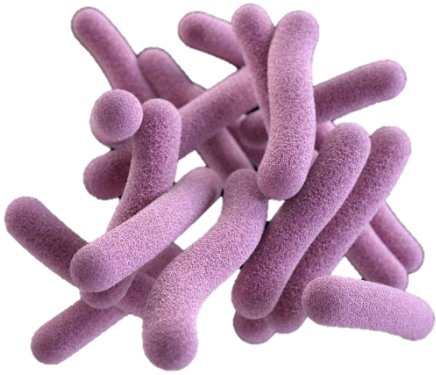
Union TB Meeting
October 25, 2018



Impact of maternal isoniazid preventive therapy (IPT) timing on acquisition of infant TB infection (TBI) in the IMPAACT P1078/TB APPRISE trial

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Gratitude to the amazing TB APPRISE/P1078 Study Team

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Disclosures

- Amita Gupta has no financial disclosures

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Background

- TB is the #1 infectious disease killer globally, surpassing HIV[1]
- TB is leading cause of child mortality and most deaths occur before age 5 years[2]
- Prevention of TB in infants critical as infants at very high risk of progression after exposure[3]
- Maternal TB can be a source for infant TB so provision of IPT to mothers could result in reduction of infant TB infection, which is associated with increased progression to TB disease[4,5]
- TST conversion[6] and high QuantiFERON values at 1 year of life associated with increased risk of TB disease[7]

[1] WHO Global TB Report 2018; [2] Dodd Lancet Global Heath 2017; [3] Marais NEJM; [4] Gomes Thorax; [5] Mathad CID 2012; [6] Martinez Lancet Child Adolesc Health 2018; [7] Andrews Lancet Respiratory Dis 2017

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Objectives

- To compare prevalence of infant TB infection at week 44 by test type and timing of maternal INH preventive therapy
- To assess predictors of QFT-GIT and TST positivity
- To evaluate agreement of IGRA (QuantiFERON Gold In tube) and TST in infants

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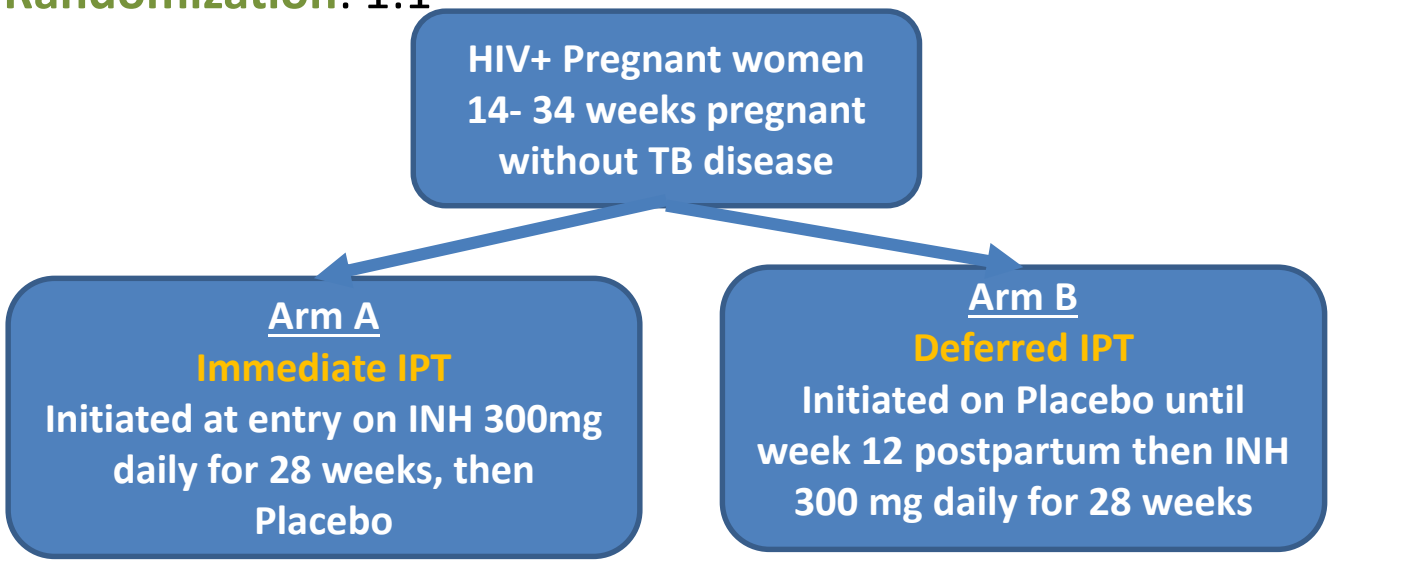
TB APPRISE: IMPAACT P1078 Study Design

- **Design**: **Phase IV multicenter, randomized, double-blind, placebo-controlled, non-inferiority trial**
- **Population**: HIV-infected pregnant women ≥ 14 weeks through ≤ 34 weeks gestation who live in a **high TB burden area**, defined as TB prevalence ≥ 60/100,000 population
- **Randomization**: 1:1



Study drugs (INH/Placebo), open label Pyridoxine (vitamin B_6) and open label prenatal multivitamin terminated at 40 weeks postpartum

End of follow-up: 48 weeks postpartum

Gupta et al CROI 2018

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Methods

- QFT-GIT and TST assessed at week 44 of infant life
  - QFT-GIT+ definitions using manufacturers and published thresholds definitions
  - TST+ if >= 10mm (HIV-uninfected) or TST+ >=5mm if HIV-infected

- Predictors of Infant TB infection status assessed by logistic regression
  - Study arm, HIV status, TB exposure, INH use, BCG vaccination and scar, WHO weight for age Z score, infant exclusive breastfeeding

- Test concordance measured by Kappa measure of agreement

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Characteristics of Infant Cohort with either QFT-GIT or TST, n=749

Infant Characteristic	N	%
Maternal Treatment Group Immediate INH Deferred INH	 369 380	 49% 51%
HIV-infected	7	1%
TB exposure	20	3%
Infant INH use	9	1%
BCG vaccination with record of receipt or BCG scar with documented record of receipt	692 486	92% 65%
BCG scar	603	81%
WHO weight for age z score, mean (sd)	-0.4	(2.2)
Exclusive Breastfeeding duration, weeks, median (IQR)	24	(12,24)
Exclusively breastfed (any duration)	599	80%

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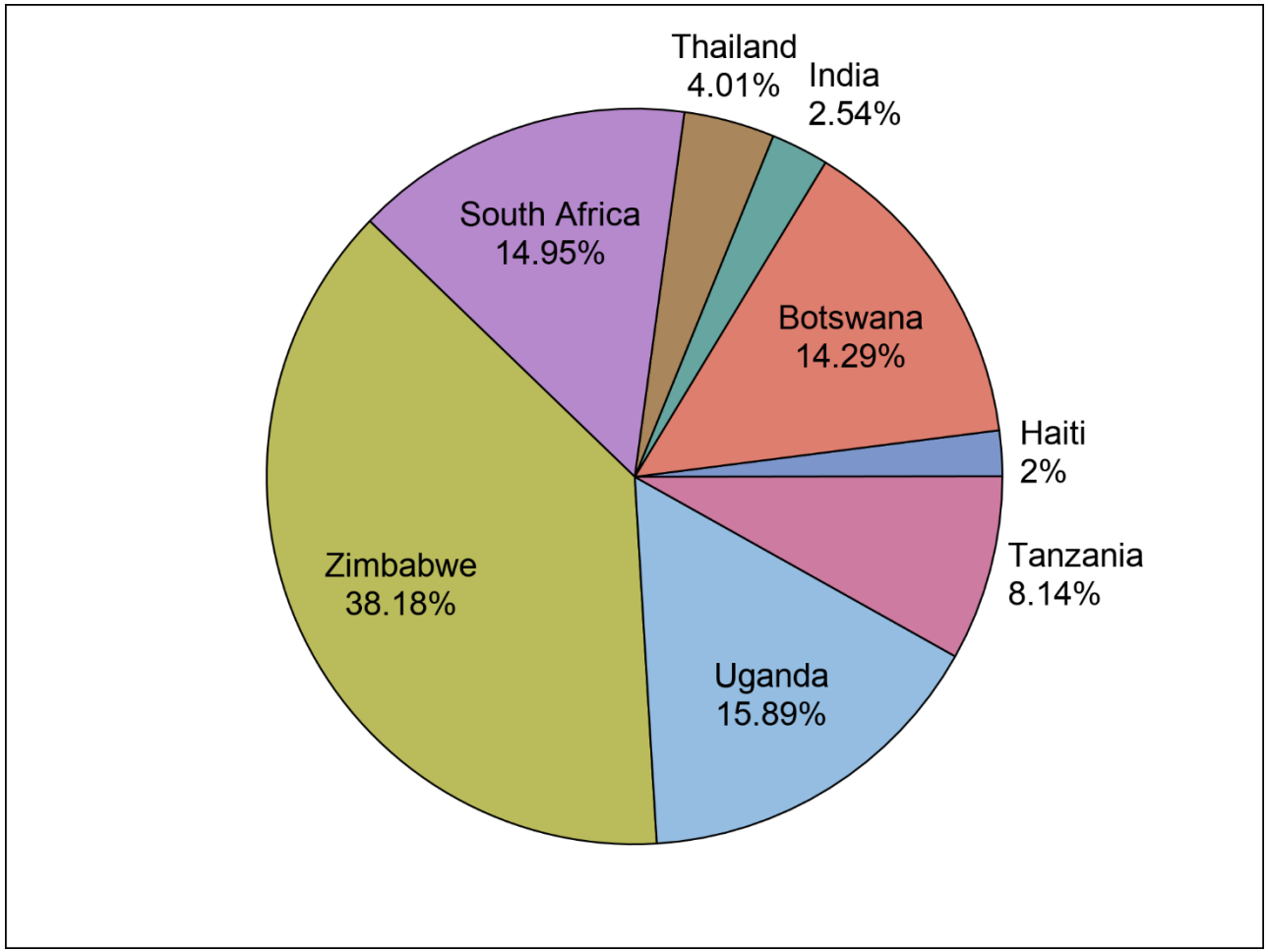
Percent of infants by site countries represented



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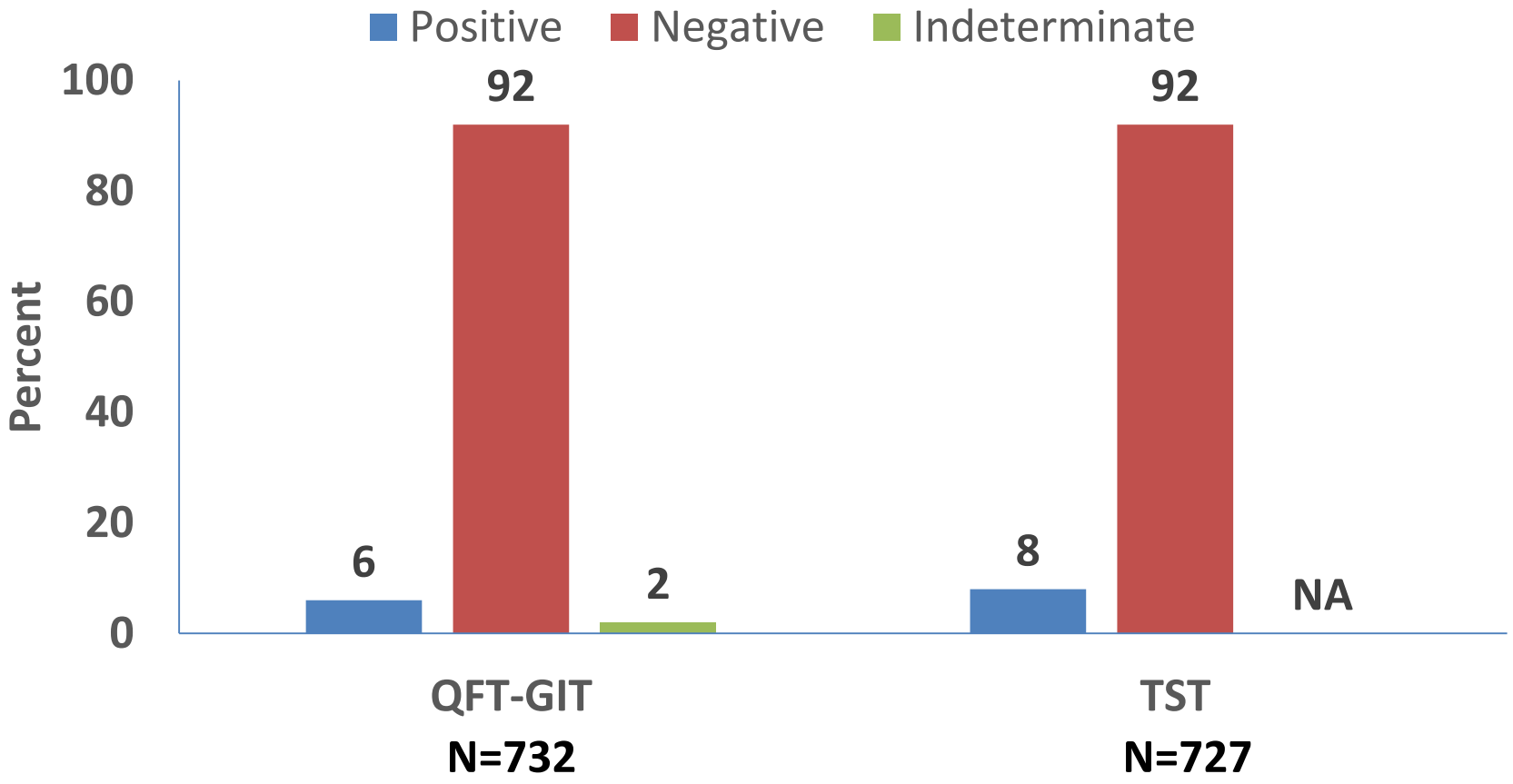
Infant TB infection testing results by QFT-GIT and TST at week 44



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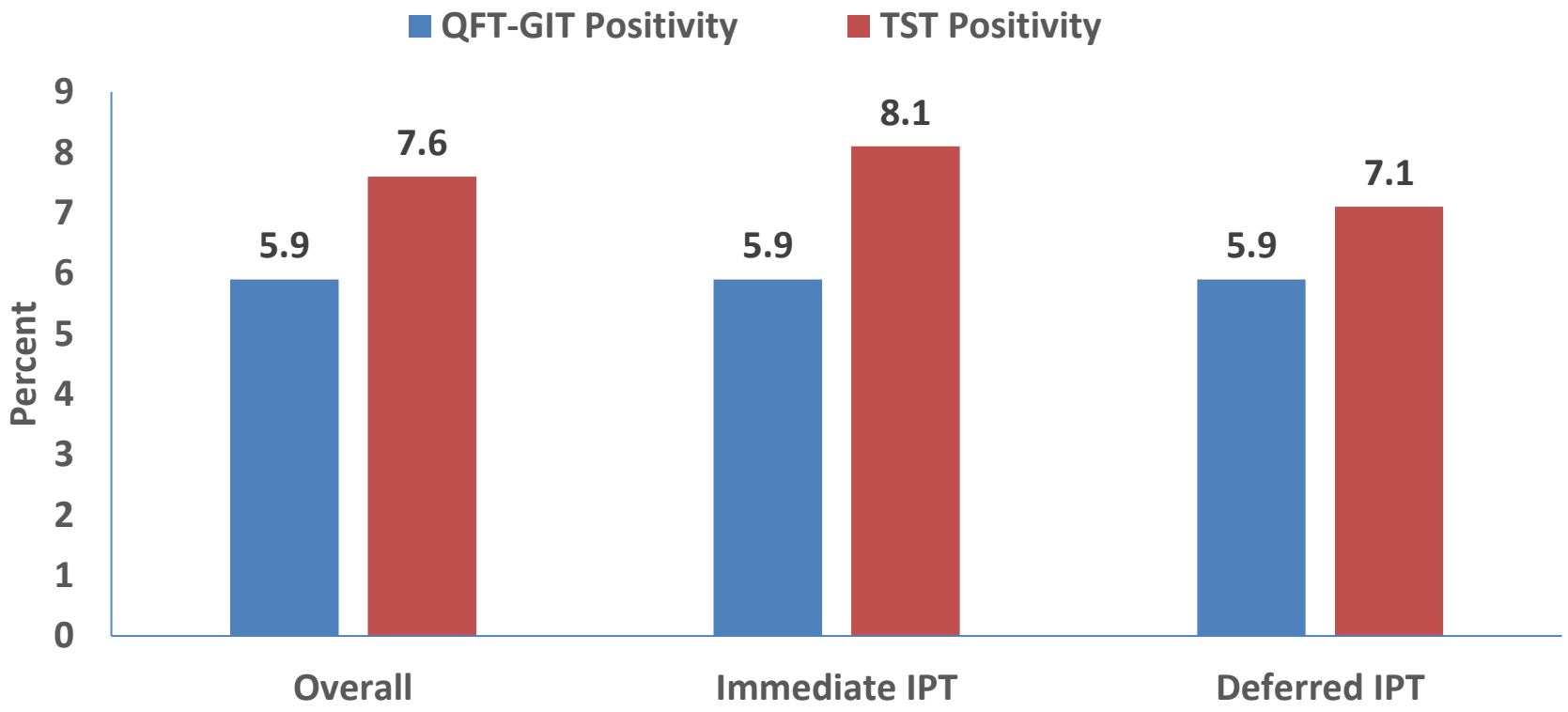
Prevalence of Infant TB Infection at Week 44 by Study Arm



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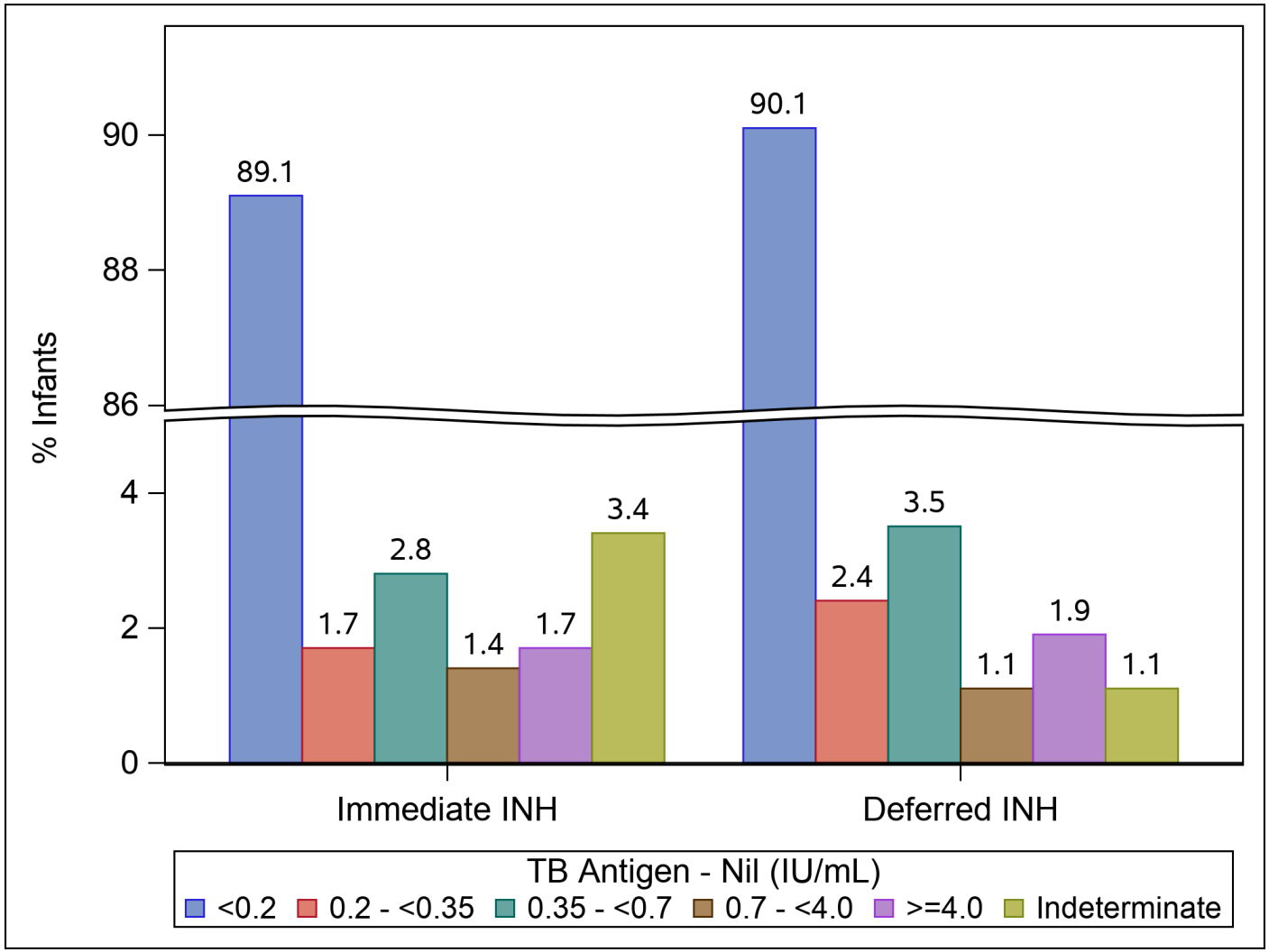
QFT-GIT Quantitative Results by Maternal IPT arm



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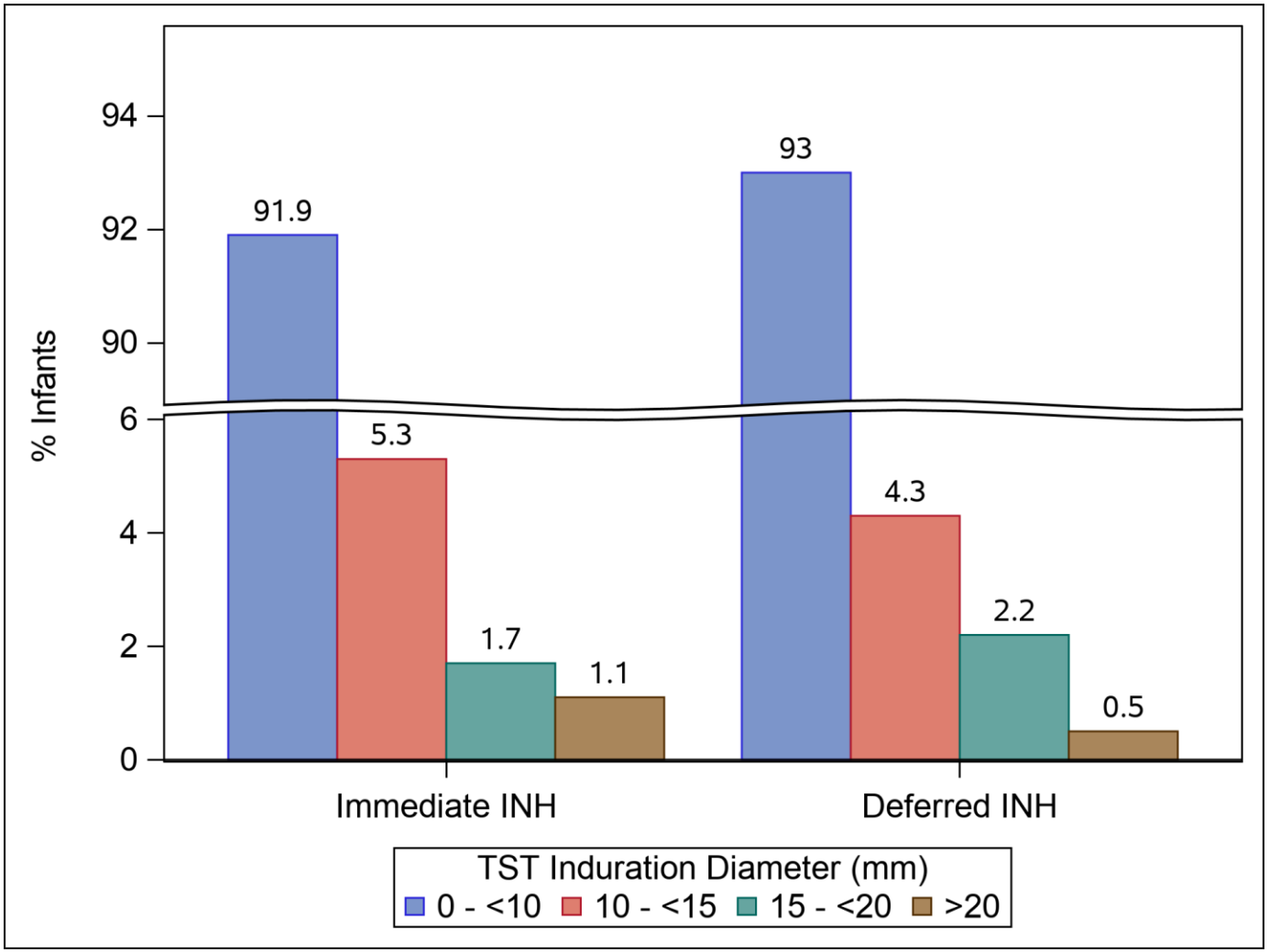
TST Quantitative Results by Maternal IPT arm



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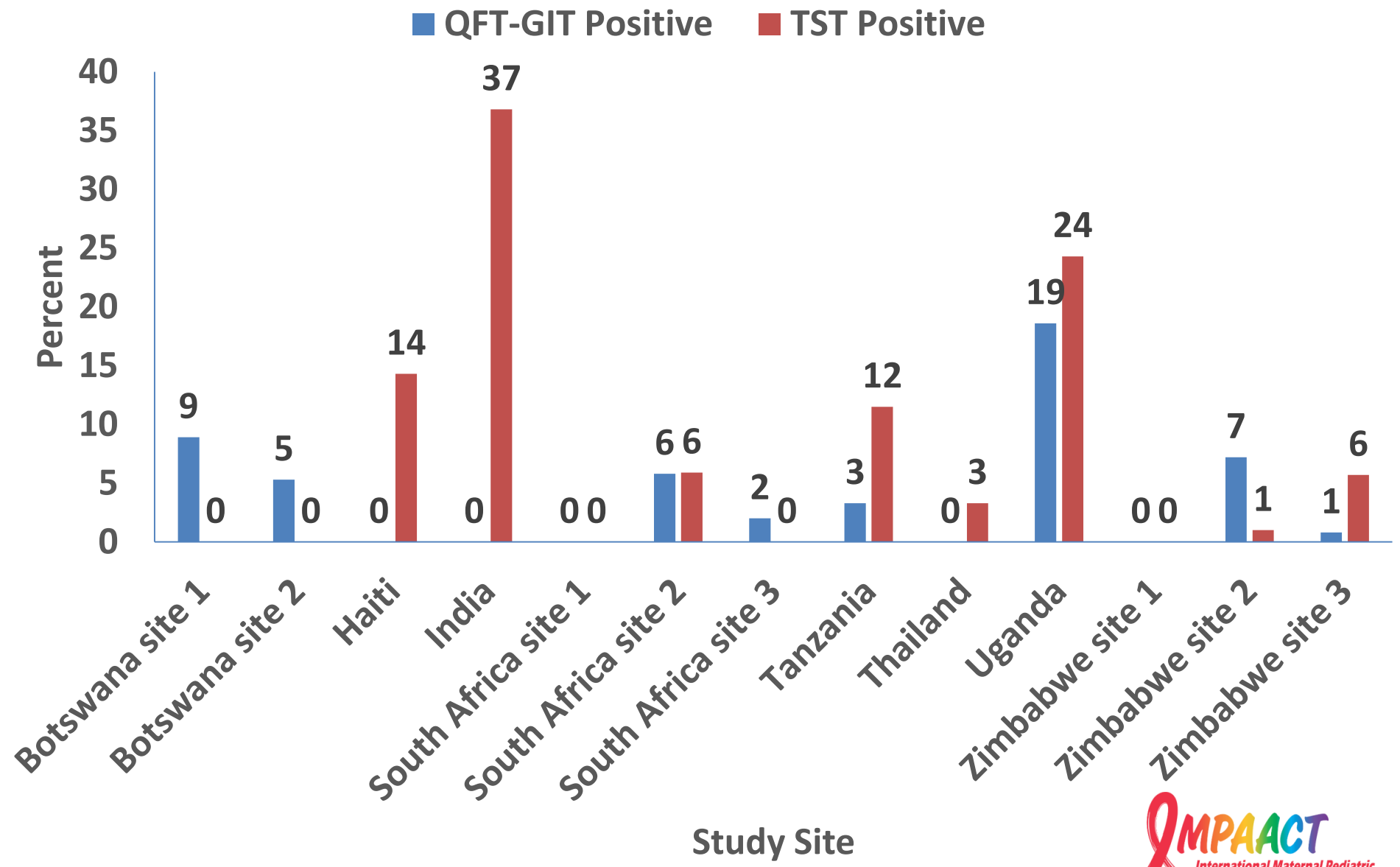
Substantial site variation in QFT-GIT and TST



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Predictors of QFT-GIT positivity in infants

Characteristic		Positive N=43	Negative N=689	OR	P value
Treatment Group	Immediate Deferred	21 (49%) 22 (51%)	336 (49%) 353 (51%)	1.00 (0.54,1.86)	0.99
HIV Infected	Yes No	0 (0%) 43 (100%)	7 (1%) 682 (99%)	NC	1.000
TB exposure	Yes No	2 (5%) 41 (95%)	17 (2%) 672 (98%)	1.93 (0.43,8.63)	0.39
INH Use	**Yes No**	**2 (5%) 41 (95%)**	**6 (1%) 683 (99%)**	**5.55 (1.09,28.37)**	**0.039**
BCG vaccination (record)	**Yes No**	**36 (84%) 7 (16%)**	**440 (64%) 249 (36%)**	**2.91 (1.28, 6.64)**	**0.011**
BCG scar	Yes No	35 (81%) 8 (19%)	556 (81%) 127 (18%)	1.00 (0.45,2.21)	1.00
WHO WAZ score	N, mean (sd)	43,-0.7 (1.1)	689, -0.4 (2.2)	0.90 (0.71,1.13)	0.36
Exclusively breastfed	Yes No	36 (84%) 7 (16%)	547 (79%) 142 (21%)	1.33 (0.58, 3.06)	0.50

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Predictors of TST positivity in infants

		Positive N=55	Negative N=672	OR	P value
Treatment Group	Immediate Deferred	29 (53%) 26 (47%)	329 (49%) 343 (51%)	1.16 (0.67,2.02)	0.59
HIV Infected	Yes No	0 (0%) 55 (100%)	7 (1%) 665 (99%)	NC	1.000
TB exposure	**Yes No**	**4 (7%) 51 (93%)**	**14 (2%) 658 (98%)**	**3.69 (1.17, 11.61)**	**0.026**
INH Use	**Yes No**	**4 (7%) 51 (93%)**	**5 (1%) 667 (99%)**	**10.46 (2.73, 40.17)**	**<0.001**
BCG vaccination (record)	**Yes No**	**45 (82%) 10 (18%)**	**427 (64%) 245 (36%)**	**2.58 (1.28,5.21)**	**0.008**
BCG scar	**Yes No**	**51 (93%) 3 (5%)**	**535 (80%) 132 (20%)**	**4.19 (1.29, 13.65)**	**0.017**
WHO WAZ score	N, mean (sd)	55,-0.4 (1.1)	672, -0.4 (2.3)	1.00 (0.88, 1.14)	0.97
Exclusively breastfed (any duration)*	**Yes No**	**53 (96%) 2 (4%)**	**523 (78%) 149 (22%)**	**7.54 (1.82, 31.3)**	**0.005**

EBF duration for >12 to 36 weeks vs 0 weeks associated with increased OR

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Agreement/concordance poor between QFT-GIT and TST

- 710 infants with both IGRA and TST at week 44

	TST Result		Total
	Positive	Negative	
IGRA			
Positive	8	34	42
Negative	46	622	668
Total	54	656	710

Kappa coefficient = 0.107 (95% CI 0.002, 0.212)

McNemar's test p =0.18

Among those with both TST and IGRA, when results were discordant, TST was more likely to be positive than IGRA, but this was not significant.

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Conclusions

- **Timing of Maternal IPT did not affect infant TB infection acquisition**
- **Infant TB infection differed across sites and by type of test used**
  - **Small proportion had QFT-GIT at 4.0 IU or higher**
- **Agreement between infant TST and IGRA was poor**

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