



PHOENIX

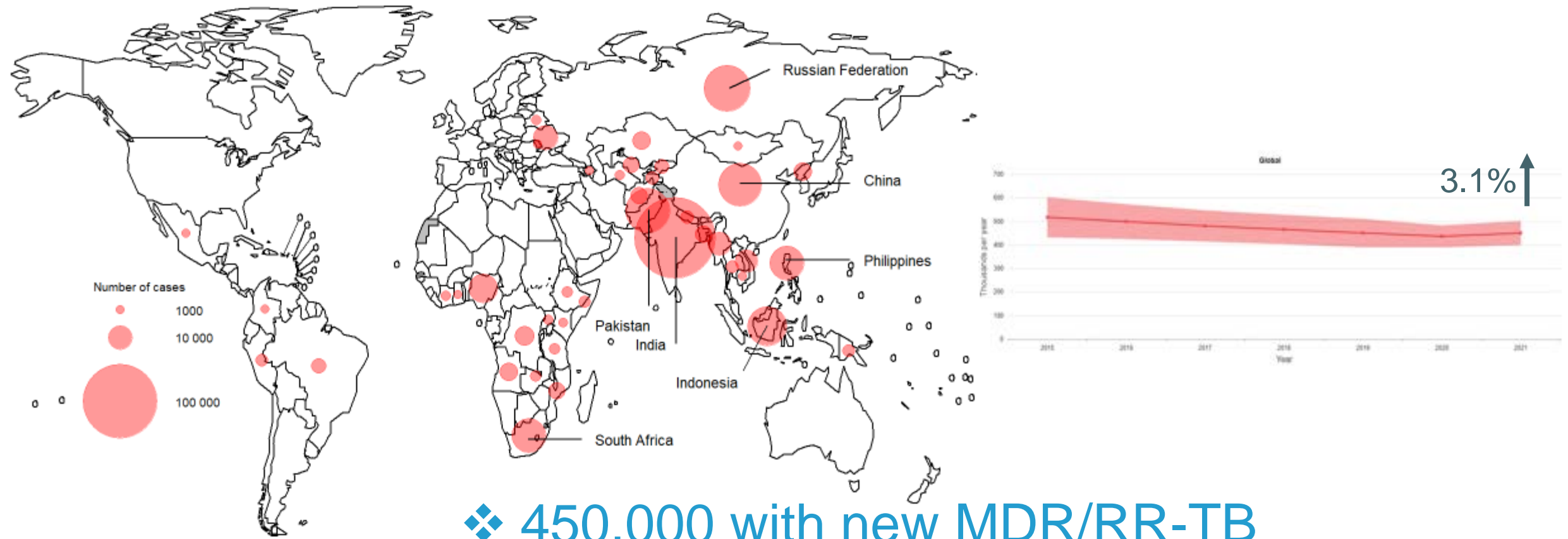
Protecting Households On Exposure to Newly Diagnosed Index
Multidrug-Resistant Tuberculosis Patients
(A5300B/I2003B/PHOENIX)

Amita Gupta MD MHS FIDSA on behalf of an incredible team
Protocol Co-chair, PHOENIX A5300B/IMPAACT 2003
Johns Hopkins Baltimore India CTU co-PI,
Site 31441 BJGMC Pune India



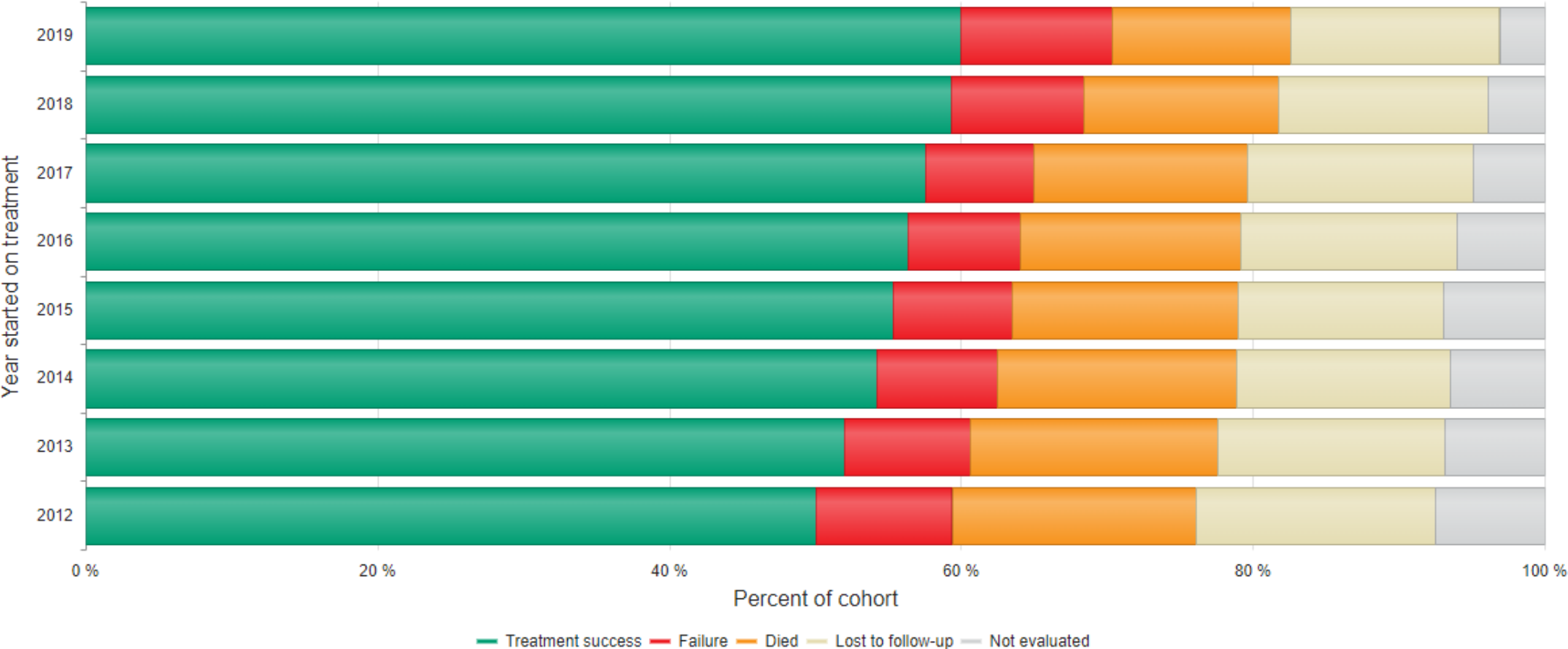


Global Burden of MDR TB in 2021



- ❖ 450,000 with new MDR/RR-TB
- ❖ 20% pre-XDR
- ❖ 191,000 deaths

Poor treatment outcomes with MDR TB



More expensive regimens, more side effects



Each MDR TB case infects many others

10–15 people
If left untreated,

each person with active TB infects, on average,
this number of people every year.



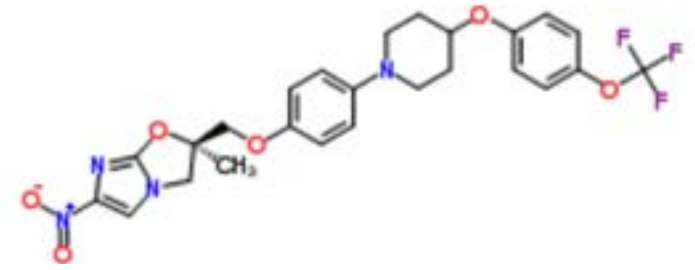
**Global burden of latent multidrug-resistant tuberculosis:
trends and estimates based on mathematical modelling**

Gwenan M Knight, C Finn McQuaid, Peter J Dodd, Rein M G J Houben**

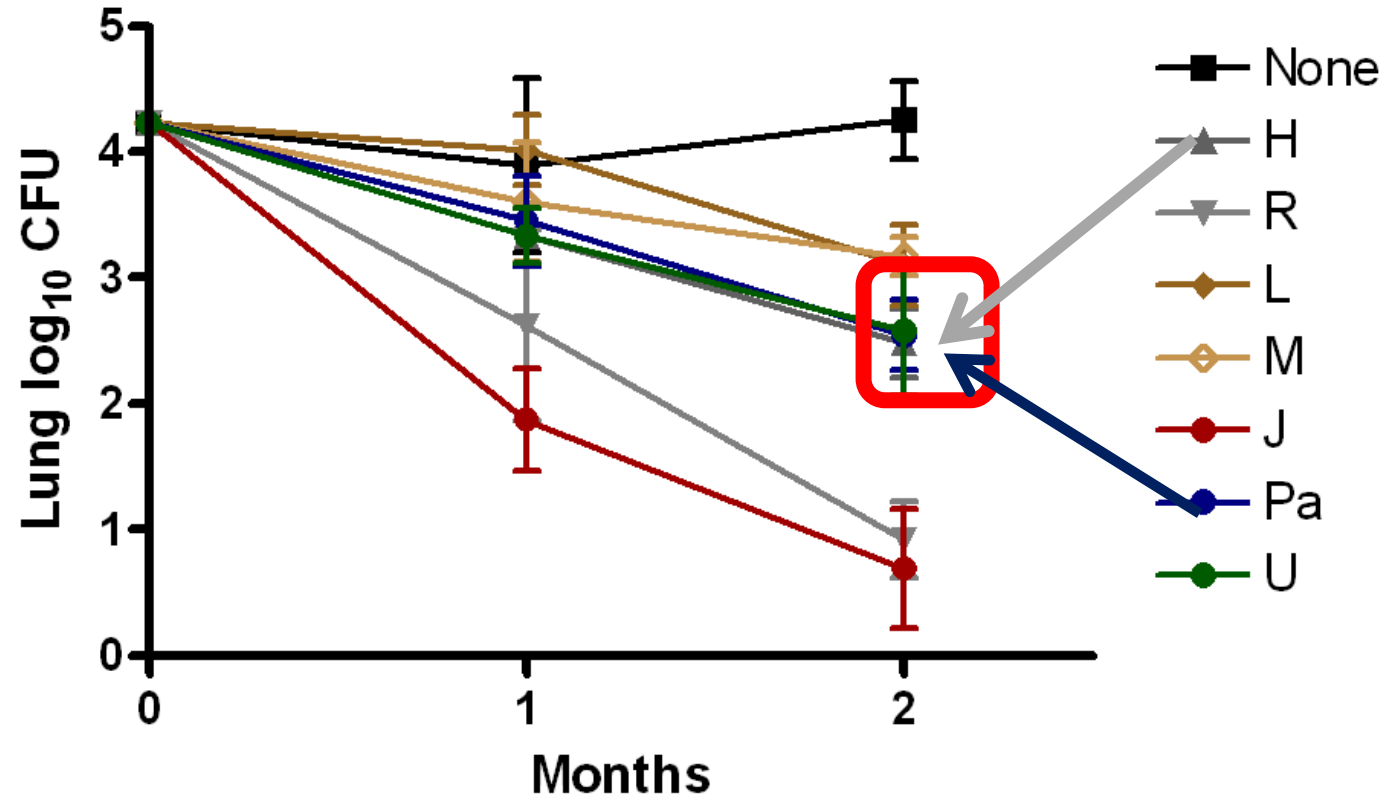
19.1 million MDR LTBI

Children <15 years 2.65 times
increased risk of developing TB disease

Delamanid (DLM)

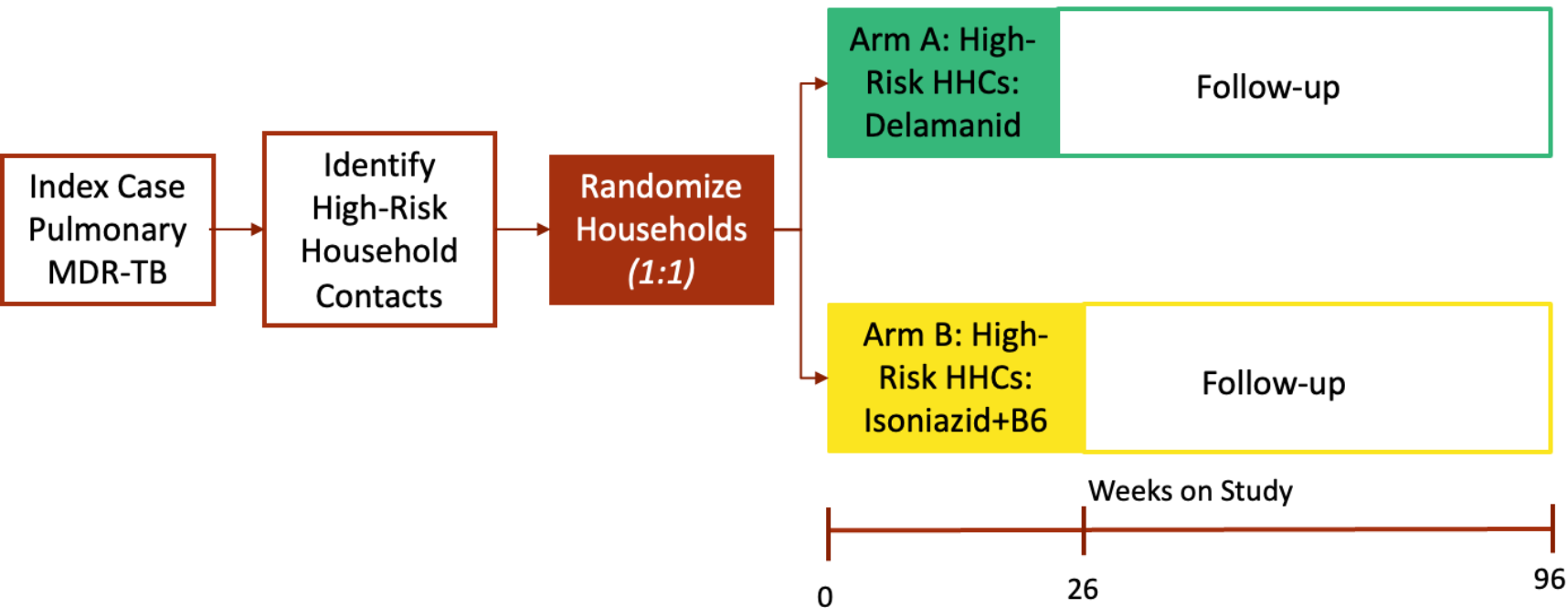


- Novel drug, inhibits mycolic acid synthesis and has potent bactericidal activity
- Mouse model DLM similar efficacy to INH
- DLM does not induce or inhibit cytochrome P450 enzymes or common drug transporters
- Minimal DDI potential





PHOENIX: Efficacy and Safety of Delamanid TB Preventive Therapy vs INH



Phase III open-label, multi-center, cluster-randomized, superiority trial

High-Risk Household Contacts

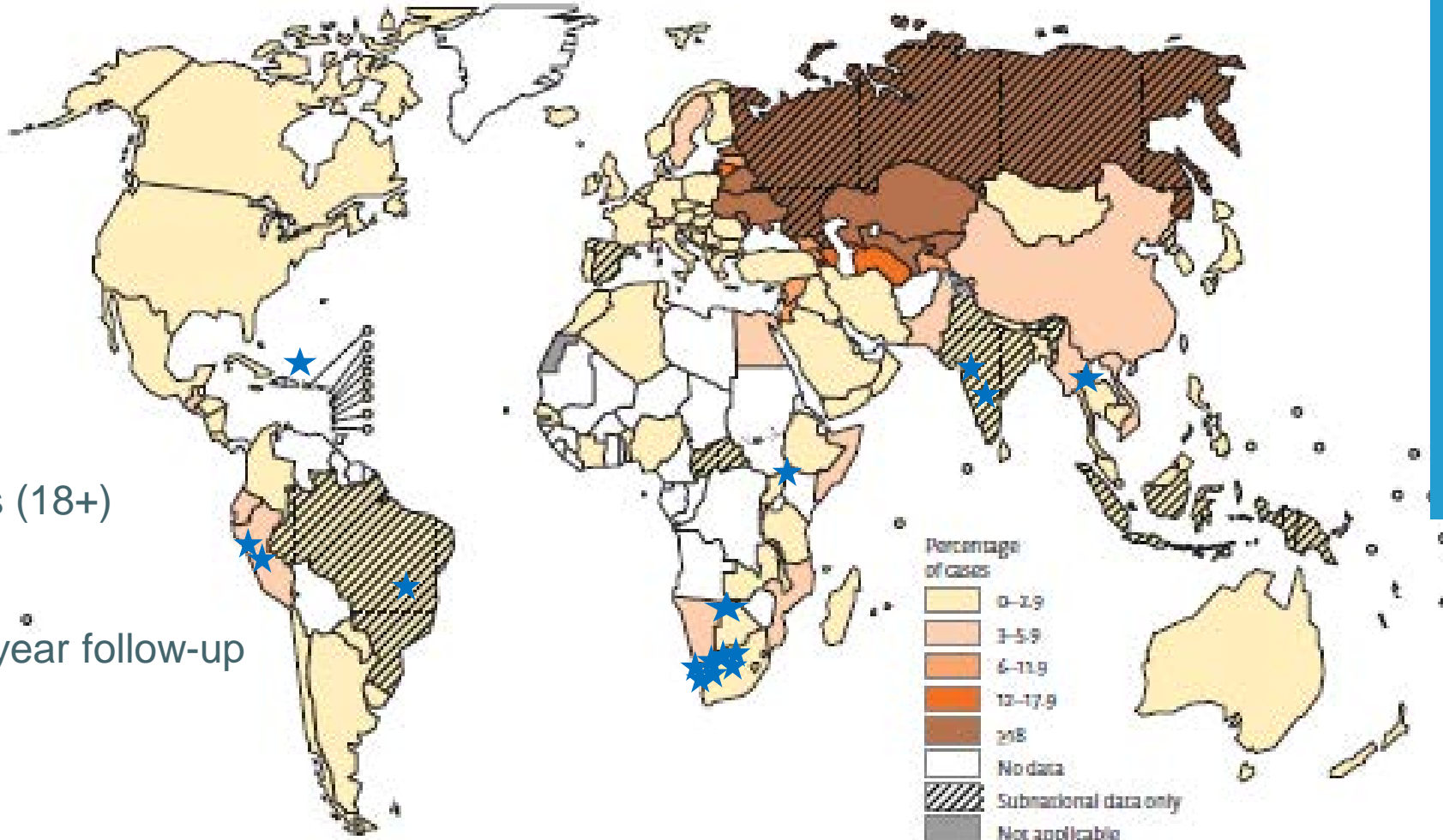
- Children <5 years old
- ≥5 years of age who are
 - HIV-infected or non-HIV immunosuppressed
 - TST positive (≥5mm) and/or IGRA positive

3,452 high-risk household contacts



PHOENIX Feasibility Study

16 sites in 8 high burden countries



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

300 index cases (18+)
1016 contacts

Baseline and 1 year follow-up

RESEARCH ARTICLE Open Access

Drug susceptibility patterns of *Mycobacterium tuberculosis* from adults with multidrug-resistant tuberculosis and implications for a household contact preventive therapy trial

Anne-Marie Demers¹, Soyoon Kim², Sara McCullum³, Kathleen Eisenach⁴, Michael Hughes⁵, Linda Naini⁶, Alberto Mendez-Ticona⁷, Neeta Pradhan⁸, Kim Naransky⁹, Selvamuthu Poongulam¹⁰, Sharlasa Badal-Faesen¹¹, Caryn Upton¹², Elizabeth Smith¹³, N. Sarita Shah¹⁴, Gavin Churchyard^{15,16}, Amita Gupta¹⁷, Anneke Hesseling¹⁸, Susan Swindells^{19,20} and for the ACTG A5300/IMPACT 2003 PHOENIX Feasibility study team

Feasibility of Identifying Household Contacts of Rifampin- and Multidrug-resistant Tuberculosis Cases at High Risk of Progression to Tuberculosis Disease

Amita Gupta¹, Susan Swindells^{2,3}, Soyoon Kim⁴, Michael D. Hughes⁵, Linda Naini⁶, Xingye Wu⁷, Rodney Dawson⁸, Vidya Mave⁹, Jorge Sanchez¹⁰, Alberto Mendez-Ticona¹¹, Pedro Gonzalez¹², Nagalingarawan Kumarasamy¹³, Kyle Comins¹⁴, Francesca Corradie¹⁵, Justin Shenje¹⁶, Sandy Nerette Fontain¹⁷, Anthony Garcia-Pratt¹⁸, Aida Anselash¹⁹, Supalert Neduwon²⁰, Lerato Mofaga²¹, Umesh G. Lalloo²², Ana Cristina Garcia Ferreira²³, Christopher Mughal²⁴, Mark Harrington²⁵, Lynn Jones²⁶, Sanyas R. Gee²⁷, Betsy Smith²⁸, N. Sarita Shah²⁹, Anneke C. Hesseling³⁰ and Gavin Churchyard^{31,32}, for the AIDS Clinical Trials Group (ACTG) 1200/International Maternal Pediatric Adolescent AIDS Trials (IMPACT) 2003 Protecting Households an Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients (PHOENIX) Feasibility Study Team

Caregiver willingness to give TPT to children living with drug-resistant TB patients

V. Rouzier¹, M. Murrill², S. Kim³, L. Naini⁴, J. Shenje⁵, E. Mitchell⁶, M. Raesi⁷, M. Lourens⁸, A. Mendoza⁹, F. Corradie¹⁰, N. Suryavanshi¹¹, M. Hughes¹², S. Shah¹³, G. Churchyard^{14,15}, S. Swindells¹⁶, A. Hesseling¹⁷, A. Gupta¹ for the PHOENIX Feasibility Study team

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10 Publications

Willingness to Take Multidrug-resistant Tuberculosis (MDR-TB) Preventive Therapy Among Adult and Adolescent Household Contacts of MDR-TB Index Cases: An International Multisite Cross-sectional Study

Nishi Suryavanshi^{1,2}, Matthew Merrill³, Amita Gupta^{4,5}, Michael Hughes⁶, Anneke Hesseling⁷, Soyoon Kim⁸, Linda Naini⁹, Lynn Jones¹⁰, Betsy Smith¹¹, Nikhil Gupta¹², Rodney Dawson¹³, Vidya Mave¹⁴, Sushant Mishra¹⁵, Alberto Mendez-Ticona¹⁶, Jorge Sanchez¹⁷, Nagalingarawan Kumarasamy¹⁸, Kyle Comins¹⁹, Francesca Corradie²⁰, Justin Shenje²¹, Sandy Nerette Fontain²², Anthony Garcia-Pratt²³, Aida Anselash²⁴, Supalert Neduwon²⁵, Lerato Mofaga²⁶, Umesh Laloo²⁷, Ana Cristina Garcia Ferreira²⁸, Shikha Dhoke²⁹, Susan Swindells³⁰, Gavin Churchyard^{31,32} and N. Sarita Shah³³, for the ACTG 1200 Study Team

High Prevalence of Tuberculosis Infection and Disease in Child Household Contacts of Adults With Rifampin-resistant Tuberculosis

Soyoon Kim, ScD,¹ Xingye Wu, MS,² Michael D. Hughes, PhD,³ Caryn Upton, MD,⁴ Kim Naransky, MD,⁵ Alberto Mendez-Ticona, MD,⁶ Sushant Mishra, MD,⁷ Pedro Gonzalez, MD,⁸ Sharlasa Badal-Faesen, MD,⁹ Justin Shenje, MD,¹⁰ Aytonde Onoz-Oarhe, MD,¹¹ Vanessa Rontice, MD,¹² Anthony J. Garcia-Pratt, MD, PhD,¹³ Anne-Marie Demers, MD,¹⁴ Linda Naini, MA,¹⁵ Elizabeth Smith, MD,¹⁶ Gavin Churchyard, MD,^{17,18} Susan Swindells, MD,^{19,20} N. Sarita Shah, MD, MPH,²¹ Amita Gupta, MD,²² and Anneke C. Hesseling, MD, PhD,²³ for the ACTG A5300/IMPACT 2003 PHOENIX Feasibility Study Team

The cascade of care for household contacts of people with drug-resistant TB

Dear Editor,
In 2021, the WHO issued a recommendation for initiating TB preventive therapy (TPT) for high-risk contacts of people diagnosed with multidrug-resistant TB (MDR-TB) while acknowledging the paucity of

evidence in practice existed across the six health centers (Table). Three were smaller health centers or clinics, two were tertiary hospitals and one was located within a district hospital exclusively serving MDR-TB patients. Further, multiple issues related

1-Year Incidence of Tuberculosis Infection and Disease Among Household Contacts of Rifampin- and Multidrug-Resistant Tuberculosis

Soyee Krishnan^{1,2}, Xingye Wu³, Soyoon Kim⁴, Katie McIntire⁵, Linda Naini⁶, Michael D. Hughes⁷, Rodney Dawson⁸, Vidya Mave^{9,10}, Sanjay Galikwad¹¹, Jorge Sanchez¹², Alberto Mendez-Ticona¹³, Pedro Gonzalez¹⁴, Kyle Comins¹⁵, Justin Shenje¹⁶, Sandy Nerette Fontain¹⁷, Aytonde Onozarhe¹⁸, Lerato Mofaga¹⁹, Umesh G. Laloo²⁰, Ana Cristina Garcia Ferreira²¹, Christopher Mughal²², Mark Harrington²³, N. Sarita Shah²⁴, Anneke C. Hesseling²⁵, Gavin Churchyard^{26,27}, Susan Swindells²⁸ and Amita Gupta^{29,30}, for the AIDS Clinical Trials Group A5300/International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPACT) 2003 Protecting Households an Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients Feasibility Study Team* (Additional study group members are listed in the Acknowledgment section)

Resource utilization for multidrug-resistant tuberculosis household contact investigations (A5300/I2003)

S. Swindells,¹ A. Gupta,¹ S. Kim,¹ M. D. Hughes,² J. Sanchez,³ V. Mave,⁴ R. Dawson,⁵ N. Kumarasamy,⁶ K. Comins,⁷ B. Smith,⁸ R. Rustomjee,⁹ L. Naini,¹⁰ N. S. Shah,¹¹ A. Hesseling,¹² G. Churchyard,^{13,14,15,16} for the ACTG5300/IMPACT2003 Phoenix Feasibility Study Team

Resistance to *Mycobacterium tuberculosis* Infection Among Household Contacts: A Multinational Study

Devit Balisevili¹, Neel R. Gandhi², Soyoon Kim³, Michael Hughes⁴, Vidya Mave⁵, Alberto Mendez-Ticona⁶, Pedro Gonzalez⁷, Kim Naransky⁸, Prasegopal Selvamuthu⁹, Sharlasa Badal-Faesen¹⁰, Caryn Upton¹¹, Linda Naini¹², Elizabeth Smith¹³, Amita Gupta¹⁴, Gavin Churchyard^{15,16}, Susan Swindells¹⁷, Anneke Hesseling¹⁸ and N. Sarita Shah¹⁹, for the ACTG1200 PHOENIX Feasibility study team

Factors associated with prevalent *Mycobacterium tuberculosis* infection and disease among adolescents and adults exposed to rifampin-resistant tuberculosis in the household

Soyoon Kim^{1,2}, Anneke C. Hesseling³, Xingye Wu⁴, Michael D. Hughes⁵, N. Sarita Shah⁶, Sanjay Galikwad⁷, Mishi Kumarasamy⁸, Erika Mitchell⁹, Mey Leon¹⁰, Pedro Gonzalez¹¹, Sharlasa Badal-Faesen¹², Maleniwe Lourens¹³, Sandy Nerette¹⁴, Justin Shenje¹⁵, Petra de Kokar¹⁶, Supalert Neduwon¹⁷, Lerato Mofaga¹⁸, Umesh A. Chakalisa¹⁹, Rosie Mughal²⁰, Rodrigo Otávio de Silva Escada²¹, Samuel Duma²², Barbara Heckman²³, Linda Naini²⁴, Amita Gupta²⁵, Susan Swindells²⁶, Gavin Churchyard²⁷, on behalf of the ACTG A5300/IMPACT 2003 PHOENIX Feasibility Study Team²⁸

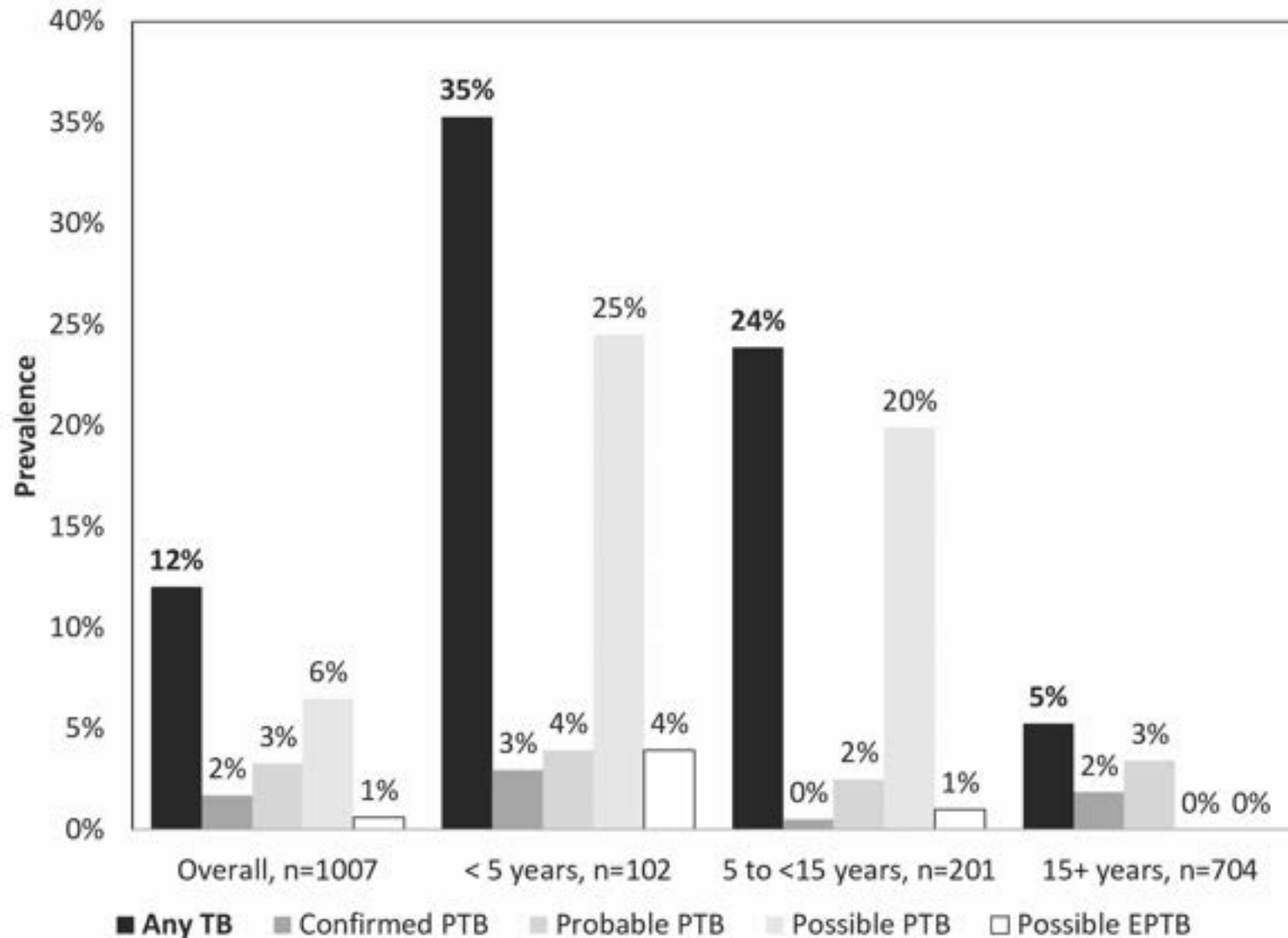
MDR TB Index Case Characteristics

Characteristic	Index (N=308)
HIV	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) (n=290)	148 (70%)
Xpert positive	141 (51%)
MGIT culture positive	75 (27%)
MDR TB treatment duration, median (range)	8.4 weeks (0-27wks)

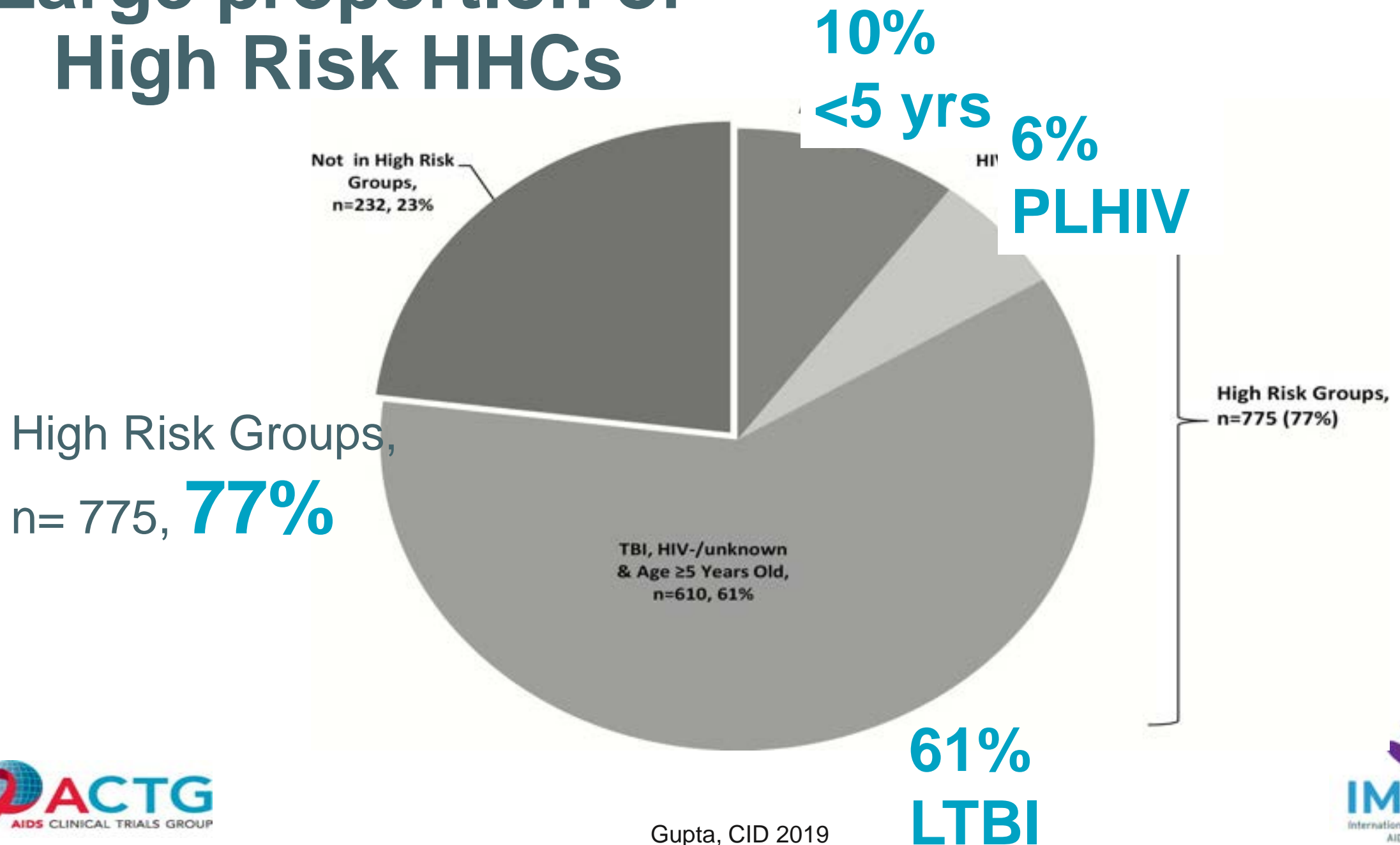
Learnings from 1016 household contacts

- **24% had Signs/symptoms related to TB:** 23% HHCs <15 yrs, 24% of >=15 yrs
- **17% had abnormal CXR:** 971 (96%) got CXR, 886 (91%) were good quality
 - 22 of 55 children <15 years with abnormal CXR had CXR suggestive of TB
- **13% had prevalent TB**
 - **Confirmed** 26, **3%** (includes 9 that were already diagnosed at time of contact tracing)
 - **Probable** 33, **3%**
 - **Possible** 71, **7% (all children)**
 - 31 households had more than 1 contact with prevalent TB
- Yield varied by site

HHC Prevalence of TB disease



Large proportion of High Risk HHCs



HHC Characteristics Associated with TB Infection by IGRA



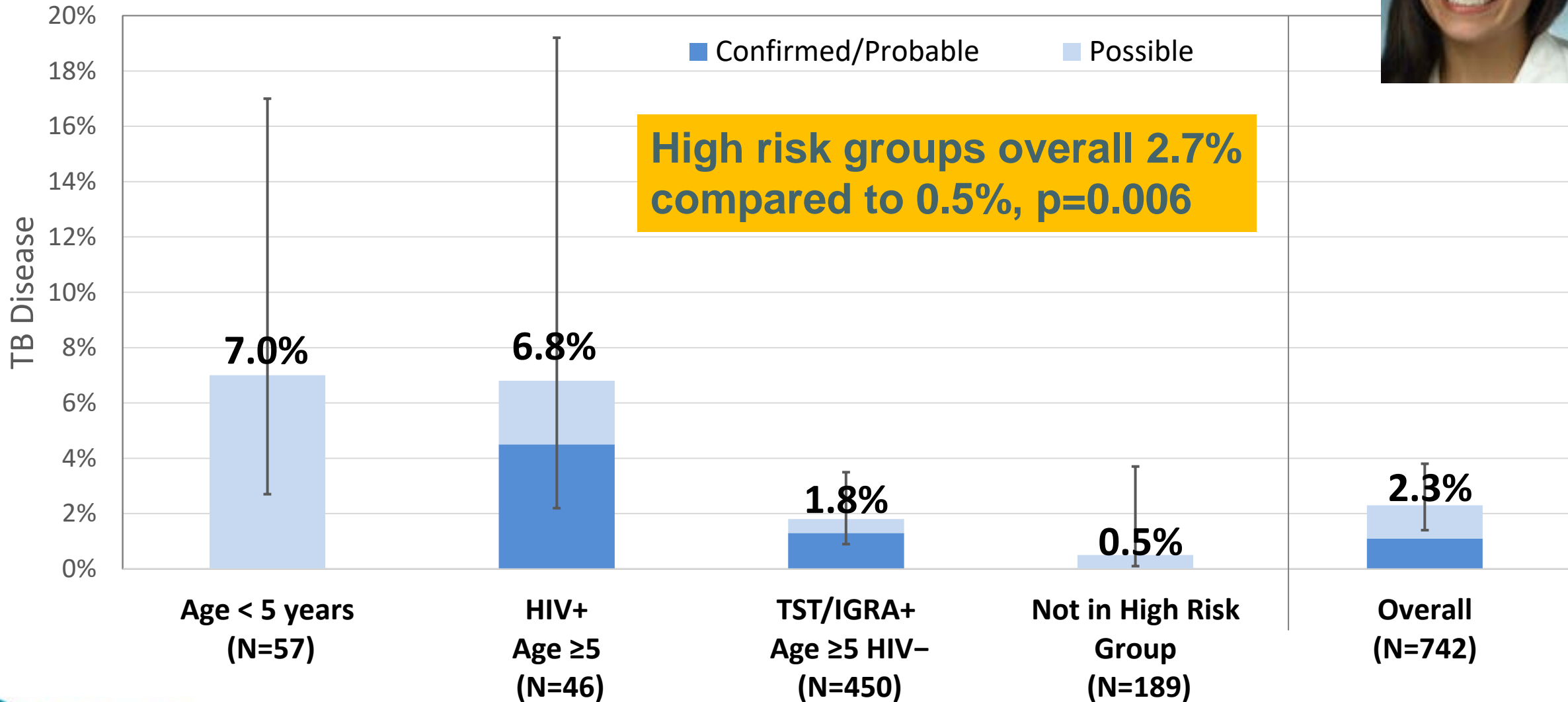
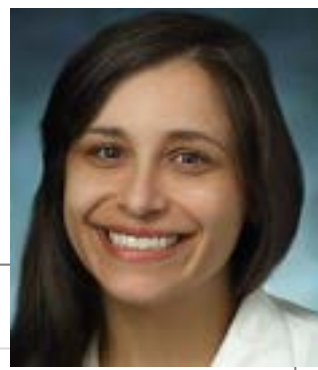
Characteristics	Adjusted OR	P value
Age 25-49 years	1.5 [0.99, 2.3]	<0.001
Previous TB Treatment	1.9 [0.96, 3.8]	0.049
Incarceration, Substance and Alcohol Use†	7.3 [1.5, 34]	<0.001
Sleeping in same room with IC	2.4 [1.4, 4.2]	0.04
Smokers in Household‡	1.6 [1.04, 2.4]	0.029
Home Exterior Wall <i>Adobe, rammed earth, sticks or stones & mud, wood, straw, tin</i>	1.8 [1.2, 2.8]	0.008

Learnings from the Feasibility Study

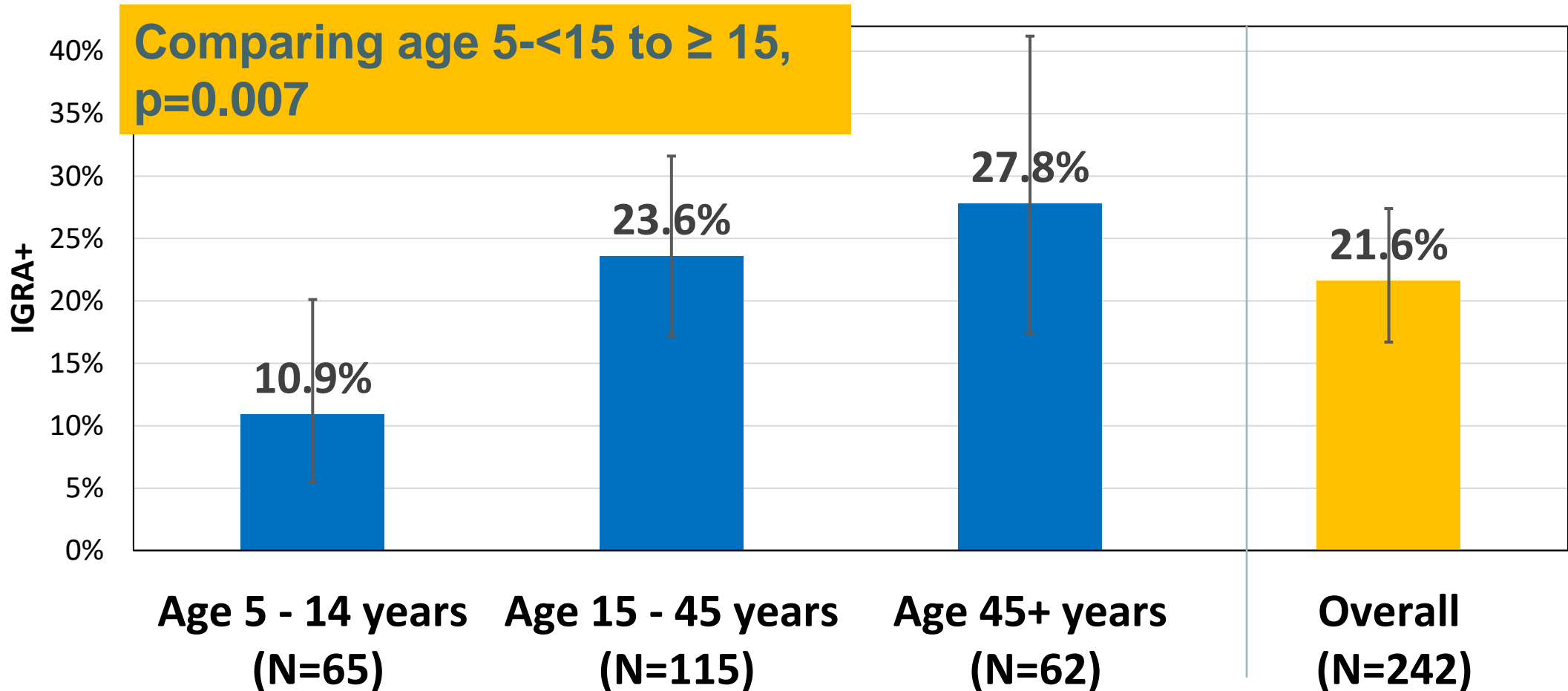
- Of HHCs eligible for preventive therapy **only 5% received it**
 - TPT regimens taken were INH+EMB+LVX or INH only
- **High willingness to take TPT: 79%** *Suryavanshi, Murrill et al. CID 2019*
- **High willingness for caretakers to provide TPT to their children: 89%** *Rouzier, Murill et al, IJTLD 2022*



Cumulative incidence of TB Disease significantly differs by risk group



Increasing age-specific incidence of TB infection (IGRA conversion) at 1 year of follow-up

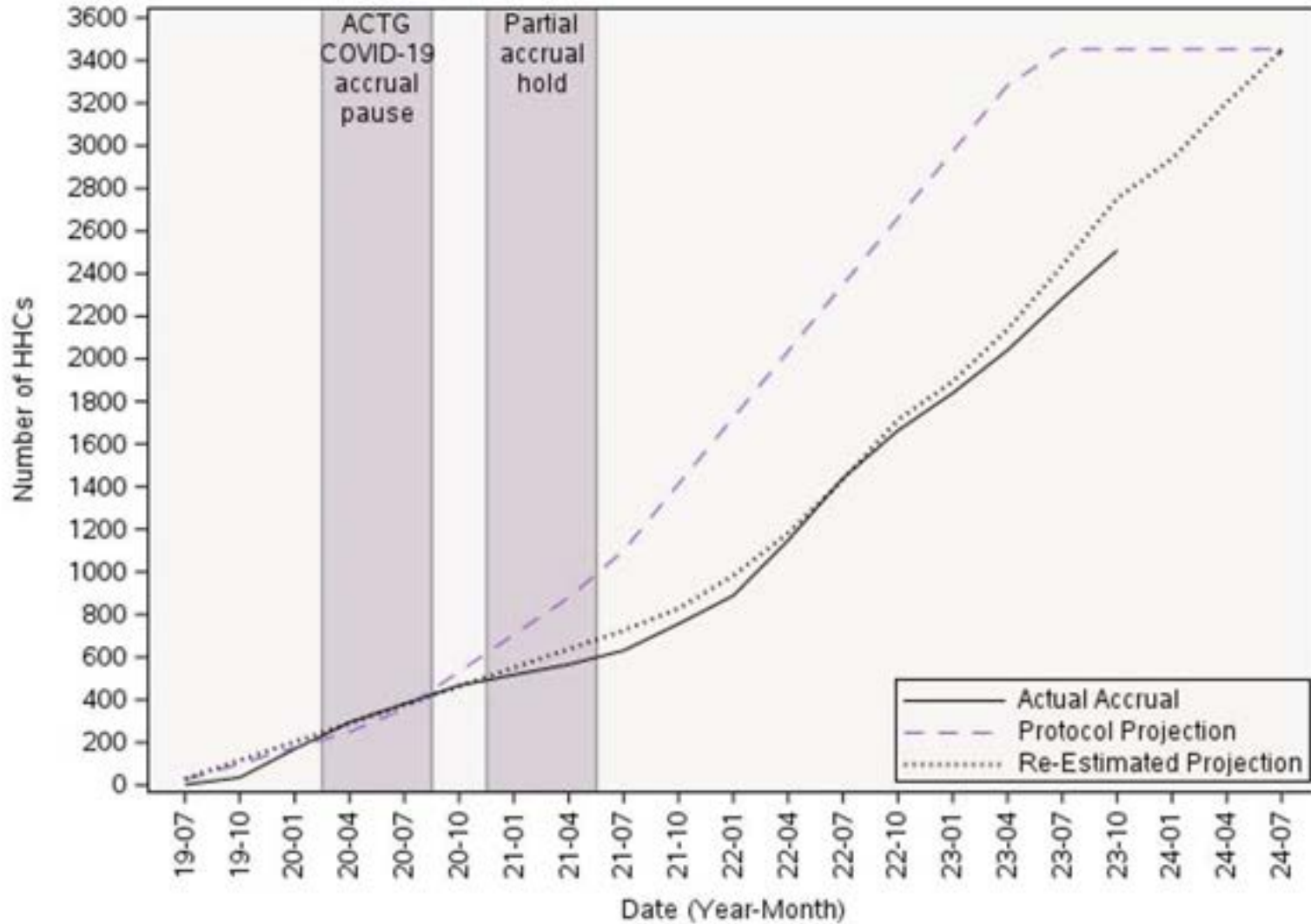


Timeline of PHOENIX trial



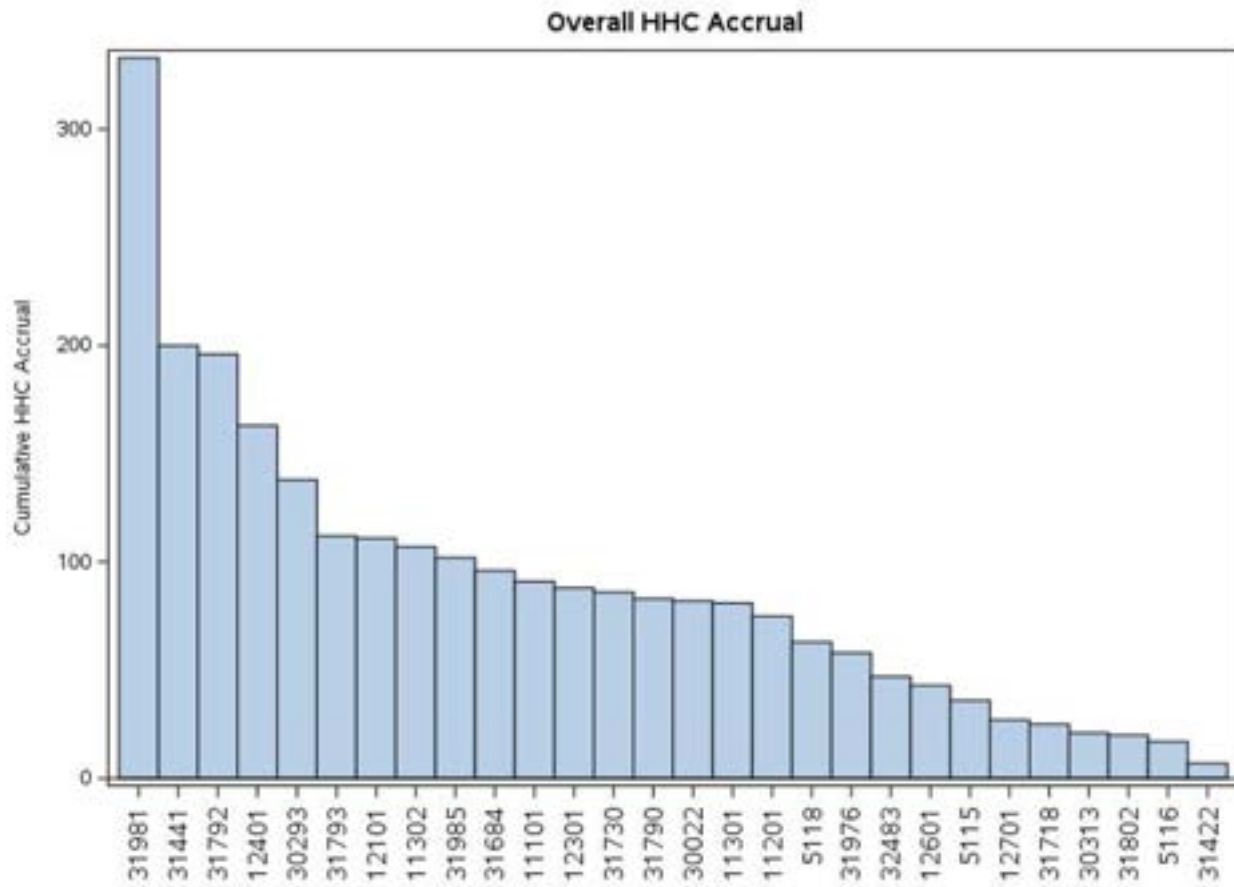
- **June 20, 2018:** Version 1.0
- **June 3, 2019:** Open to accrual under Version 2.0 after FDA and DAIDS changes
- **June 13, 2019:** 1st index case enrolled
- **July 10, 2019:** 1st HHC Enrolled
- **March 18, 2020:** COVID pause
- **March 31, 2020:** Version 3.0
- **15 July 2020:** COVID pause lifted
- **November 5, 2020:** pause of pediatric <15 yrs enrolment due to unanticipated neuropsychiatric side effects
- **March 13, 2021:** FDA lifted hold on pediatric enrolment
- **May 15, 2022:** RFA for additional sites
- **November 30, 2022:** Version 4.0

2508 / 3452 (73%) HHCs have been enrolled as of 11OCT2023



- 2365 Index cases screened
- 1337 Index cases enrolled
- **2508/3452 (73%) HHCs enrolled**

26 sites in 12 countries



Site ID	Site	Cumulative HHC Accrual
31981	Philippines, Cavite De La Salle CRS	333
31441	India, Pune BJMC CRS	200
31792	South Africa, Cape Town UCTLI CRS	196
12401	Uganda, Kampala JCRC CRS	163
30293	Uganda, Kampala MUJHU CRS	138
31793	South Africa, Cape Town SATVI CRS	112
12101	Brazil, Rio de Janeiro Chagas CRS	111
11302	Peru, Lima San Miguel CRS	107
31985	Peru, Lima SES CRS	102
31684	South Africa, Rustenburg Aurum CRS	96
11101	South Africa, Johannesburg WITS CRS	91
12301	South Africa, Soweto CRS	88
31730	Haiti, Port-au-Prince GHEKIO-IMIS CRS	86
31790	South Africa, Cape Town DTTC CRS	83
30022	Haiti, Port-au-Prince GHEKIO-INLR CRS	82
11301	Peru, Lima Barranco CRS	81
11201	South Africa, Durban CRS	75
5118	Tanzania, Moshi KCMC CRS	63
31976	South Africa, PHRU Matlosana CRS	58
32483	Vietnam, Hanoi National Lung Hosp CRS	47
12601	Kenya, Eldoret Ampath MOI CRS	43
5115	Thailand, Bangkok Siriraj CRS	36
12701	Botswana, Gaborone CRS	27
31718	South Africa, Cape Town TASK CRS	25
30313	Zimbabwe, Harare Milton Park CRS	21
31802	Thailand, Bangkok Thai Red Cross CRS	20
5116	Thailand, Chiang Mai Chiangrai CRS	17
31422	South Africa, Durban CAPRISA CRS	7
Total		2508

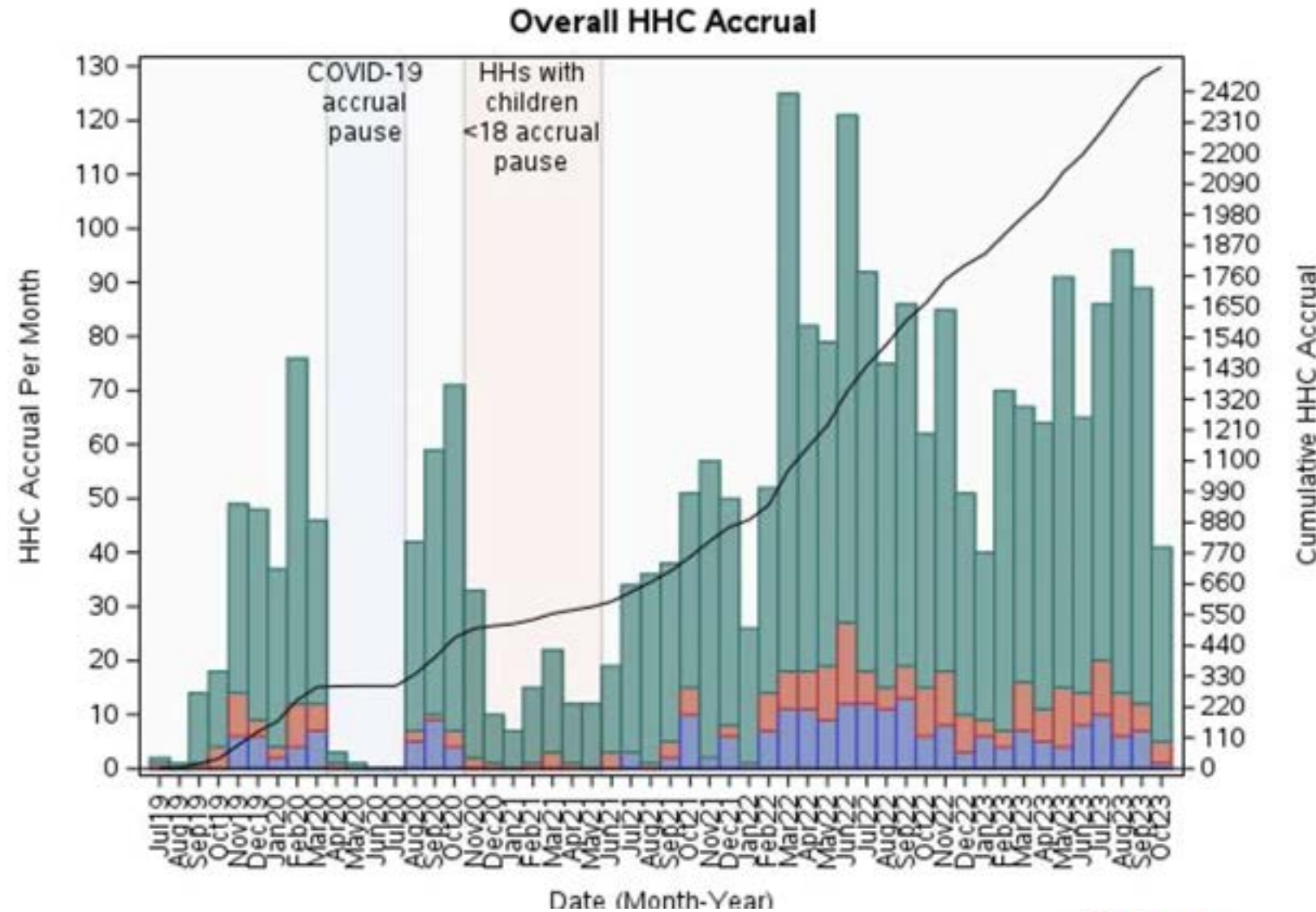
Accrual of high-risk HHCs

82.4% LTBI+

35.3% <18 years

9.1% <5 years

8.5% HIV



Baseline Characteristics

Household Contacts (N=2062)

- **# HHCs enumerated:** 3890
- **# HHCs screened:** 3264 (84% of those enumerated)
- **# HHCs enrolled:** 2062 (63% of those screened)
- **# HHCs enrolled per HH:** median=2.0 and mean=2.8, Range=1-19
- **Median (Q1, Q3) days to enrolling 1st HHC** from index case
 - MDR-TB treatment start: 49 (32, 76)
 - Enrollment: 15 (9, 23)
- **Median age:** 24 years (range: 0-88 years)
- **Female:** 55%

Ongoing efforts

- **Two new ACTG sites**
 - NLH - Hanoi, Vietnam (Activated)
 - Currently enrolled 4 index cases and 2 HHCs
 - CAPRISA - Durban, S. Africa (Pending activation)
- **Two new protocol-specific sites being activated**
 - India – YRGCARE
 - Vietnam - University of Sydney (V-QUIN site)
- **Economic** evaluation at 4 sites
- **Adherence** monitoring
- Additional **PK** studies
- Biobanking for planned **Biomarker** and **genomic** studies
- AWAIT CHANGES THAT MAY BE NEEDED AS A RESULT OF VQUIN, TB CHAMP

Start date

Apr 2023

June 2023

December 2023

December 2023



Summary

- PHOENIX is a truly global collaboration
- Households of MDR cases have a high burden of infection and age-specific risk of developing TB disease
- Incredible participant and study team narratives
- Model generated followed by PK studies have confirmed appropriate Delamanid once-daily dosing
- 73% accrued and 4 new sites joined to accelerate completion
- Much more to come!

Thank you!

LEAVE
NO ONE

BEHIND

UNITE TO END TB

IMPAACT

14 June 2023
International Maternal Pediatric Adolescent
AIDS Clinical Trials Network



Acknowledgments

Study Participants, Site Community Advisory Boards, Communities

Co-chairs: Gavin Churchyard, Amita Gupta, Anneke Hesselning,
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Suryvanshi, Ma Tarcela, Alberto Mendoza, Pedro Gonzalez,
Kyla Comins, Francesca Conradie, Justin Shenje, Sandy Nerette
Fontain, Anthony Garcia-Prats, Aida Asmelash, Supalert
Nedsuwan, Lerato Mohapi, Umesh G. Laloo, Ana Cristina
Garcia Ferreira, Christopher Mugah and many more

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Field Representatives: Savita Kanade, Janet Nicotera

Laboratory technologists: Patricia Anthony, Christopher Lane,
Will Murtaugh

Community Scientific Subcommittee Representatives:

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International Site Specialist: Akbar Shahkolahi

Data Managers: Lynne Jones, Barbara Heckman

Laboratory Data Manager: Adam Manzella

Otsuka Pharmaceuticals

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