A5300/I2003/PHOENIx Trial Update

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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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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

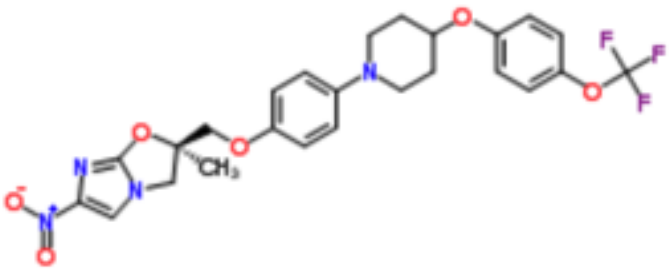
WHO 2014 Guidelines for Preventive Therapy for MDR TB Contacts

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

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

Primary objective

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

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

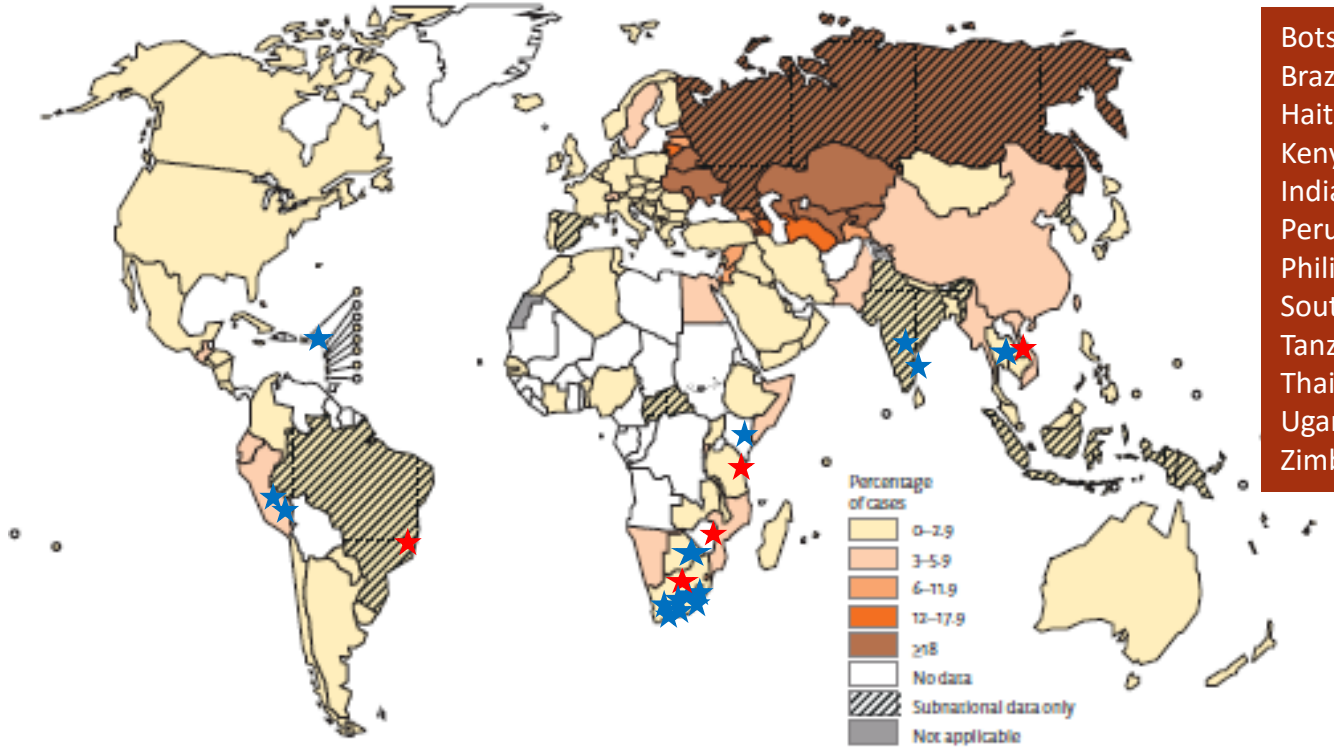
Household contact

- 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

High risk household contacts

- **Newborns to children <5 years old**
- **Adults and children ≥5 years of age** that are:
  - HIV-infected or non-HIV immunosuppressed
  - TST positive (≥5mm) and/or IGRA positive

Planned 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)

Delaminid dosing

- Adults & children ≥30kg: DLM 200 mg daily
- Children <30kg: Weight-banded based dosing per MOP
- Daily dosing for children will be based on modeled dose (Elin Svenson and colleagues at Uppsala)
- DLM dosing will be separated in time from other drugs by at least one hour
- DLM will be supplied by Otsuka as a film-coated and dispersible tablets

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

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

ACTG: Gavin Churchyard, Susan Swindells, Sarita Shah
IMPAACT: Anneke Hesseling, Amita Gupta

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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 with 1 year follow-up added on as LOA

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

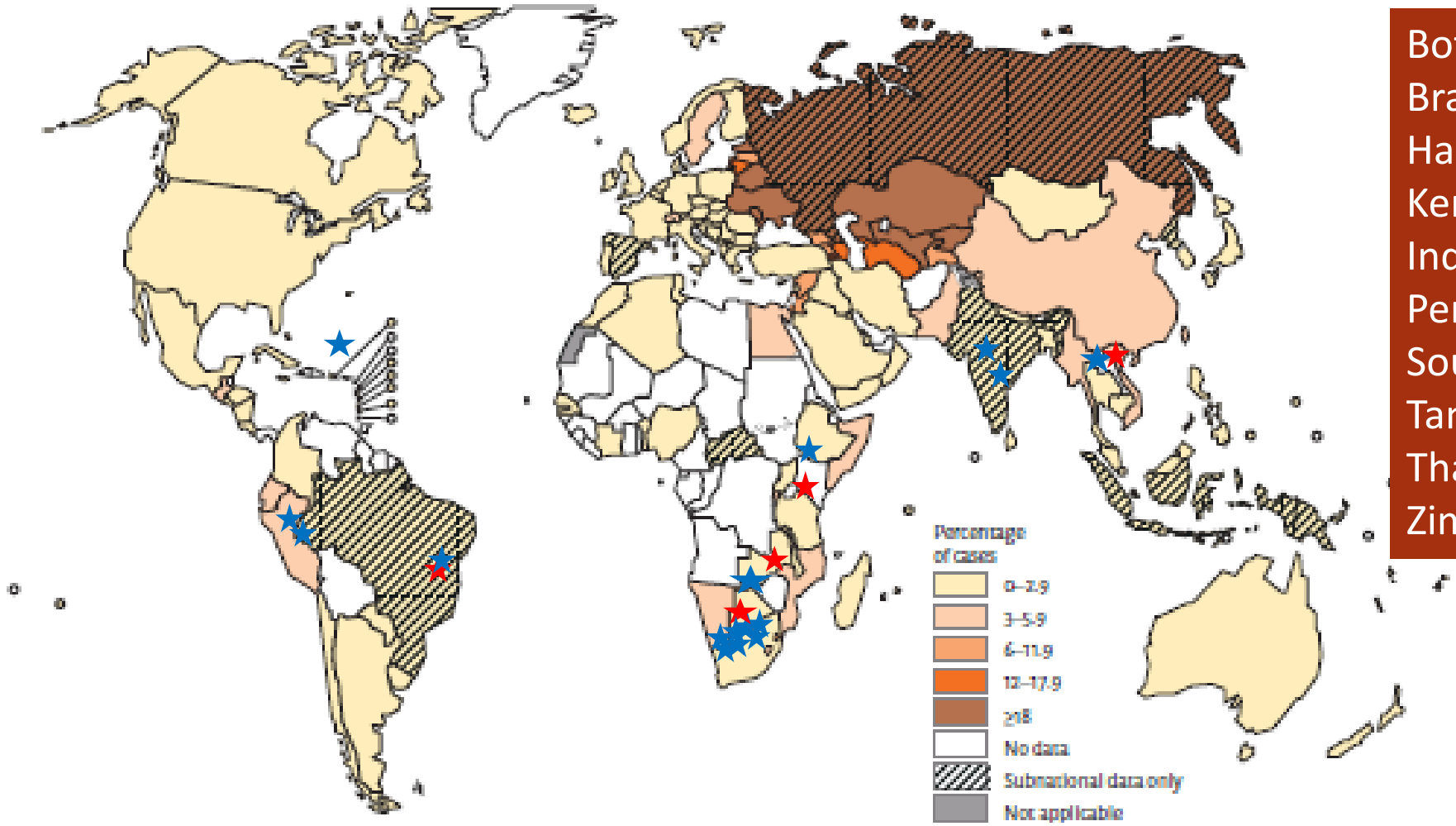
- Medical history
- Documentation of chest imaging and HIV status
- Sputum for drug-susceptibility testing

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

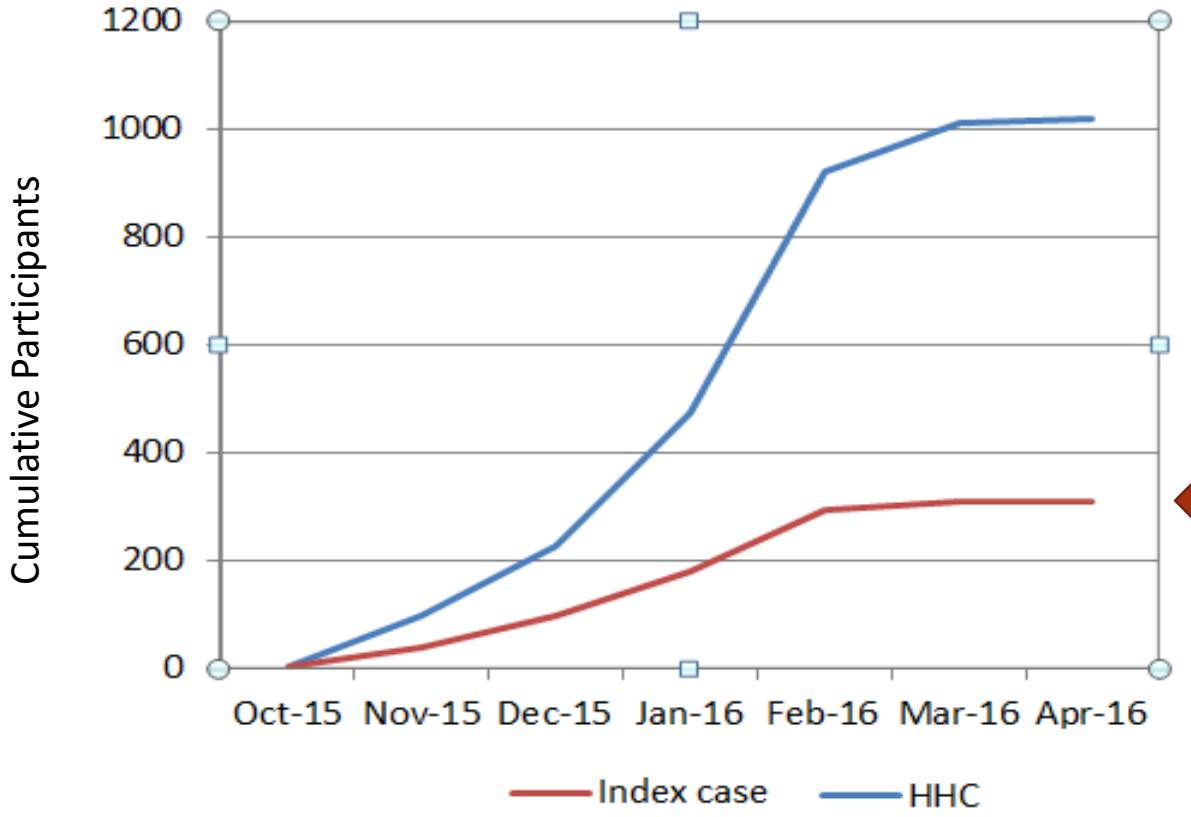
★ 16 sites activated ★ 4 sites not activated Median activation time: 11.7 weeks



- 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

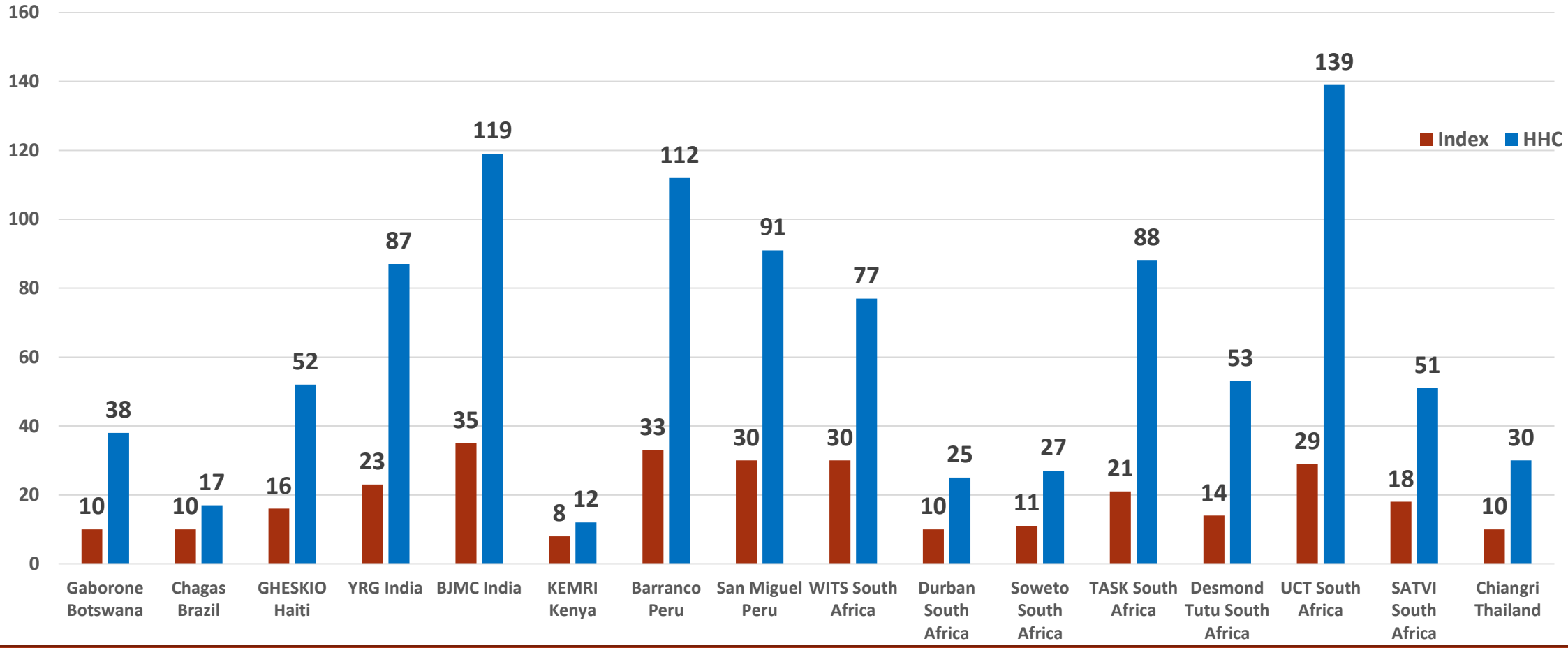


Target enrollment: 300 index cases

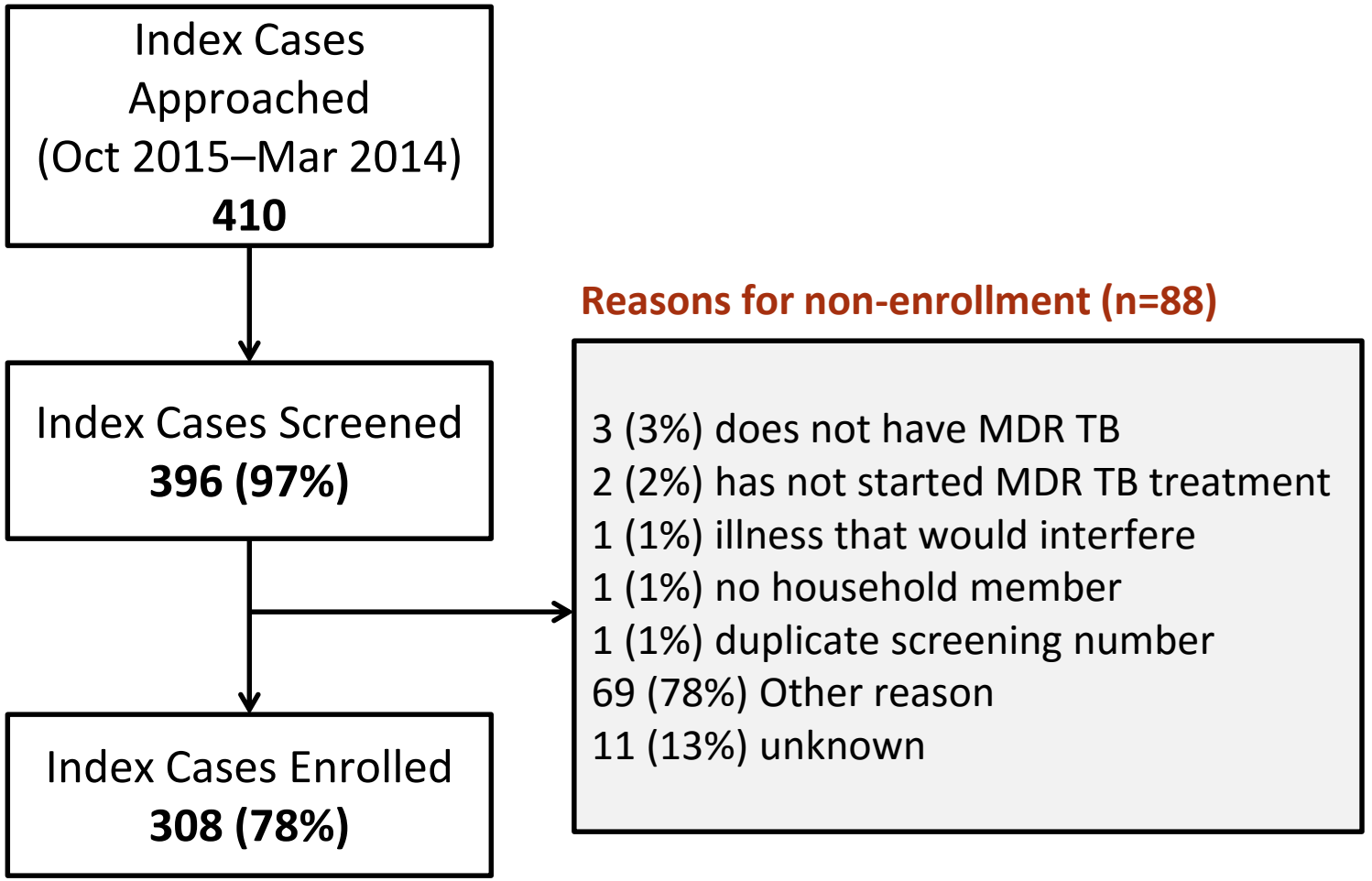
Index & Household Contact Enrollments

(29 October 2015 to 14 April 2016)

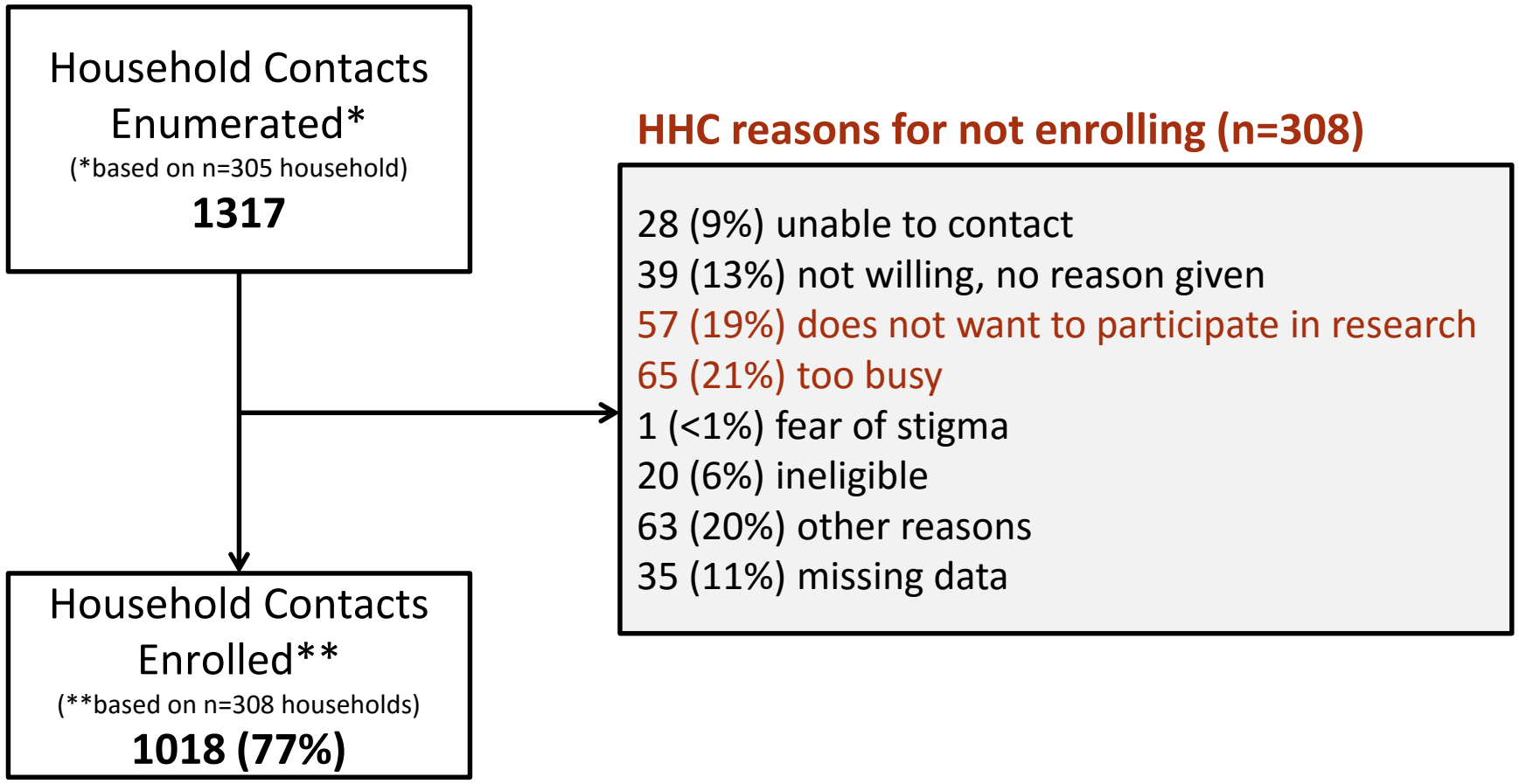
Total enrolled: Index cases=308 HHCs=1018
at 16 sites on 3 continents



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

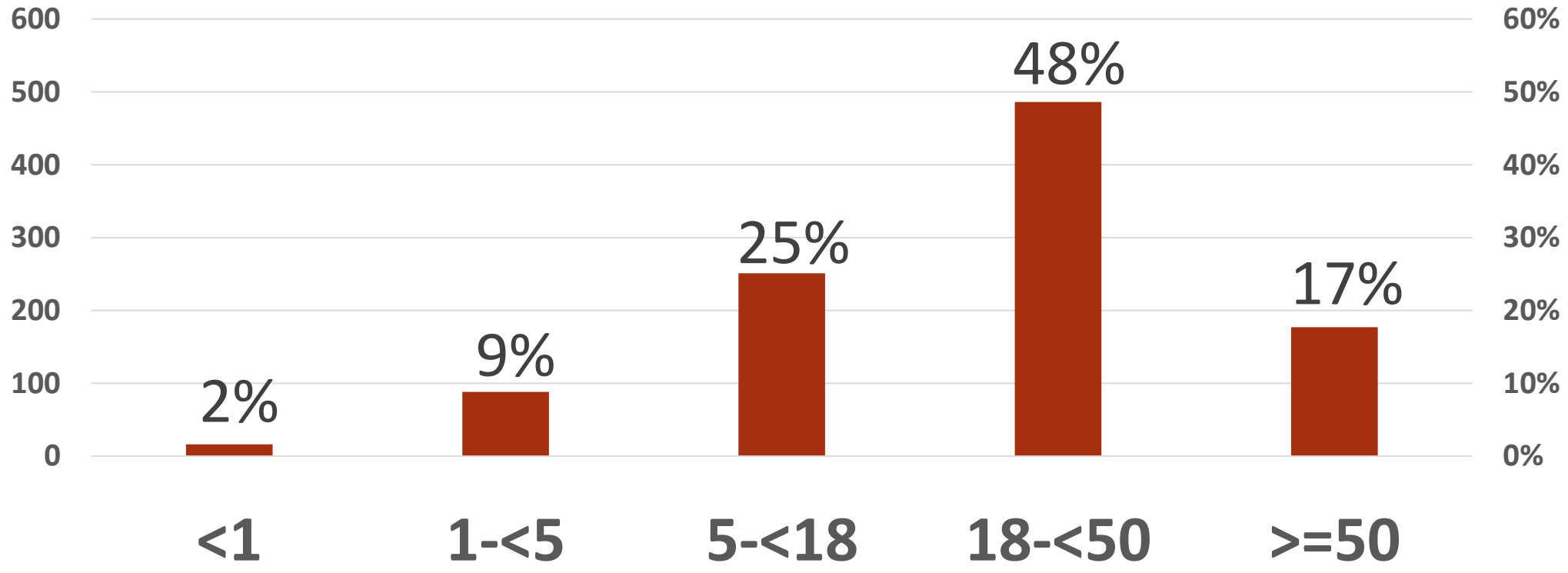
Index cases, n=308

- 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 documented**
    - 13 had RIF R and INH susceptibility
    - 63 had no INH testing 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

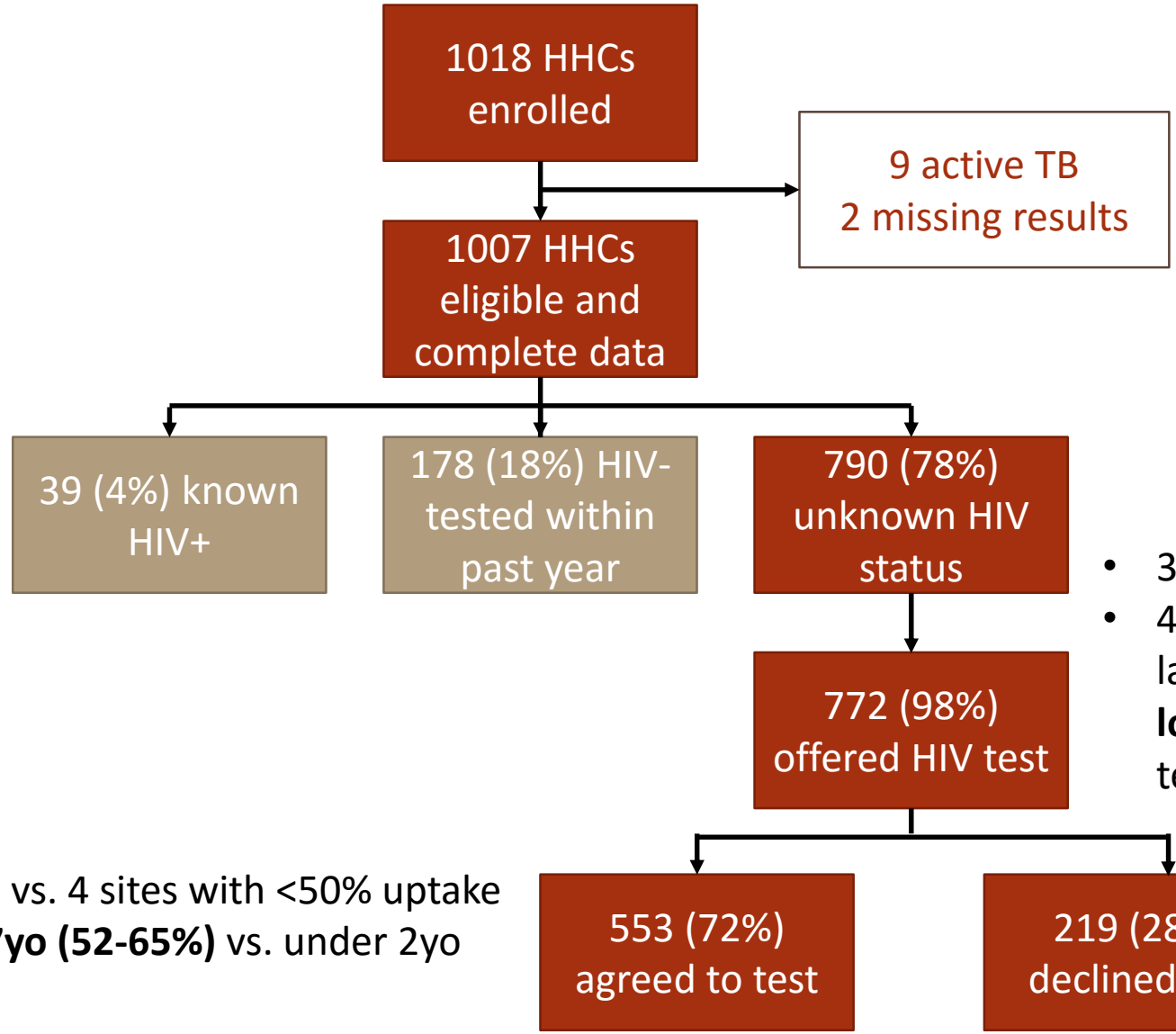
MDR TB Index Case Characteristics

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



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

- 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%)

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%)

Yield of Contact Tracing, n=1016 contacts

- **Signs/symptoms related to TB**: 23% HHCs <15 years and 24% of >=15 years
- **CXR**: 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

Risk factors for Prevalent TB

- Sex: Males> females diagnosed with prevalent TB 16% vs 9%
- LTBI+:
  - 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
- Age: No difference in confirmed/probable by three age groups <5, 5-<15 , 15+ years
- HIV: No difference by HIV status
- High risk group: No difference by high risk group
  - 7% (7 of 102) <5years
  - 5% (3 of 63) HIV and 5+years
  - 6% (39 of 610) positive IGRA or TST

Potentially Eligible High Risk Household Contacts

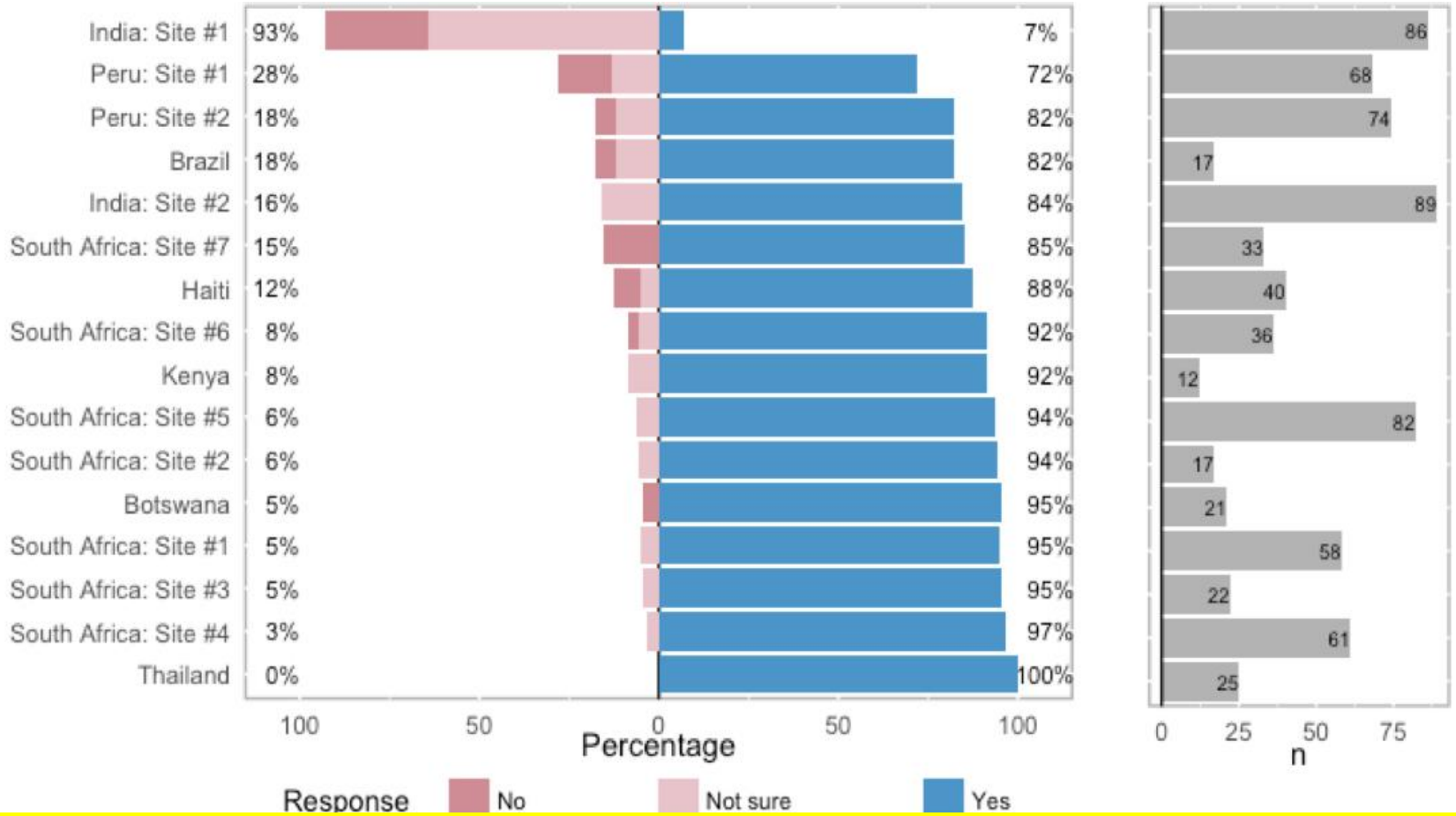
Characteristic	N (%)
Ineligible (had prevalent TB or not high risk)	350 (34%)
Potentially eligible	666 (66%)
<5 years	66 (10%)
≥ 5 years and HIV+	60 (9%)
LTBI+ (TST or IGRA+)	540 (81%)
Median # of eligible contacts per household	2 (IQR 1–3)

Potentially eligible children <18yo:

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

Willingness to take Preventive therapy

n=741 HHCs
median age 33
62% women
42% primary or less education



- HHC willingness to take preventive therapy was high (79%) with significant site-level variation

Suryavanshi, Murill et al Poster at American Thoracic Society 2017

Characteristics of MDR-TB/RR-TB household contacts (n = 741) and factors associated with their willingness to take MDR-TB preventive therapy (PT)

Variables	Summary Statistics			Marginal Logistic Models (GEE with robust SE estimates)			
	Total n (%)	Willingness to take MDR-TB PT		Simple (adjusted for site only)		Multivariable*	
		Yes n (%)	No / Not Sure n (%)	aOR (95% CI)	p-value	aOR (95% CI)	p-value
HOUSEHOLD CONTACT LEVEL VARIABLES							
Demographics							
Not currently employed or in school	400 (54%)	309 (77%)	91 (23%)	0.73 (0.46, 1.13)	0.159	**0.53 (0.30, 0.93)**	**0.028**
TB-related Knowledge and Attitudes							
Partial knowledge-related to TB	248 (33%)	139 (56%)	109 (44%)	**0.35 (0.21, 0.59)**	**<0.001**	**0.51 (0.28, 0.93)**	**0.027**
Belief: will not die of MDR-TB without treatment	116 (16%)	41 (35%)	75 (65%)	**0.25 (0.11, 0.55)**	**0.001**	0.43 (0.17, 1.19)	0.075
Perception: family of someone with TB will not be rejected	596 (80%)	482 (81%)	114 (19%)	**0.46 (0.22, 0.95)**	**0.035**	0.56 (0.28, 1.15)	0.116
Barriers to Preventive Therapy							
Not comfortable telling family about preventive therapy	248 (33%)	145 (58%)	103 (42%)	**0.34 (0.21, 0.55)**	**<0.001**	**0.40 (0.22, 0.71)**	**0.002**
Not confident in properly taking preventive therapy	337 (45%)	196 (58%)	141 (42%)	**0.12 (0.06, 0.25)**	**<0.001**	**0.13 (0.06, 0.29)**	**<0.001**
Medical and Social History							
Known previous treatment for TB	77 (10%)	67 (87%)	10 (13%)	0.72 (0.35, 1.51)	0.389	0.46 (0.17, 1.22)	0.118
HOUSEHOLD LEVEL VARIABLES							
Household Characteristics							
No child <5 years of age in household	496 (67%)	365 (74%)	131 (26%)	0.66 (0.37, 1.19)	0.170	**0.50 (0.26, 0.98)**	**0.044**
Pregnant household contact in household	60 (8%)	43 (72%)	17 (28%)	**0.43 (0.19, 0.97)**	**0.042**	**0.29 (0.10, 0.81)**	**0.019**

Suryavanshi, Murill et al Poster at American Thoracic Society 2017

PHOENIx Main Trial Timeline

- Protocol currently being revised and awaits pediatric modeled dosing (expected early July 2017)
- SIP June 8 2017
- CRFs, MOP, LPC in development
- Submit for Regulatory Review: End of july 2017
- Submit to RCC: 08/18/17
- Submit to FDA: 08/25/17
- Protocol to Sites: 08/28/17
- Regional Trainings: November 2017 onwards
- Study open to accrual 1st or 2nd quarter 2018

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
- Much learned from the feasibility study
- Anticipate opening of study in early-mid 2018

Thank you