# Antimicrobial resistance in *Neisseria gonorrhoeae*: Challenges in LMICs

# Evolution of AMR in NG in the U.S.



# Recommended Treatment for NG

	WHO global*	Europe	UK	Australia	USA	Canada	Japan	China	Uganda
Ceftriaxone (Intramuscular)	250 mg	1 g	1 g	500 mg	500 mg	250 mg	1 g	1 g	
Cefixime (Oral)									400 mg
Azithromycin (Oral)	1 g	2 g		1 g		1 g			
Doxycycline (Oral) – 7 days If <i>Chlamydia trachomatis</i> cannot be excluded		100 mg	100 mg		100 mg		100 mg		100 mg
Alternative treatments	Cefixime 400 mg plus Azithromycin 1 g			2 g Azithromycin (pharyngeal)	1 g ceftriaxone (≥150 kg)			Spectinomycin 2 g intramuscular (cervicitis - 4 g)	

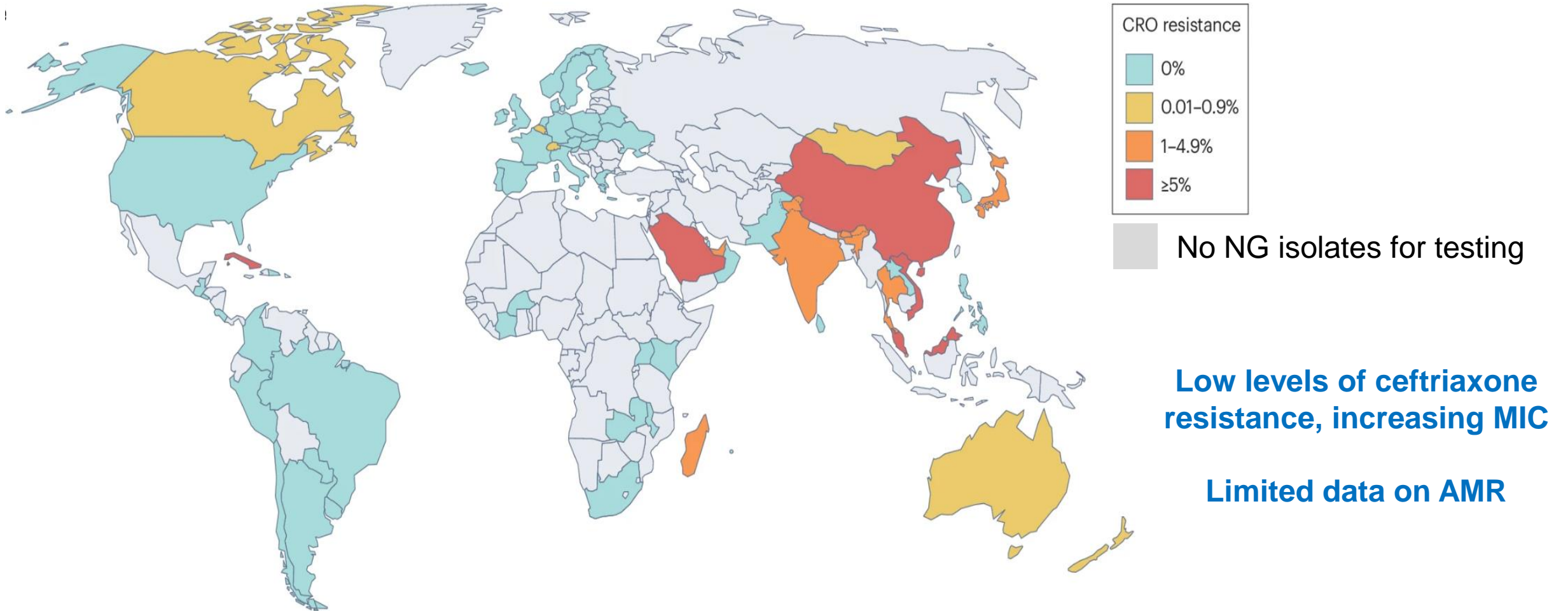
\*Updated guidelines (ceftriaxone monotherapy) expected in 2024

Fifer et al. Int J STD AIDS 2020; 31: 4-15

Jensen & Unemo. Nat Rev Microbiol 2024 Mar 20.

# Ceftriaxone Resistance\* - 2020

\*denotes resistance or decreased susceptibility to ceftriaxone



MIC – minimum inhibitory concentration

Jensen & Unemo. Nat Rev Microbiol. 2024 Mar 20.

# AMR in NG in Ugandan Men

BMC Infectious Diseases

May 2022

RESEARCH

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High burden of untreated syphilis, drug resistant *Neisseria gonorrhoeae*, and other sexually transmitted infections in men with urethral discharge syndrome in Kampala, Uganda

Matthew M. Hamill<sup>1\*</sup>, Annet Onzia<sup>2</sup>, Tza-Huei Wang<sup>3</sup>, Agnes N. Kiraggwa<sup>2</sup>, Yu-Hsiang Hsieh<sup>1</sup>, Rosalind Parkes-Ratanshi<sup>2</sup>, Ethan Gough<sup>4</sup>, Peter Kyambadde<sup>5</sup>, Johan H. Melendez<sup>1</sup> and Yukari C. Manabe<sup>1,2</sup>



RESEARCH ARTICLE **PLOS ONE** March 2024

Antibiotic overuse, poor antimicrobial stewardship, and low specificity of syndromic case management in a cross section of men with urethral discharge syndrome in Kampala, Uganda

Matthew M. Hamill<sup>1\*</sup>, Annet Onzia<sup>2</sup>, Rosalind M. Parkes-Ratanshi<sup>2</sup>, Peter Kyambadde<sup>3</sup>, Emmanuel Mande<sup>2</sup>, Vivian Nakate<sup>2</sup>, Johan H. Melendez<sup>1</sup>, Ethan Gough<sup>4</sup>, Yukari C. Manabe<sup>1,2</sup>

UDS – urethral discharge syndrome

- **NG – 100% resistance to ciprofloxacin, penicillin, and tetracycline**
- **84% - received treatment for UDS as per guidelines**

## Antimicrobial stewardship

- **Syndromic case management**
  - Sensitivity – 80.0% to 94.4%
  - Specificity – 5.6% and 33.1%
- **68% - received unnecessary treatment (metronidazole)**
- **41% - antibiotic use prior to clinic visit**
  - 89% obtained abx from a doctor, clinic, or pharmacy
  - 11% from non-healthcare settings (store or the street)
- **Abx use before clinic visit associated with longer duration of symptoms (p=0.038)**



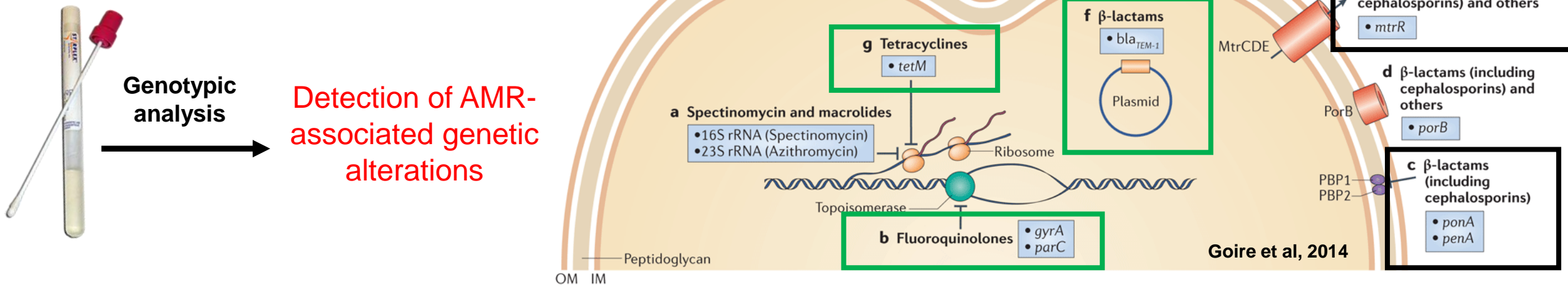
# Assessing Antimicrobial Susceptibility/Resistance

## Culture-based phenotypic AST

Ideal for surveillance of AMR; rarely performed (lack of cultures)

STIs – NAAT-based detection; faster/more sensitive than cultures, but no AST

## Molecular method for assessment of AMR – targeting of resistance markers



AST – antimicrobial susceptibility testing  
NAAT – Nucleic acid amplification test

## Molecular methods

Any sample type, but may lack sensitivity and specificity

# AMR testing in LMICs: Challenges and Potential Solutions

## Challenges

- Syndromic case management – testing rarely performed, no isolates/samples for testing
- Lack of quality-assured gonococcal surveillance programme
- Limited infrastructure and resources
- High cost of antimicrobial susceptibility testing
- Quality control and assurance

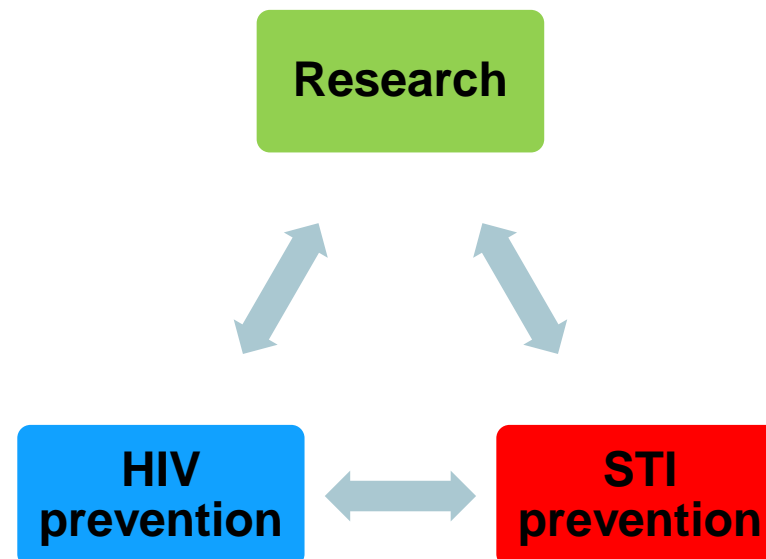
## Possible solutions

- Implement (even if limited) surveillance programme (WHO support)
- Health care system restructuring
- Supporting training of laboratory staff
- Optimizing processes to decrease cost
- Expanding quality control and assurance processes

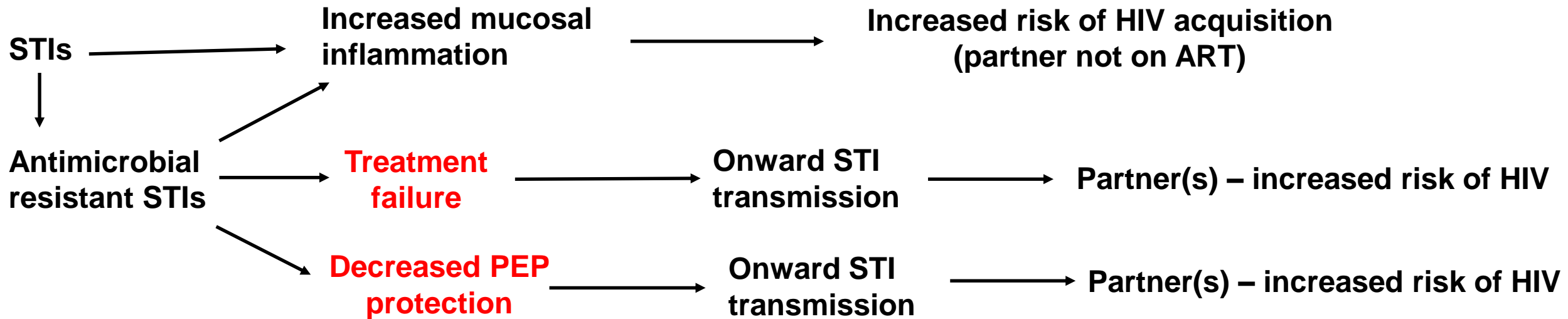
# Doxy-PEP and NG Resistance

- Multiple studies; lack of data due to small number of NG isolates
- Inconclusive data due to high baseline rates of tetracycline resistance
- Doxy-PEP – higher rates of NG with high level resistance to tetracycline
  - Is Doxy PEP efficacy less protective against strains with TET resistance?
- Adherence to Doxy-PEP – critical to assess effect of AMR
- More studies are warranted in diverse populations

# Effect of AMR on STI treatment/prevention and PLHIV



# STIs, AMR, HIV Risk and PLHIV



## Association between AMR and HIV infection (92 studies)

- Methicillin-resistant *S. aureus* – 2.12 and 1.90 higher odds for colonization, respectively
- *S. pneumoniae* (decreased penicillin susceptibility) – 2.28 higher odds of infection
- Resistance to third-generation cephalosporins (*E. coli* and *K. pneumoniae*) – 1.59 higher odds

Increased risk of AMR in PLHIV. The lack of laboratory capacity for identifying AMR, and limited access to alternative treatment options in countries with high burden of HIV, highlight the need for more research on AMR.

PLHIV

# STIs and HIV in Ugandan Men Opportunity for PrEP

Original research article

INTERNATIONAL JOURNAL OF  
**STD & AIDS**

International Journal of STD & AIDS  
2023, Vol. 34(14) 998–1003  
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## High level of HIV viral suppression in a cross-sectional study of Ugandan men with urethritis and bacterial STI

Evan J Beck<sup>1</sup> , Oliver Laeyendecker<sup>1,2</sup>, Sharada Saraf<sup>1</sup>, Swetha Ashokkumar<sup>1</sup>, Annet Onzia<sup>3</sup>, Johan H Melendez<sup>2</sup>, Justin Chan<sup>2</sup>, Peter Kyambadde<sup>4</sup>, Ethan Gough<sup>5</sup>, Rosalind Parkes-Ratanshi<sup>3</sup> , Yukari C Manabe<sup>2,3</sup> and Matthew M Hamill<sup>2</sup> 

- 20% (n=50) had reactive HIV rapid tests; 96% aware of their HIV status and on ART
- Median age - 38 years (IQR 32-45)
- 54% - transactional sex
- Viral load suppression (VLS) – 92% (46/50)
- No major resistance mutations

## Summary

High rate of untreated curable STIs (cSTIs) and AMR

High risk behaviors

Unmet need in men and women

PLHIV – older individuals, history of STIs, high rate of VLS, and ART use

Very high acceptability of STI PEP

Testing and treating cSTIs helped identify undiagnosed HIV, and identify HIV PrEP candidates

**Ugandan men seeking treatment for STIs –  
ideal target population for HIV PrEP**



# Summary and Takeaways

- Increasing AMR in STIs threatens effective treatment; need for POC diagnostics
- Limited AMR data in regions with high rates of STI/HIV
- Evaluation of diagnostics can support STI/HIV efforts
- Additional research on the effect of Doxy-PEP on AMR
- HIV prevention trials – support research for STI and AMR prevention

# Acknowledgements



Center for Innovative Diagnostics  
for Infectious Diseases

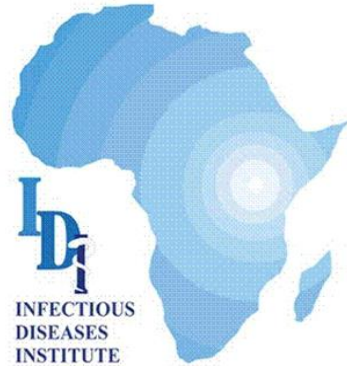
Yuka Manabe

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