A5300/I2003/PHOENIx Preparatory Study of MDR TB Cases and Their Household Contacts: Operational Feasibility to Inform PHOENIx Trial

Amita Gupta MD MHS

Co-Chair of PHOENIx Feasibility Study and Main Trial

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ACTG AIDS CLINICAL TRIALS GROUP

Protocol Team

- **Co-Chairs**: Gavin Churchyard, Amita Gupta, Anneke Hesseling, Susan Swindells
- **Clinical Representatives**: Daniel Johnson, Rohan Hazra, Elizabeth Smith
- **Clinical Trials Specialists**: Linda G. Naini, Lara Hosey
- **Statisticians**: Michael Hughes, Soyeon Kim
- **Data Manager**: Lynne Jones
- **DAIDS Pharmacist**: Thucuma Sise
- **Pharmacologists**: Kelly Dooley, Kimberly K. Scarsi
- **Investigators**: Richard E. Chaisson, Mark Harrington, Sharon Nachman, Sarita Shah
- **Consultant Cardiologist**: Richard Friedman
- **Consultant Microbiologist**: Anne-Marie Demers
- **Field Representatives**: Savita M. Kanade, Janet Nicotera
- **Laboratory Technologists**: Patricia Anthony, Christopher Lane
- **Community Scientific Subcommittee Representatives**: Ujwal Amar Kadam, Ronald Ssenyonga
- **International Site Specialist**: Akbar Shahkolahi
- **Laboratory Data Manager**: Adam Manzella
- **Industry Representative**: Jeffrey Hafkin

NIAID

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

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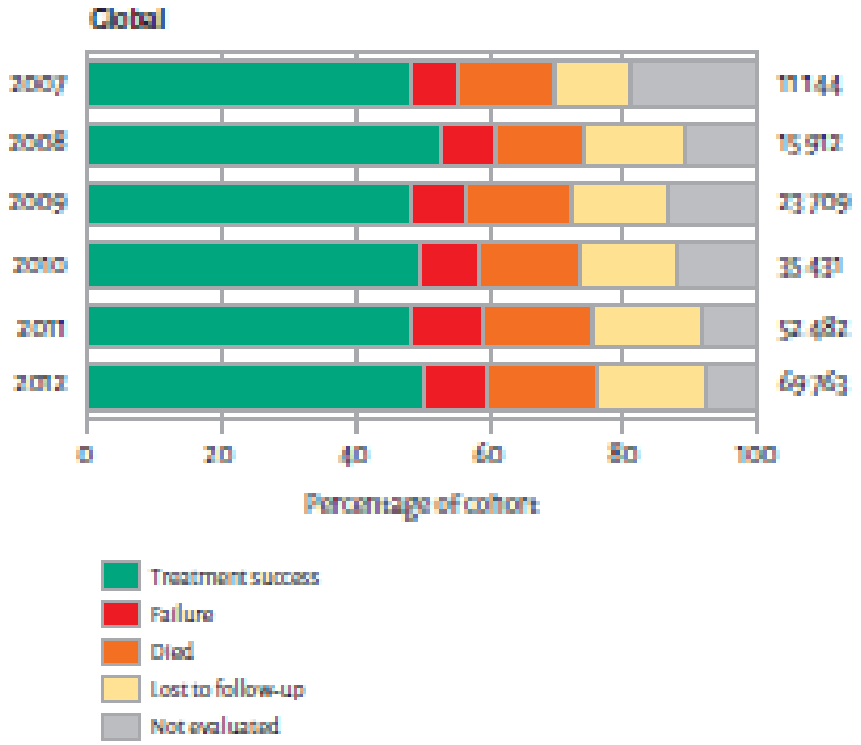
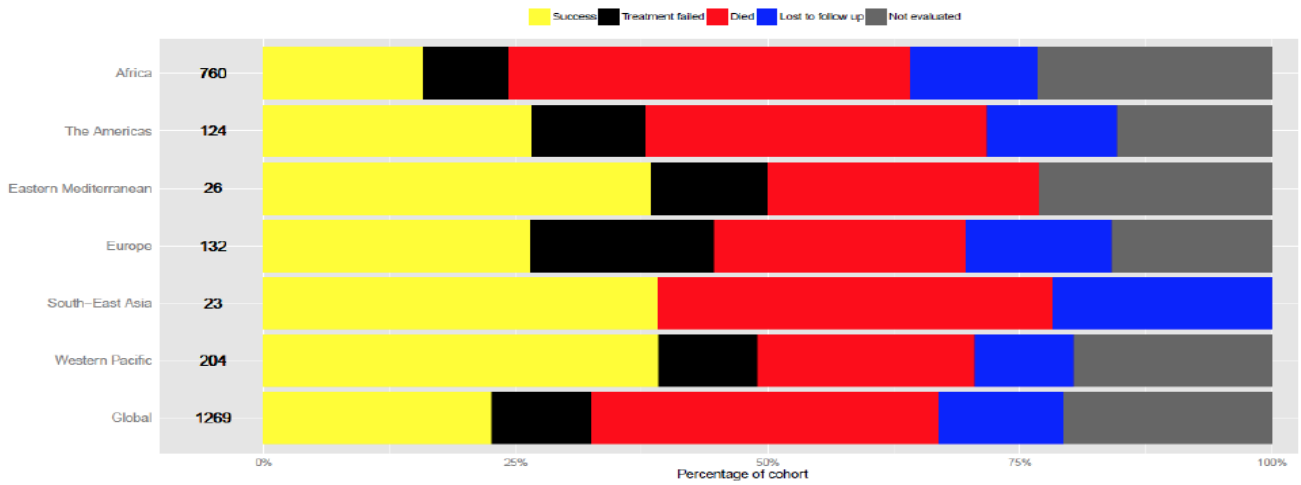
Epidemiology of Drug-resistant TB

- 480,000 cases of MDR TB worldwide (5% of all TB cases)
  - Only ~25% diagnosed, 20% receive treatment
- XDR TB reported from **105 countries**
  - 9.7% of MDR TB patients have XDR TB

Low Treatment Success and High Mortality





*number of cases observed shown over the bars

MDR TB: 50% treatment success, 16% death

XDR TB: 24% treatment success, 30% death

WHO Global TB Report 2015

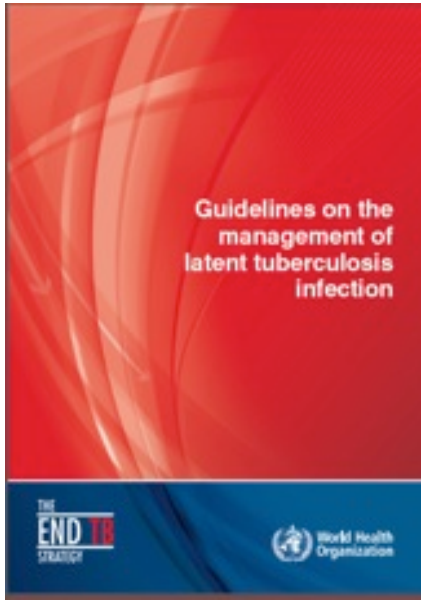
MDR TB in Household Contacts

- Contacts of MDR TB patients have high risk of TB infection and disease
  - Vast majority of MDR TB in children arises from household transmission
- Systematic review of observational studies of contacts of drug-resistant index cases
  - 4–8% proportion with incident TB
  - 44–72% of incident TB are drug-resistant
- Risk of incident TB is greatest in **first 2 years** after exposure
- Survey of 35 countries found only 11 had policies and only 3 made an effort to treat contacts
  - Most common reason for not having policies was lack of evidence

Shah et al. Clin Infect Dis 2014
Cain KP et al. Int J Tuberc Lung Dis 2010

WHO 2014 Guidelines for Preventive Therapy for MDR TB Contacts

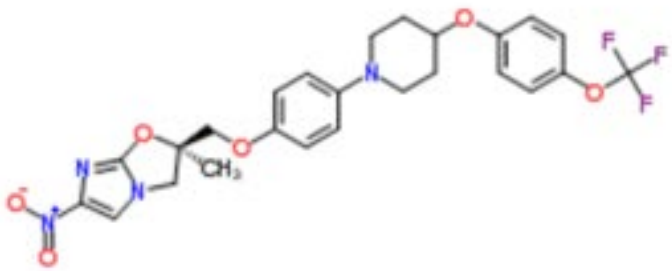
Recommendations and Research Gaps



- Treatment of presumptive MDR TB infection not recommended
  - Quality of evidence is seriously limited
- Recommend strict clinical observation and close monitoring for TB disease for at least two years
- Clinicians as part of sound clinical practice can consider individually tailored preventive treatment
- There remains an urgent need for trials of TB preventive therapy for HH contacts of MDR TB patients, particularly for those at high risk including HIV-infected, TST+ and young children to inform international evidence-based recommendations

Delamanid (DLM)

- Novel anti-TB drug, inhibits mycolic acid synthesis and has potent bactericidal activity
- As of Jan 2016, >1500 participants, including 37 children, have been exposed to DLM
- Appears to be safe & well tolerated
- Regulatory approvals: EMA, Japan, Korea
- DLM does not induce or inhibit cytochrome P450 enzymes or common drug transporters
  - Minimal DDI potential



A5300B/I2003B Study Hypothesis

- Treating HIV-infected and other child, adolescent and adult household contacts of MDR TB patients, including pre-XDR TB and XDR TB, who are at high risk of developing TB with delamanid will **substantially reduce the risk of developing TB**, compared to isoniazid

Objectives

Primary Objectives

To compare DLM vs INH with respect to:

- Efficacy in preventing confirmed or probable active TB
- Safety (permanent discontinuation of study drug due to an AE)

Objectives

Secondary Objectives

To compare DLM vs INH with respect to:

1. Efficacy and safety in each high-risk group
2. All-cause mortality
3. Drug-susceptibility pattern of the index patient vs. incident TB cases
4. Adherence and PK measures

PHOENIx Study Design

Design

- Phase III, open label, multi-center, cluster-randomized, superiority design comparing 26 weeks of DLM to 26 weeks of INH for preventing TB among high-risk household contacts of MDR TB patients

Sample size & duration

- 90% power to detect 50% reduction in TB (5% vs. 2.5%)
- 3,452 high-risk household contacts (from 1,726 households)
- Follow-up: 96 weeks for each participating household contact
- Total study duration: 304 weeks (5.9 years)

Study Population

Index case

- An adult (18 years and older) with pulmonary MDR TB who has started appropriate treatment within the past six months
  - Confirmed by phenotypic or genotypic drug resistance testing

Household contact

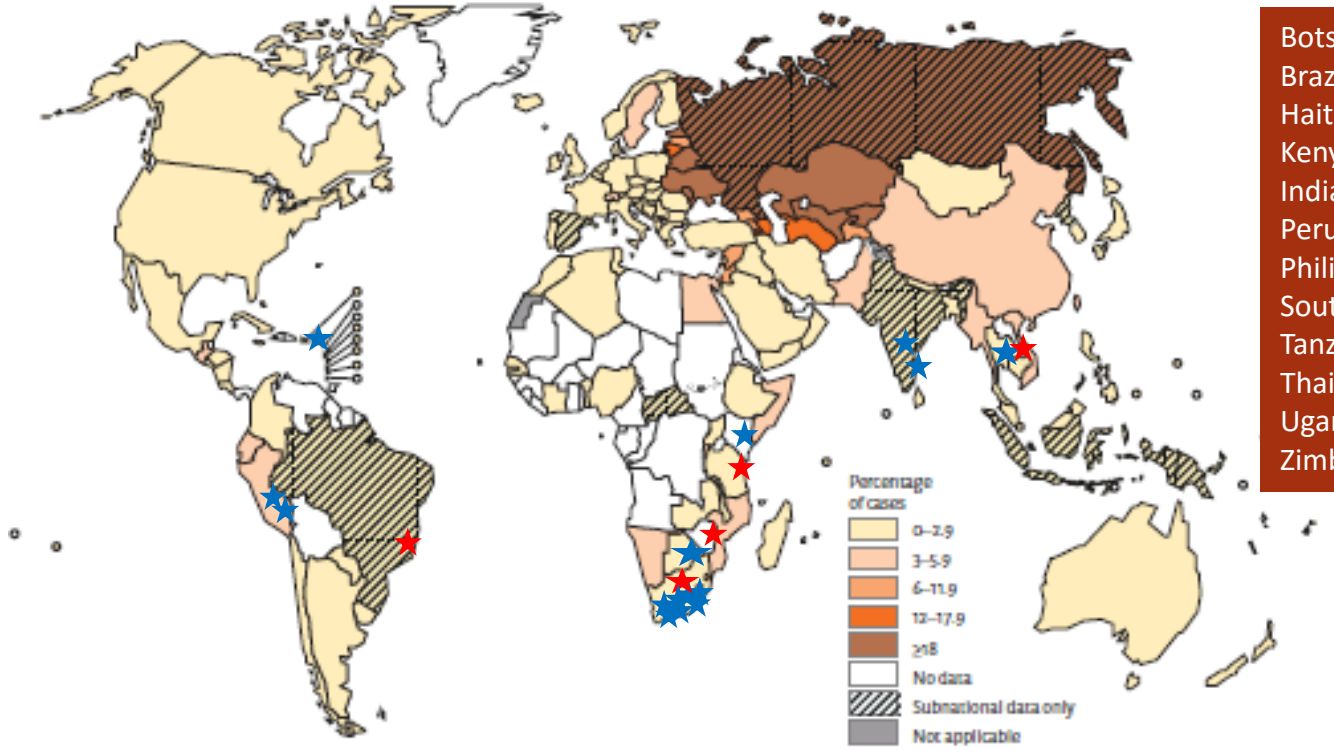
- A person who lives in the same dwelling unit and shares the same housekeeping arrangements as the index case, and who reports exposure within 6 months prior to the index case starting MDR TB treatment

Study Population

High risk household contacts

- **Newborns to children <5 years old**, regardless of TST/IGRA or HIV status
- **Adults and children ≥5 years of age** that are:
  - HIV-infected or non-HIV immunosuppressed, regardless of TST/IGRA status
  - TST positive (≥5mm) and/or IGRA positive whose HIV status is negative or unknown.

Proposed PHOENIx Study Sites, n=27 sites in 12 countries



- Botswana (1)
- Brazil (1)
- Haiti (1)
- Kenya (1)
- India (2)
- Peru (3)
- Philippines (1)
- South Africa (10)
- Tanzania (1)
- Thailand (2)
- Uganda (1)
- Zimbabwe (1)

Run-in-phase
(*Early intensive evaluation)*

- All sites will enrol HH contacts of at least 10 index cases within 16 weeks and do all study procedures
- The first 10 household contacts enrolled at each site will have
  - Intensive safety and ECG monitoring
  - Adherence assessed by PK measures
- **Pediatric intensive PK** study at selected sites
- Data will contribute to sample size re-estimation and the main analysis

Safety Issues

- Pregnant women will be excluded
- Team will review safety data monthly
- Adverse events
  - DLM: GI upset, QTc prolongation, hepatotoxicity
  - INH: hepatotoxicity, seizures, peripheral neuropathy, psychosis, hypersensitivity rash
- EKG monitoring for QTc prolongation
  - For all participants at screening then week 8 for the first 40 contacts in the 0-5, 6-14 & ≥15 years age groups
- FDA consult planned to review safety monitoring & pediatric dosing

Feasibility Considerations

Enrollment

- May be done at homes, mobile clinics or CRS or other settings

MDR TB burden

- MDR TB trial of this scale not previously conducted by networks

Site capacity and resource needs

- Unique considerations for conducting household-based enrolment, such as staffing, specimen transport, infection control

Willingness to take MDR TB preventive therapy

- Would household contacts be willing to participate in research with an investigational drug to protect against MDR TB?

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Objectives

- To describe the feasibility of identifying, recruiting, and characterizing adult MDR TB index cases and their adult and child household contacts

- To describe the prevalence of LTBI, TB disease and HIV infection among adult and child household contacts

Methods

Design

- Cross-sectional study in non-US sites with ability to identify at least 10 MDR TB cases in a 16 week period. 1 year follow-up added

Sample size

- 300 adult MDR index cases and all eligible household contacts

Population

- **Index Case**: An adult (18 years or older) with pulmonary MDR TB as defined in the main protocol
- **Household contact**: Defined as in the main protocol, but not limited to high risk groups

Evaluations

Site-level

- MDR TB case load
- Resource utilization survey

Index Cases

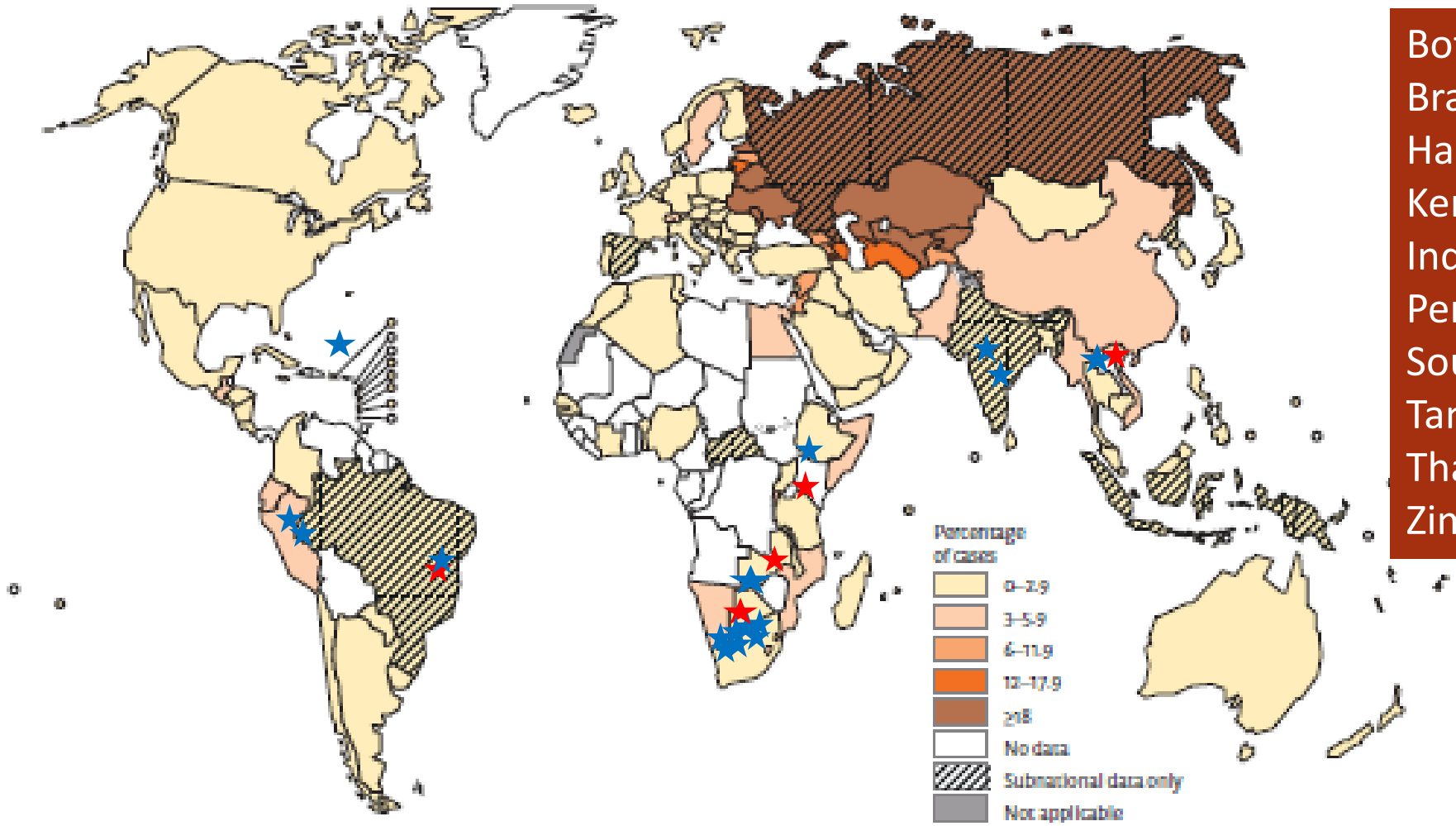
- Medical history
- Documentation of chest imaging and HIV status
- Sputum for drug-susceptibility testing

Household Contacts

- Household enumeration
- Medical history
- Documentation of HIV status (HIV testing, if unknown)
- Latent TB infection testing
- Chest x-ray
- Respiratory samples for TB diagnosis
- Knowledge, attitude and practices (KAP) survey

PHOENIx Feasibility Study Sites

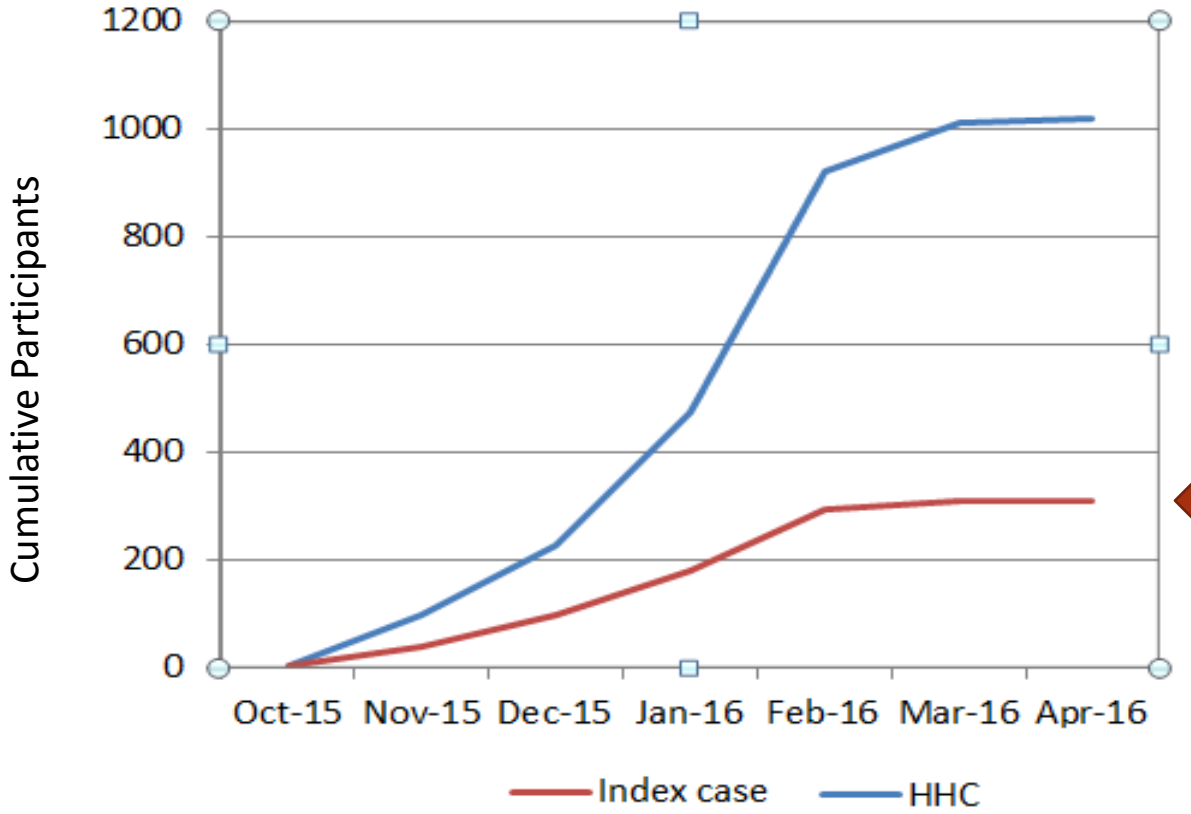
★ 16 sites activated ★ 4 sites not activated Median activation time: 11.7 weeks



- Botswana (1)
- Brazil (1)
- Haiti (1)
- Kenya (1)
- India (2)
- Peru (2)
- South Africa (8)
- Tanzania (1)
- Thailand (2)
- Zimbabwe (1)

Index & Household Contact Enrollments

Total enrolled: Index cases=308 HHCs=1018

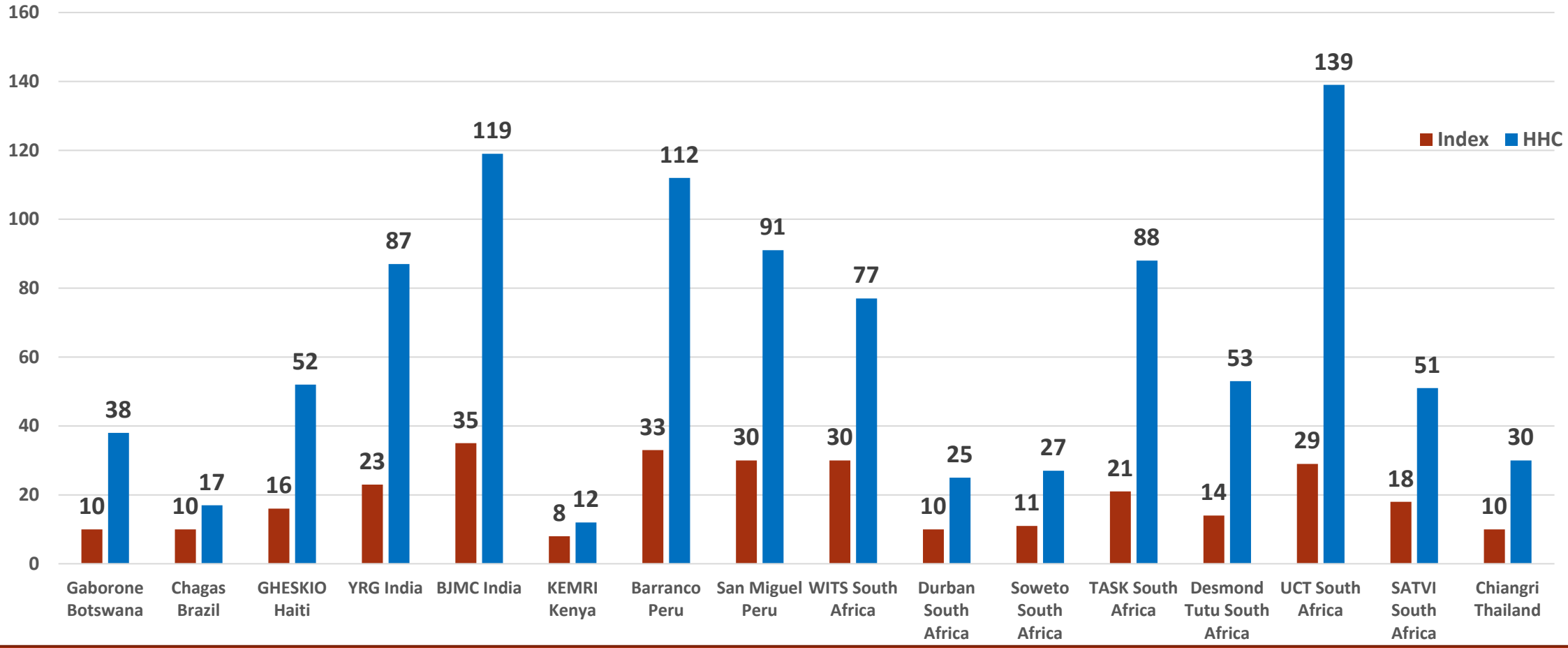


Target enrollment: 300 index cases

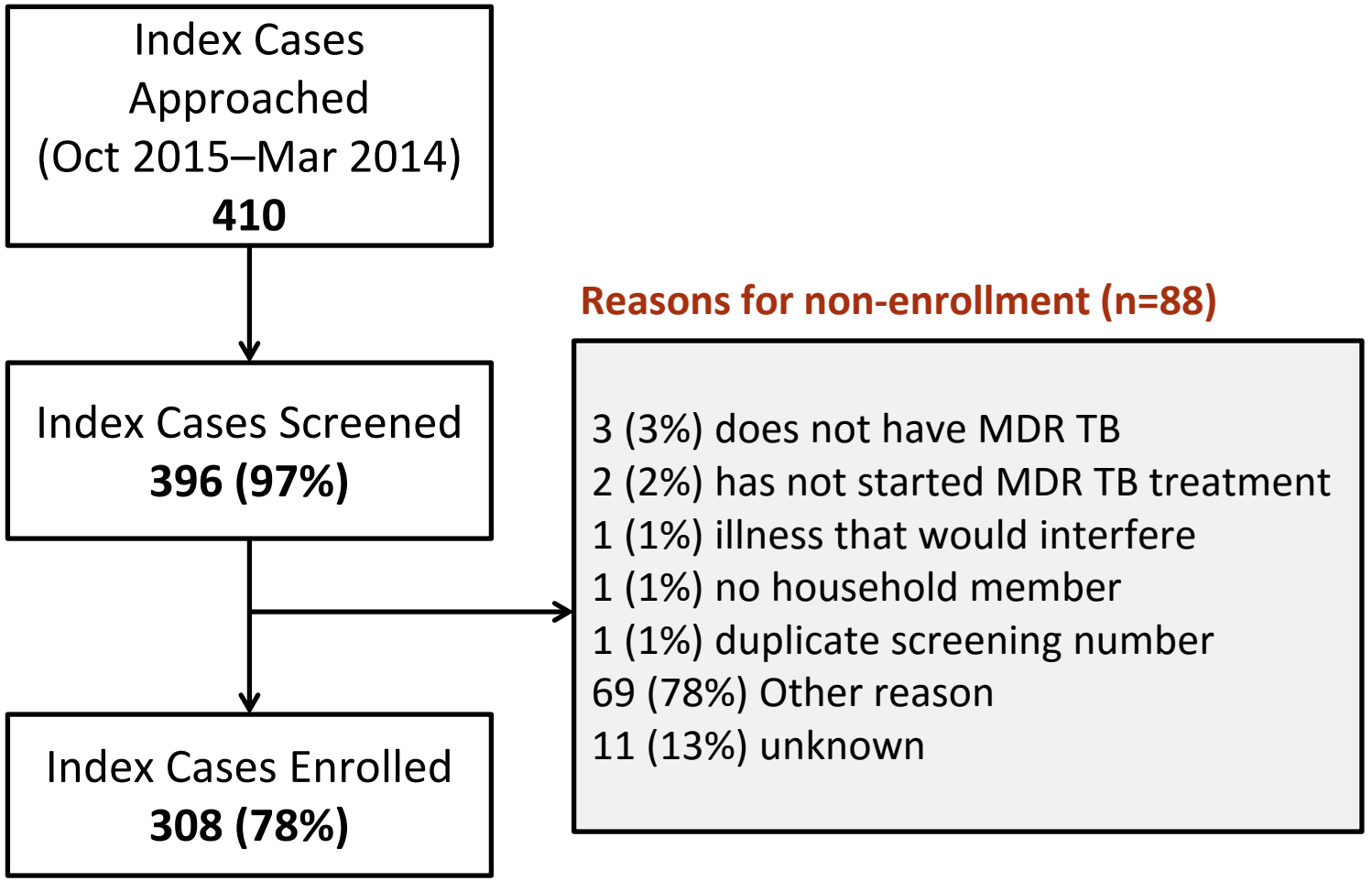
Index & Household Contact Enrollments

(29 October 2015 to 14 April 2016)

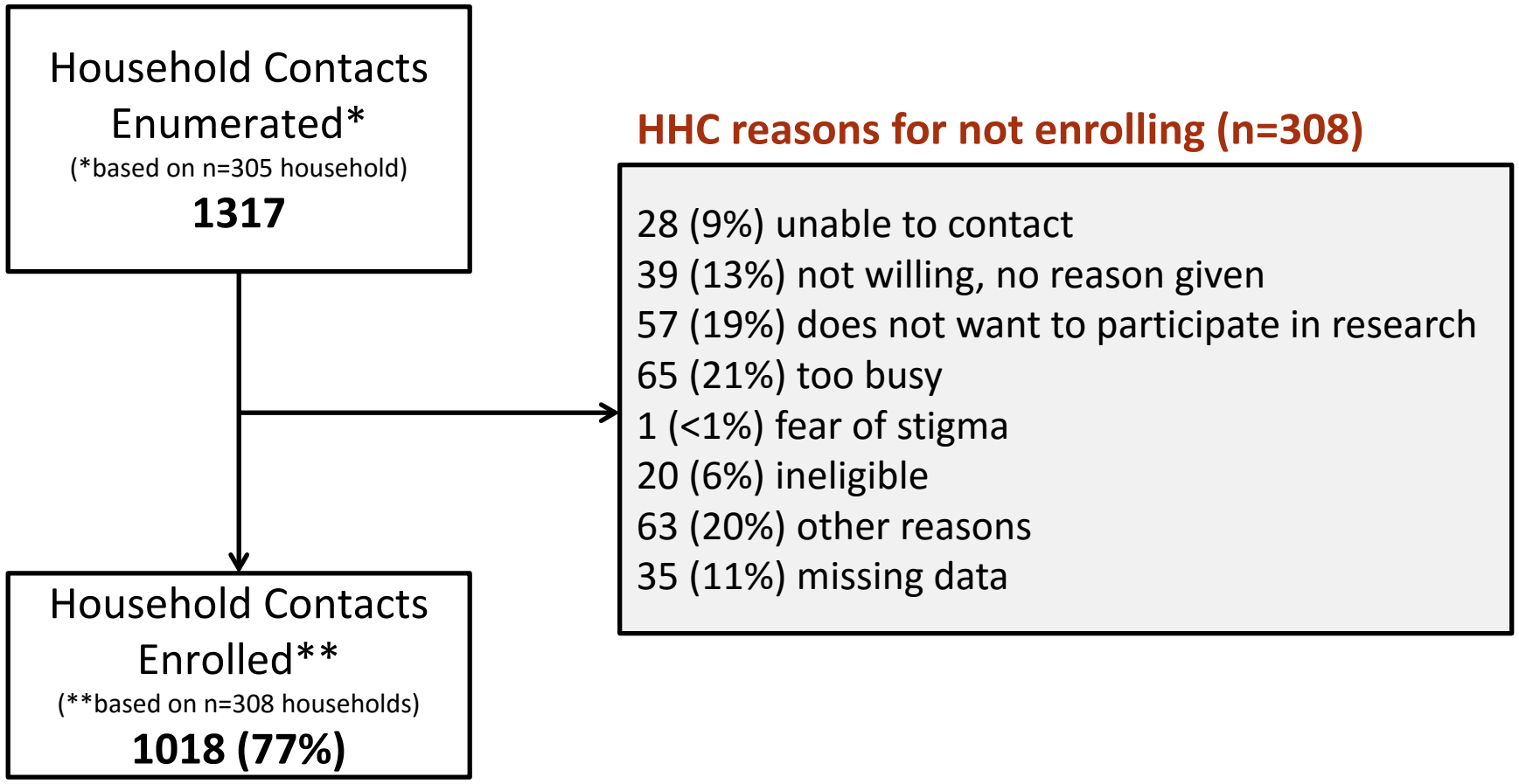
Total enrolled: Index cases=308 HHCs=1018
at 16 sites on 3 continents



MDR TB Index Case Enrollment



Household Contacts Enrollment



*Total contacts enumerated is pending.

Participant Characteristics

Characteristic	Index (N=308)	HHC (N=1018)
Median age, years (range)	36 (18-74)	26
Female	133 (43%)	600 (59%)*
Countries (# sites)		
Botswana (1)	10 (3%)	38 (4%)
Brazil (1)	10 (3%)	17 (2%)
Haiti (1)	16 (5%)	52 (5%)
India (2)	58 (19%)	206 (20%)
Kenya (1)	8 (3%)	12 (1%)
Peru (2)	63 (20%)	203 (20%)
South Africa (7)	133 (43%)	460 (45%)
Thailand (1)	10 (3%)	30 (3%)

* 14 pregnant women

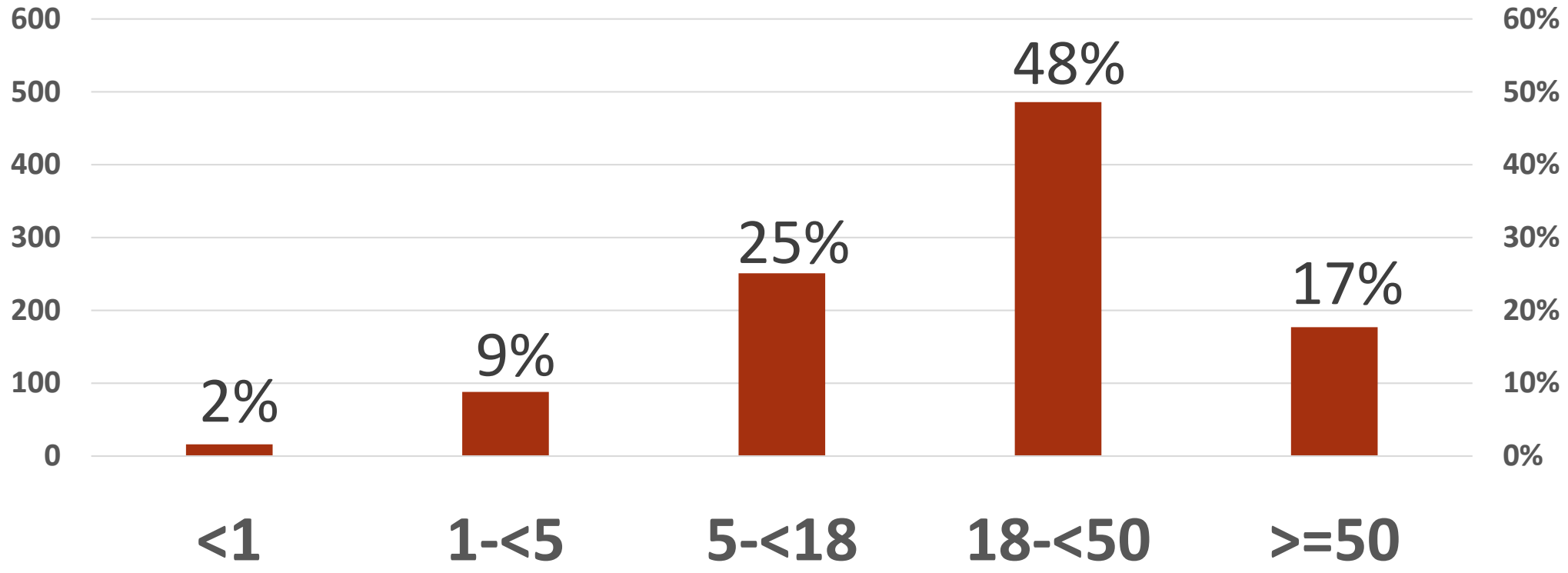
Index cases, n=308

- Identified at community clinics (53%), general hospital 16%, referral to CRS (11%), at CRS (13%), other(1%)
- Enrollments: CRS (40%), hospital/clinic other than CRS (33%), household (23%), other (4%)
- Documentation of MDR TB based on testing outside the study
  - All 308 rifampin resistance
  - **But only 232 (75%) had BOTH RIF and INH resistance**
    - 13 had RIF R and INHsusceptibility
    - 63 had no INHtesting documented (presumed mdr based on RIF R only)
    - 4 sites in south Africa, 1 Botswana, 1 India, 1 Kenya
  - THEREFORE, need to ensure both Rifampin and INH resistance is documented in main trial

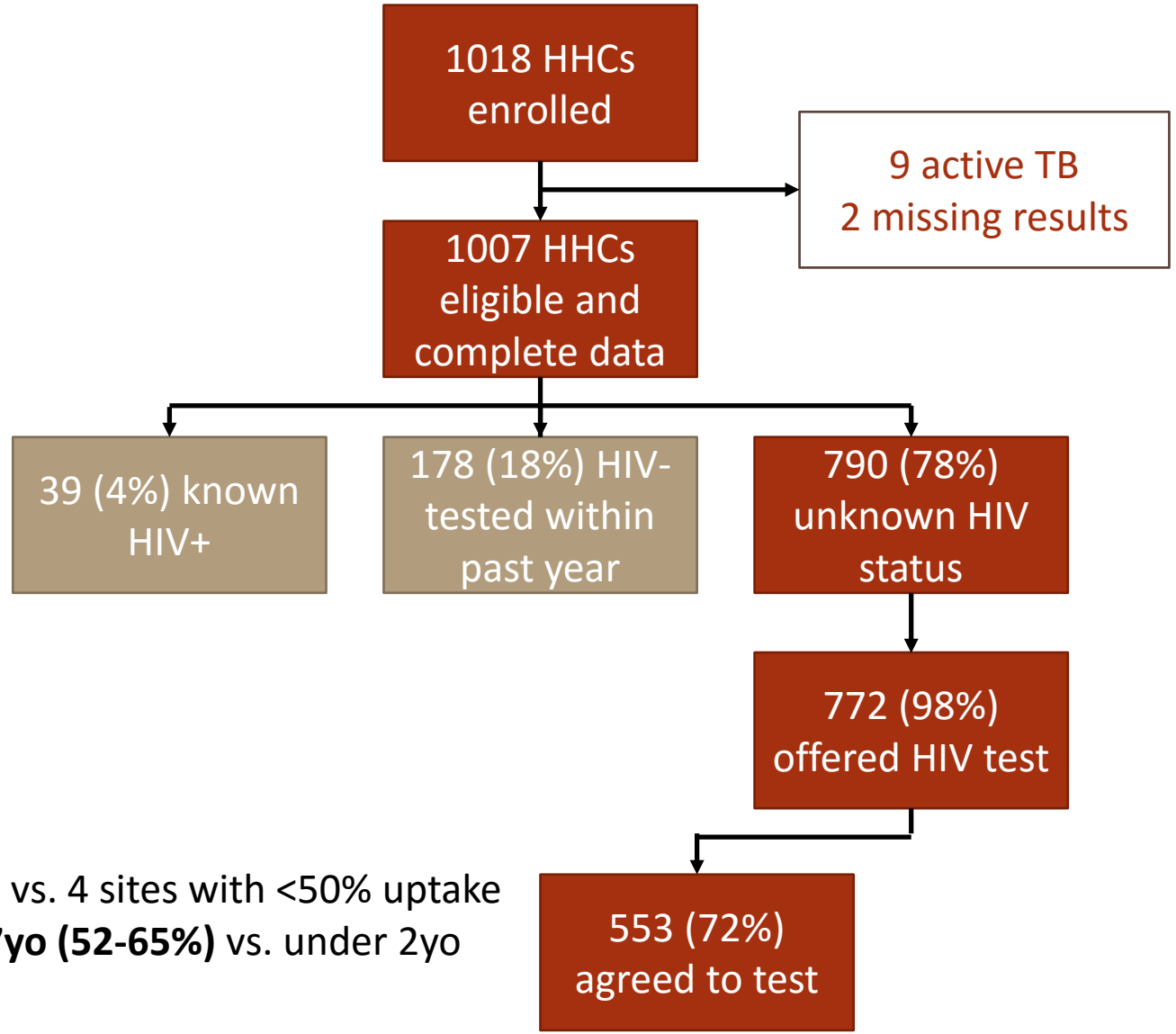
MDR TB Index Case Characteristics

Characteristic	Index (N=308)
HIV-infected	112 (36%)
Diabetes	25 (8%)
Current or former smoking	133 (43%)
No prior TB	147 (48%)
Chest x-ray cavitation	201 (65%)
AFB smear positive (n=211) 1+ at study enrollment with testing at CRS (n=290) Xpert positive MGIT culture positive	148 (70%) 94 (20%) 141 (51%) 75 (27%)
MDR TB treatment duration, median (range)	8.4 weeks (0-27wks)

Age Distribution of Household Contacts

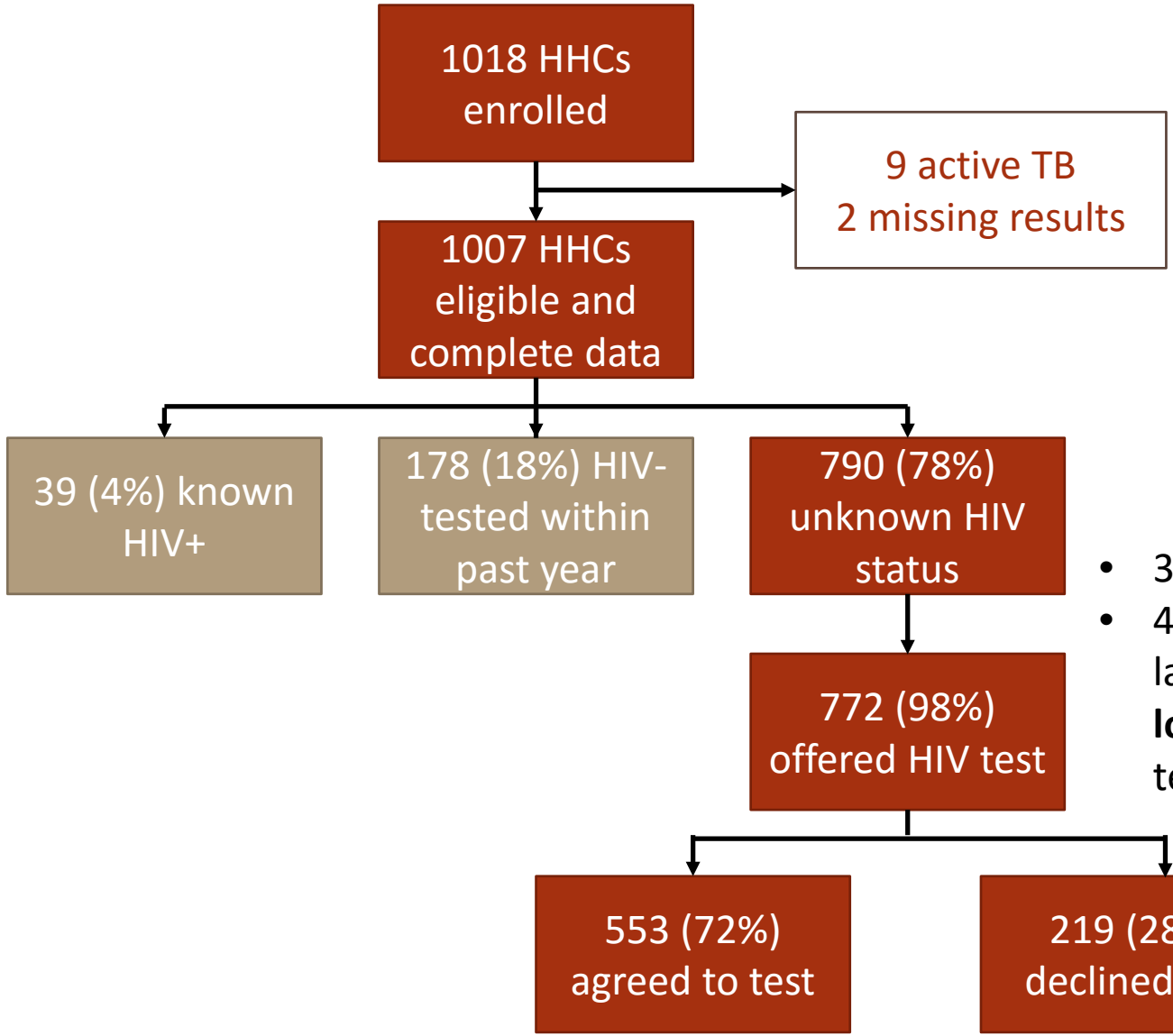


HIV Testing among HHCs



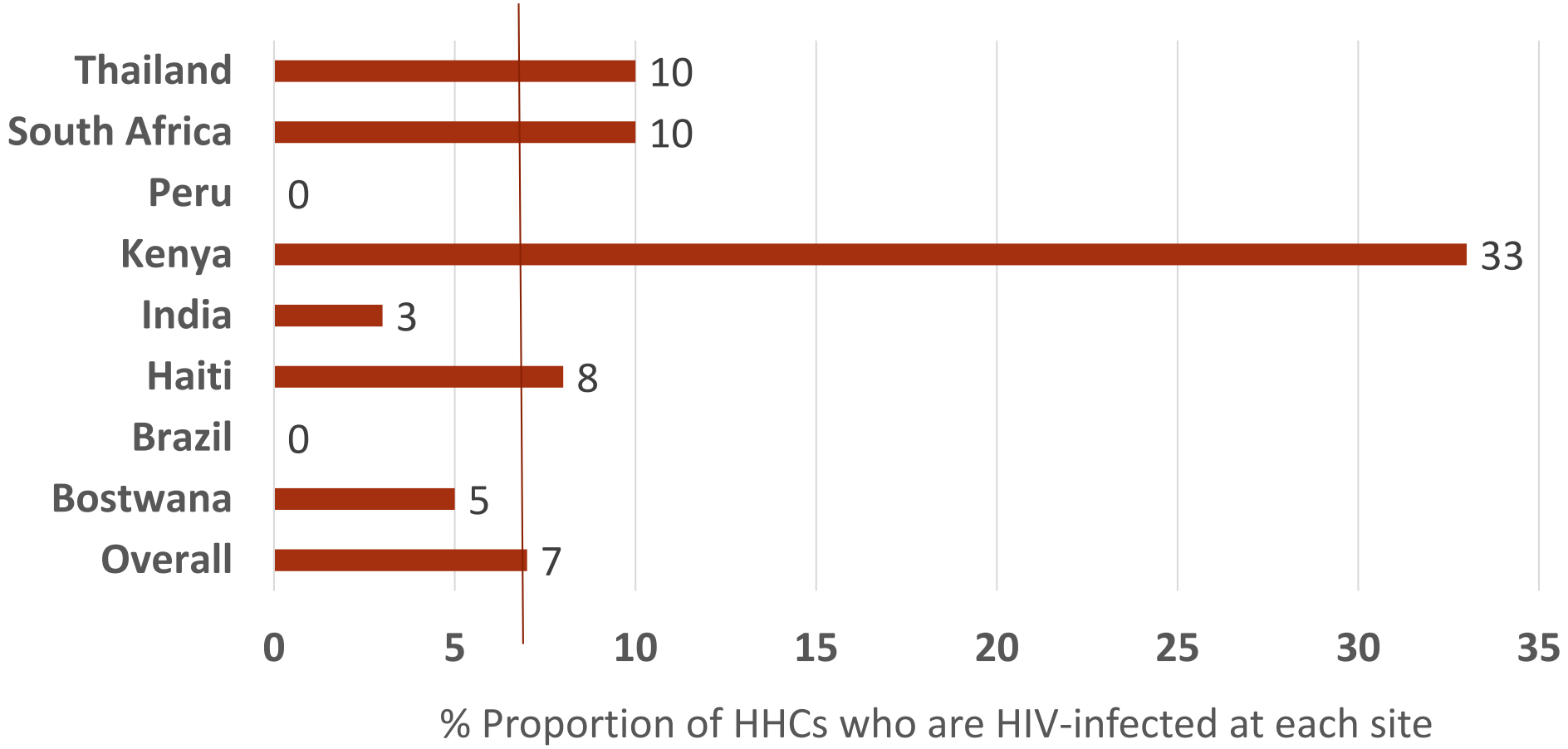
- 9 sites with **>80% uptake** vs. 4 sites with <50% uptake
- Lower uptake in **age 2-17yo (52-65%)** vs. under 2yo (77%) and adults (78%)

HIV Testing among HHCs



- 36% did not specify reason
- 47% reported "other" reason, largely related to **perceived low risk** (particularly affected testing of children)

HIV Infection among HHCs by Country



Latent TB Infection Results

LTBI Testing	n (%)
No TST done*	300 (30%)
TST tested	705 (64%)
TST+	392 (56%)
TST-	304 (43%)
Tested but no result	9 (1%)
No IGRA done	26 (3%)
IGRA tested	973 (97%)
IGRA+	629 (65%)
IGRA-	330 (34%)
Tested but no result	14 (1%)

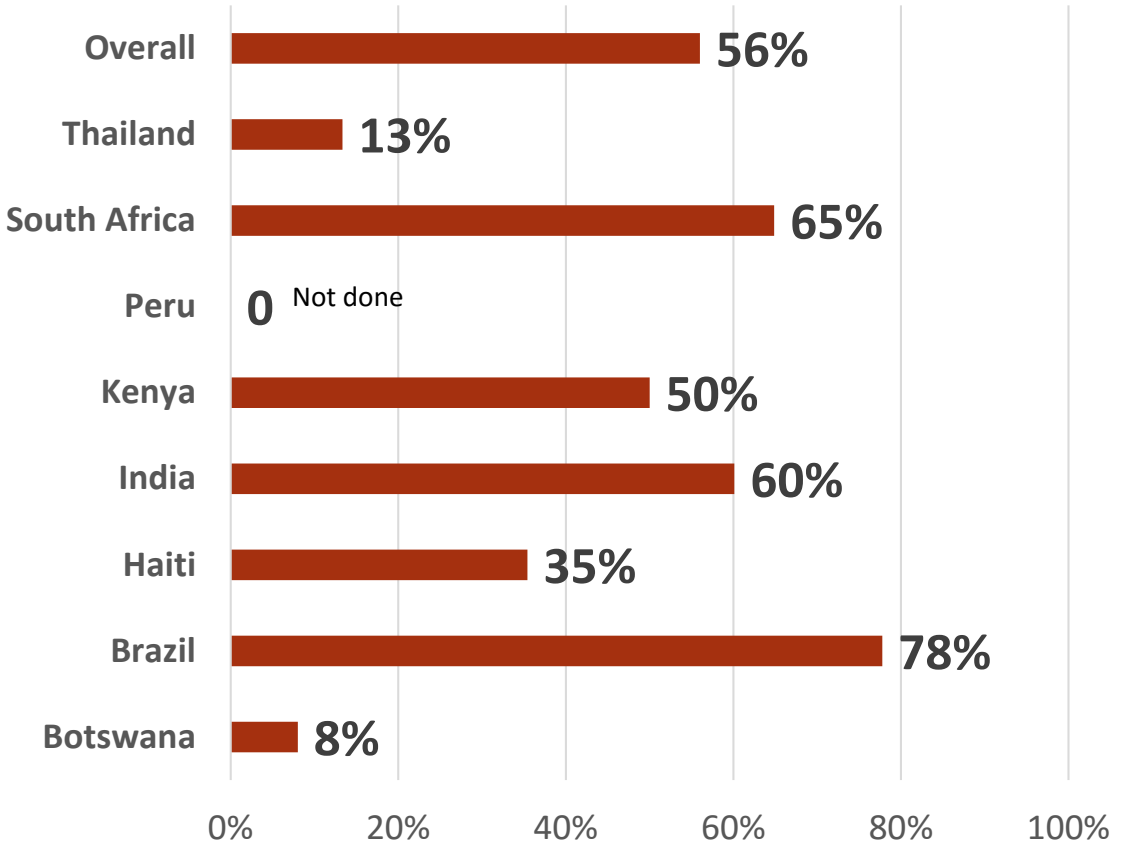
*TST not done at 3 of 16 sites (2 Peru and 1 South Africa)

LTBI status with combined testing

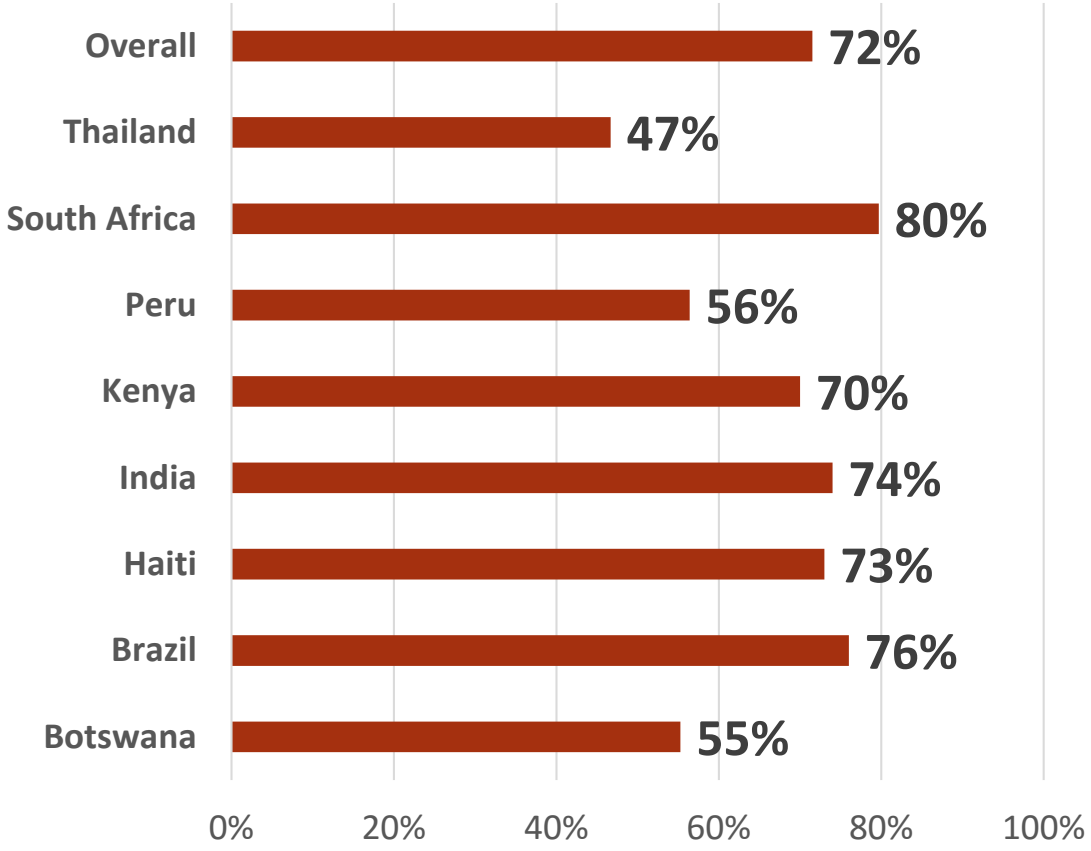
LTBI	N (%)
TST+ or IGRA+	708 (70%)
TST- and IGRA-	272 (27%)
Unknown	27 (3%)

TST+ and IGRA+ by Country

- **TST+ by country**



- **IGRA+ by country**



Yield of Contact Tracing, n=1016 contacts

- 23% HHCs <15 years and 24% of >=15 years had signs/symptoms may be related to TB
- 24% of 971 (96%) got CXR, 886 (91%) were good quality, 169 (17%) abnormal
  - 22 of 55 children <15 years with abnormal had CXR suggestive of TB
- Of 36 contacts without CXR, 16 were pregnant
- **130 (13%) prevalent TB cases from 83 of 284 households**
  - 31 households had more than 1 contact with prevalent TB
  - **Possible** 71, 7%
  - **Probable** 33, 3%
  - **Confirmed** 26, 3% (includes 9 that were already diagnosed at time of contact tracing)
- Yield varied by site

Prevalent TB

- Males> females diagnosed with prevalent TB 16% vs 9%
- Higher in TST+ 16%vs 10% in all TB; 9% vs 2% in confirmed/probable TB
- Higher in IGRA+ 14% vs 8% in all TB; 7%vs 1% in confirmed/probable TB
- No difference in confirmed/probable by three age groups <5, 5-<15 , 15+ years
- No difference by HIV status
- No difference by high risk group
  - 7% (7 of 102) <5years
  - 5% (3 of 63) HIV and %+years
  - 6% (39 of 610) positive IGRA or TST

Potentially Eligible High Risk Household Contacts

Characteristic	N (%)
Ineligible (had prevalent TB or not high risk)	350 (34%)
Potentially eligible	666 (66%)
<5 years	66 (10%)
≥ 5 years and HIV+	60 (9%)
LTBI+ (TST or IGRA+)	540 (81%)
Median # of eligible contacts per household	2 (IQR 1–3)

Potentially eligible children <18yo:

66 (<5 years) +4 (>=5y&HIV+) + 160 (LTBI+) = **194 (29%)**

One Year Follow-up as May 25, 2017

- 845 (83%) of 1016 successfully tracked
- 498 (59%) female
- Younger children had less than optimal follow-up

	Total	<5 years	5-<18	18+
Baseline	1016	103	251	662
Follow-up	845	71	219	555
%	83%	69%	88%	84%

Vanessa Rouzier will summarize lessons learned from the Feasibility Study

PHOENIX A: Feasibility and lessons learned from the field

IMPAACT Annual Meeting

Monday May 29, 2017

Vanessa Rouzier

Amita Gupta

A5300B/IMPAACT2003B

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB)

Chairs:
ACTG: GJ Churchyard, S Swindells
IMPAACT: A Gupta, AC Hesseling

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AIDS CLINICAL TRIALS GROUP

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International Maternal Pediatric Adolescent AIDS Clinical Trials Network

PHOENIX: MDR TB Prophylaxis Trial

Design

- Phase III, open label, multi-center, cluster-randomized, superiority design comparing 26 weeks of delamanid to 26 weeks of isoniazid for preventing TB among high-risk household contacts of MDR TB patients

Sample size & duration

- 90% power to detect 50% reduction in TB (5% vs. 2.5%)
- 3,452 high-risk household contacts (from 1,726 households)
- Follow-up: 96 weeks for each participating household contact
- Total study duration: 304 weeks (5.9 years)

HHC Eligible for PHOENIX intervention

1. Children < 5 y.o regardless of IGRA/TST or HIV status
2. HIV-infected children and adults, regardless of IGRA/TST results.
3. Immunocompromised children and adults (TNF treatment, chronic renal failure on dialysis, or solid organ or hematologic transplant recipients), regardless of TST or IGRA status
4. Adults and children ≥5 years with positive TST (≥5 mm) and/or positive IGRA

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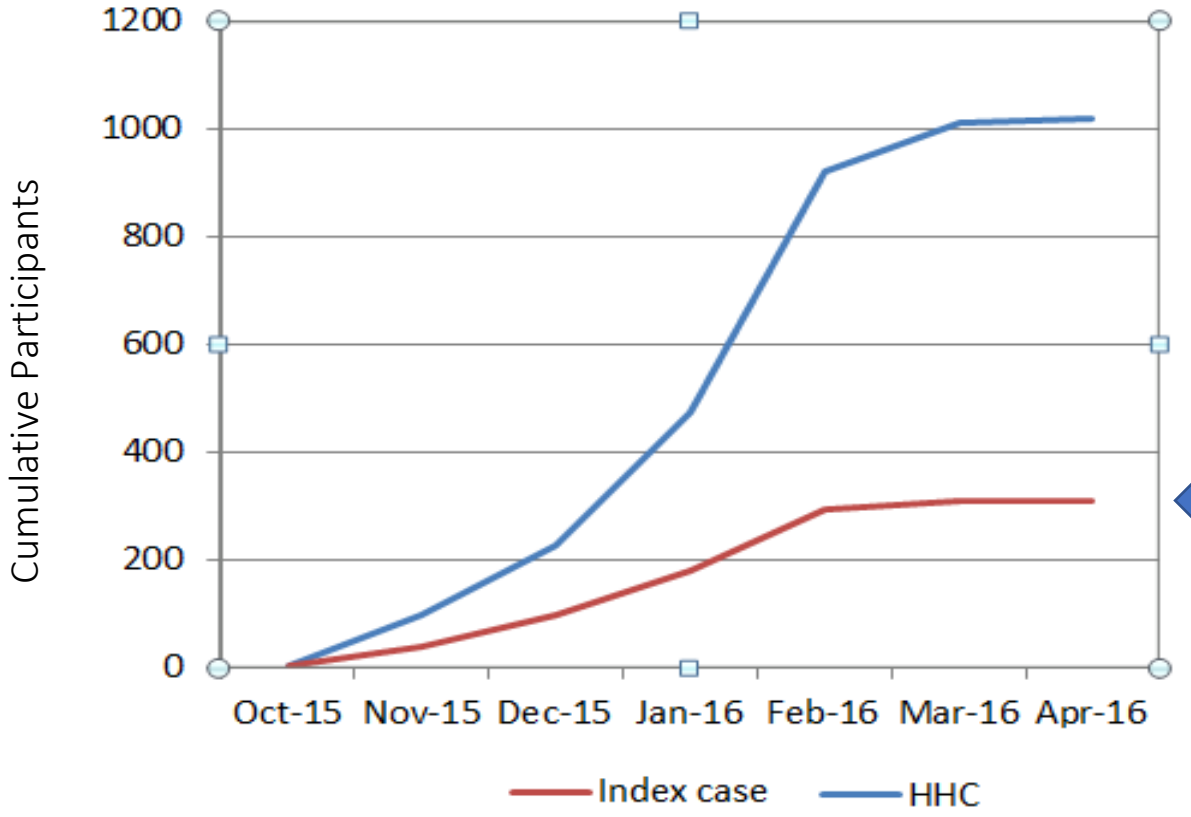
PHOENIX Feasibility Aims

1. **MDR TB Index cases**: ability to identify, recruit and characterize
   - Identify confirmed MDR TB cases from routine programs/labs
   - Recruit and obtain consent to approach HH

2. **Household Contacts**: ability to approach and evaluate HHC
   - Community contact tracing for Household randomization
     - HH enumeration and recruitment
   - Evaluate adults and children for TB (clinical, laboratory)
   - Consent adults and children

Index & Household Contact Enrollments

Total enrolled: Index cases=308 HHCs=1018



Target enrollment: 300 index cases

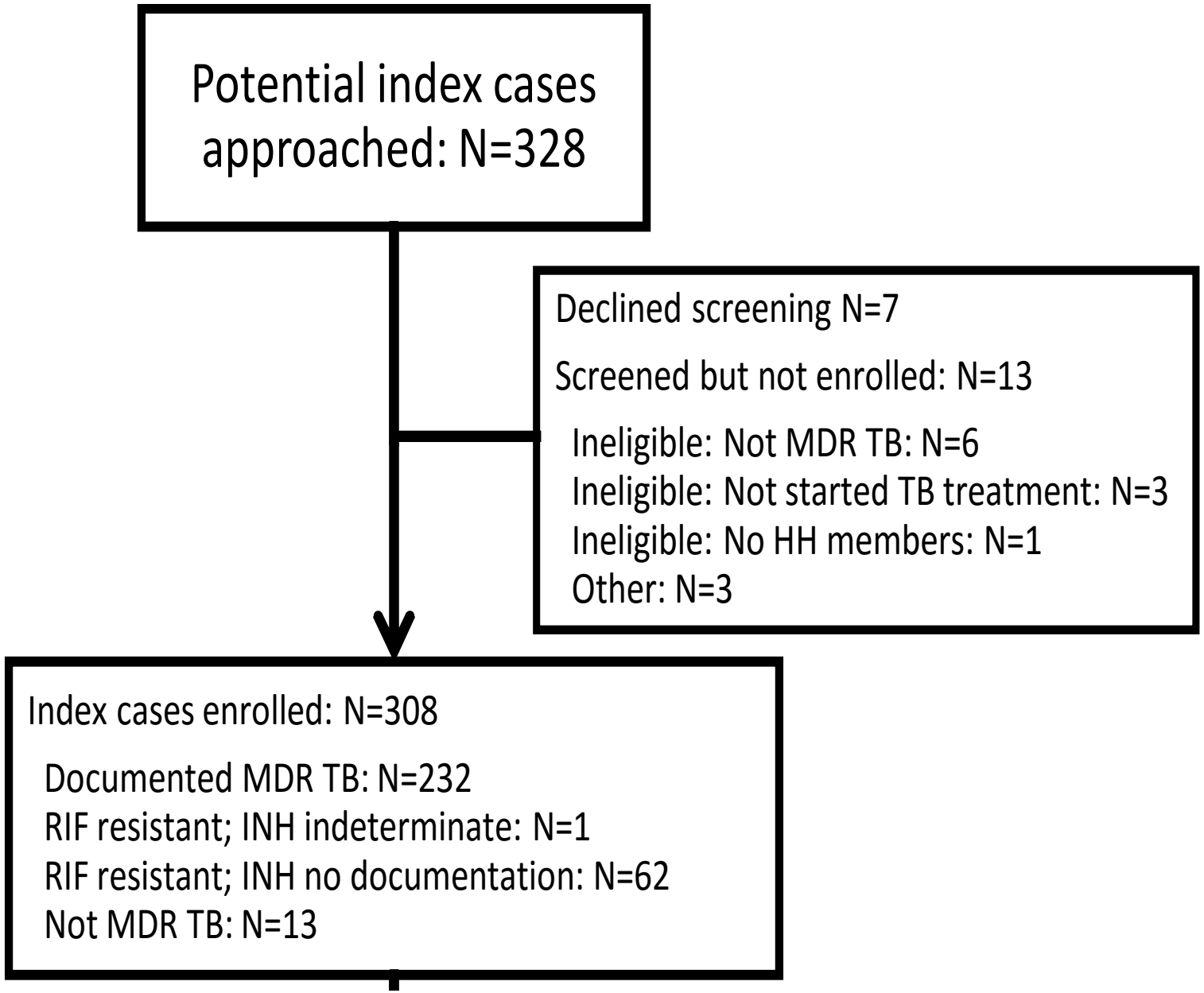
16 sites

Index Cases with MDR-TB Recruitment and Enrolment

Identification and recruitment of indexes very successful

PHOENIX feasibility: Index recruitment and enrollment

308/328 (94%)



MDR-TB Index Cases: Challenges

- Only 75% had confirmed MDR TB: lab testing variability, access to records

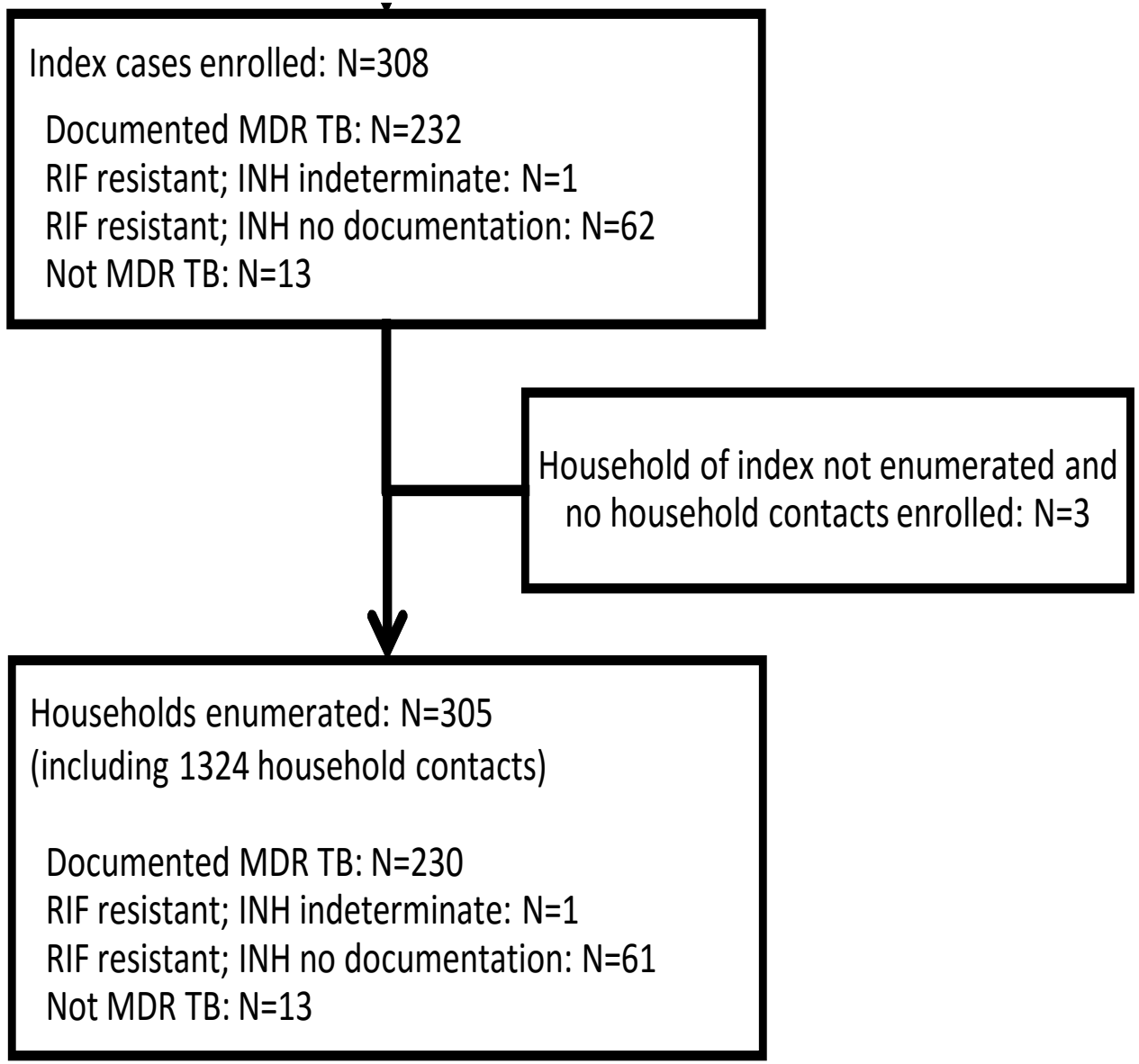
→ **Only confirmed MDR TB indexes will be eligible for PHOENIX**

→ Importance of obtaining complete lab results with DST. Linkage with labs essential

- HIV status not available for 10% of indexes

Household Enumeration

305/308 (99%)



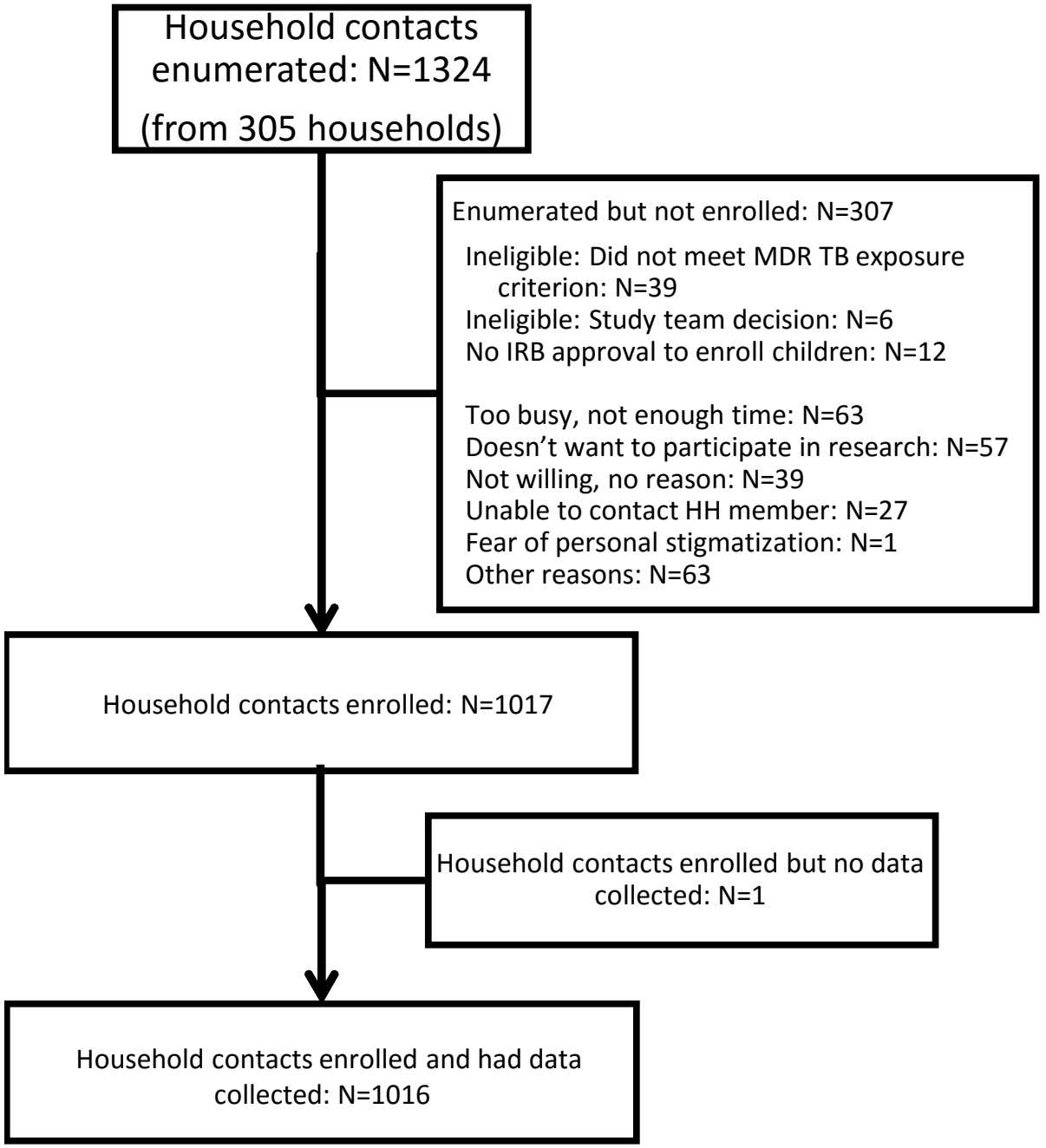
Household Contact Enrolment:

1017/1324 (76.8%)

3% no MDR TB exposure

2% not eligible

21% not enrolled



HHC Enrolment Challenges:

- IRB:
  - 2/16 (12%) sites did not obtain IRB approval to enroll children!

- HHC Enumeration/Enrolment performance:
  - High variability across sites of enrolling potentially eligible HHC: 39% to 100%
  - 24/308 (8%) HH had **zero** HHC enrolled

  → Clearer stipulations in protocol and MOP

  → Better family based approaches to improve HH enrolment

HHC Enrolment Challenges: Pediatrics

- The median age 25.6 years (15.5 years to 49.6 years).
  - 103 (10%) were <5 years
  - 251 (25%) were age 5-<18 years
  - 486 (48%) were 18-<50 years
  - 76 (17%) were ≥50 years.
- Of the 1016 contacts, 598 (59%) were female.

Targeted group!

- **<u>Pediatric capacity variable</u>**:
  - 2-50% enrolment of children < 5 yrs acrros sites!
  - **Adult only sites need support to be prepared to identify and enroll < 5yrs!**

HHC Enrolment Challenges: HIV Testing

- Variable uptake of HIV testing across sites:
  - Overall 78% of HHC had unknown HIV status prior to study entry
  - Overall 71% of HHC agreed to HIV testing: 3 to 100% across sites!!!!
  - HIV+ is eligibility criteria for study treatment!
- Reasons for not offering or refusing HIV testing:
    - Parent/guardian not available to consent or Parent/guardian refusal
    - No IRB approval for HIV testing in children
    - Parents of child HIV negative (risk perception)
- Need better strategies for HIV testing uptake at some sites!

HHC Enrolment Challenges: LTBI

- Prevalence of active TB: 9% overall
  - Value of HHC management

- TB Evaluation:
  - 20% of HHC did not have CXR overall
  - TST/IGRA in children
  - Clinical evaluation of children

What do we need to optimize enrolments in Phoenix?

- *Pediatric specific*:
  - IRB approval for participation in interventional trials of infants, children and adolescents
  - HH recruitment, enrolment of <5 y.o, retention
  - Consenting parents/legal guardians, assenting older children
  - TB/MDR TB evaluation (clinical, CXR), diagnosis (gastric aspirate, FNA), referral for TB treatment
  - Intensive/sparse PK, phlebotomy
  - ECG monitoring
  - Contraception counseling for adolescents

What do we need to optimize enrolments in Phoenix?

- TB Evaluation and Care:
  - Diagnostic
  - Clinical evaluation
  - Treatment
- Retention/adherence:
  - MERM device
  - Adherence monitoring and support
- AE monitoring:
  - ECG capacity

Site challenges

- TST access
- Uptake of HIV testing
- Recruitment of children
- Sufficient staffing
- Travel/logistics
  - Safety of outreach teams
  - Need for multiple visits, flexibility in hours/location
- Occupational exposure risk/infection control
  - Challenges of wearing personal protective equipment
  - Transporting household contacts to the site
  - Need for separate sputum sampling areas
- Stigma

Summary

- Enrolling MDR TB index cases and household contacts is feasible at ACTG and IMPAACT sites
- Need to confirm MDR TB as a substantial proportion of index cases only had RIF+ without any INH testing data
- More efforts and strategies needed to recruit and enroll young children and improve uptake of HIV testing
- Common challenges and solutions across sites: staffing, travel, flexibility in work hours/location, infection control, stigma