

Exploring early, culture-negative TB with ultrasensitive nucleic acid tests.

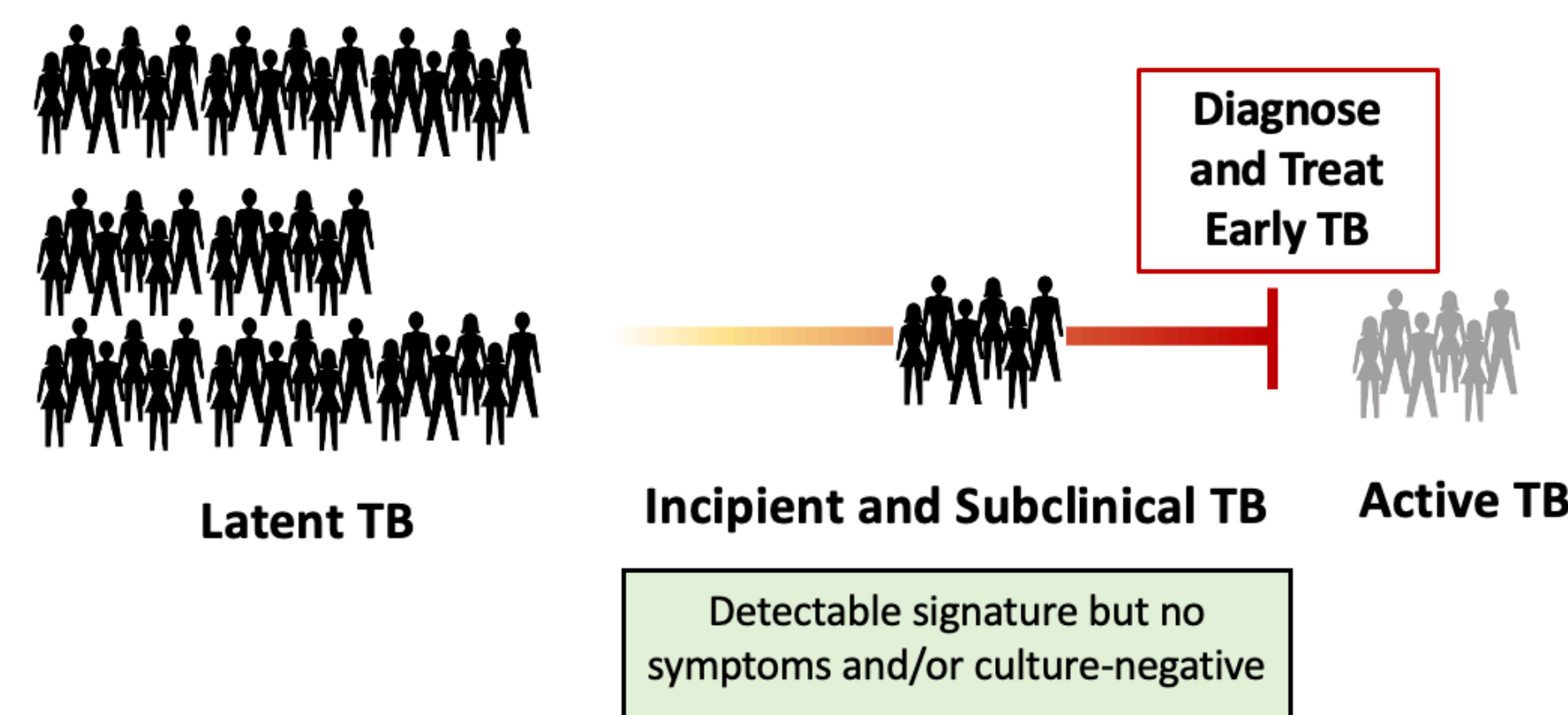
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Background

- New highly-sensitive PCR tests such as GeneXpert Ultra are replacing the culture as reference standard for diagnosis.
- There has been an increasing observation of “False-positives” (Ultra positive and culture negative)

Hypothesis

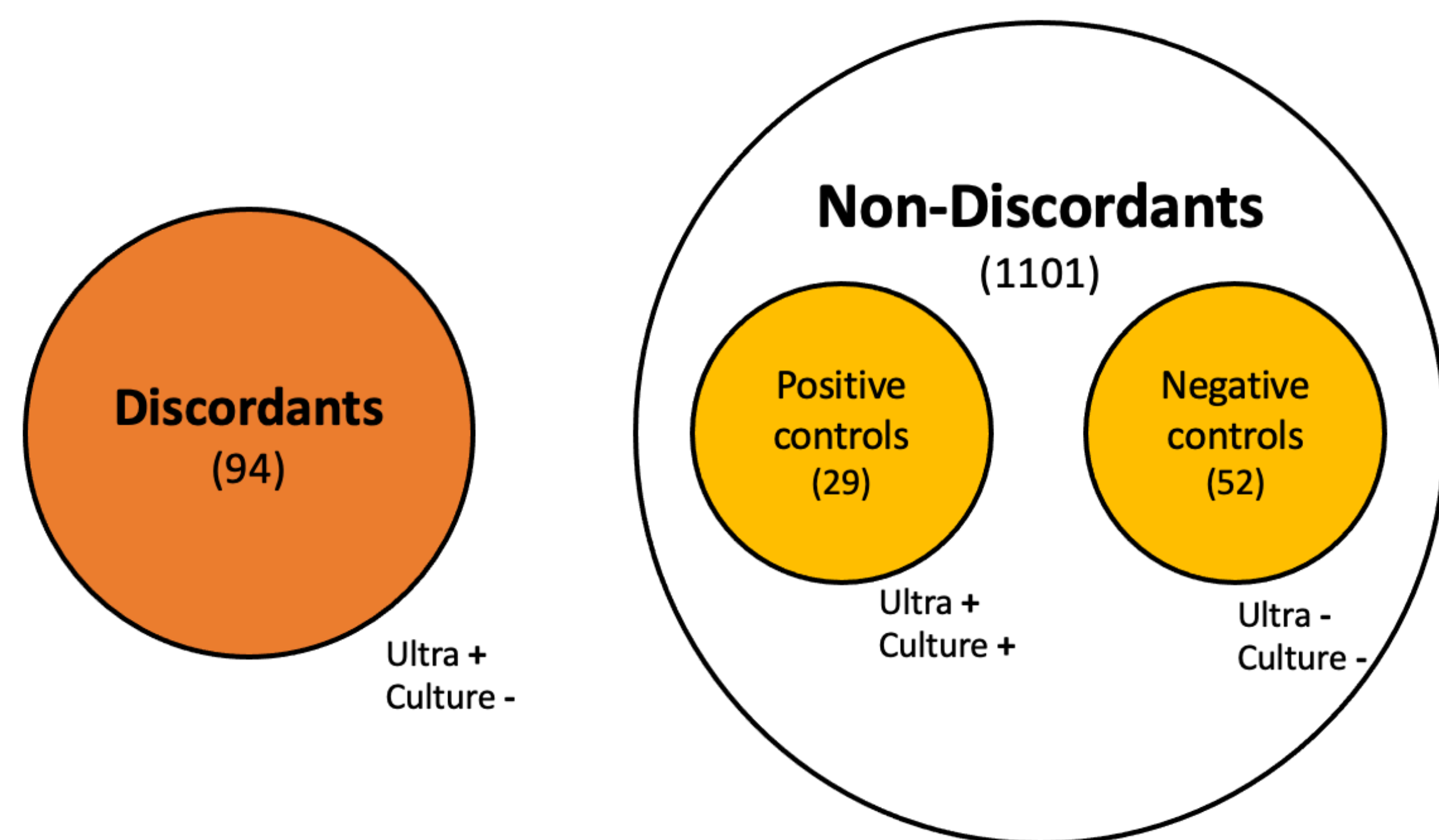
- We proposed these symptomatic individuals are not “false-positives”, but actually have early or culture-negative TB



Methods and Materials

- Substudy to a multicenter diagnostic accuracy evaluation of Ultra
- Adults with pulmonary TB signs/symptoms and without recent TB treatment in Uganda, Kenya and South Africa between July 2018 and May 2018.
- Sputum, blood and urine were collected on enrollment and follow up (over 12 months)
- Based on results participants were classified as “discordants”
- A negative control and positive control was also enrolled (Matched by age, sex HIV status, and previous TB history)

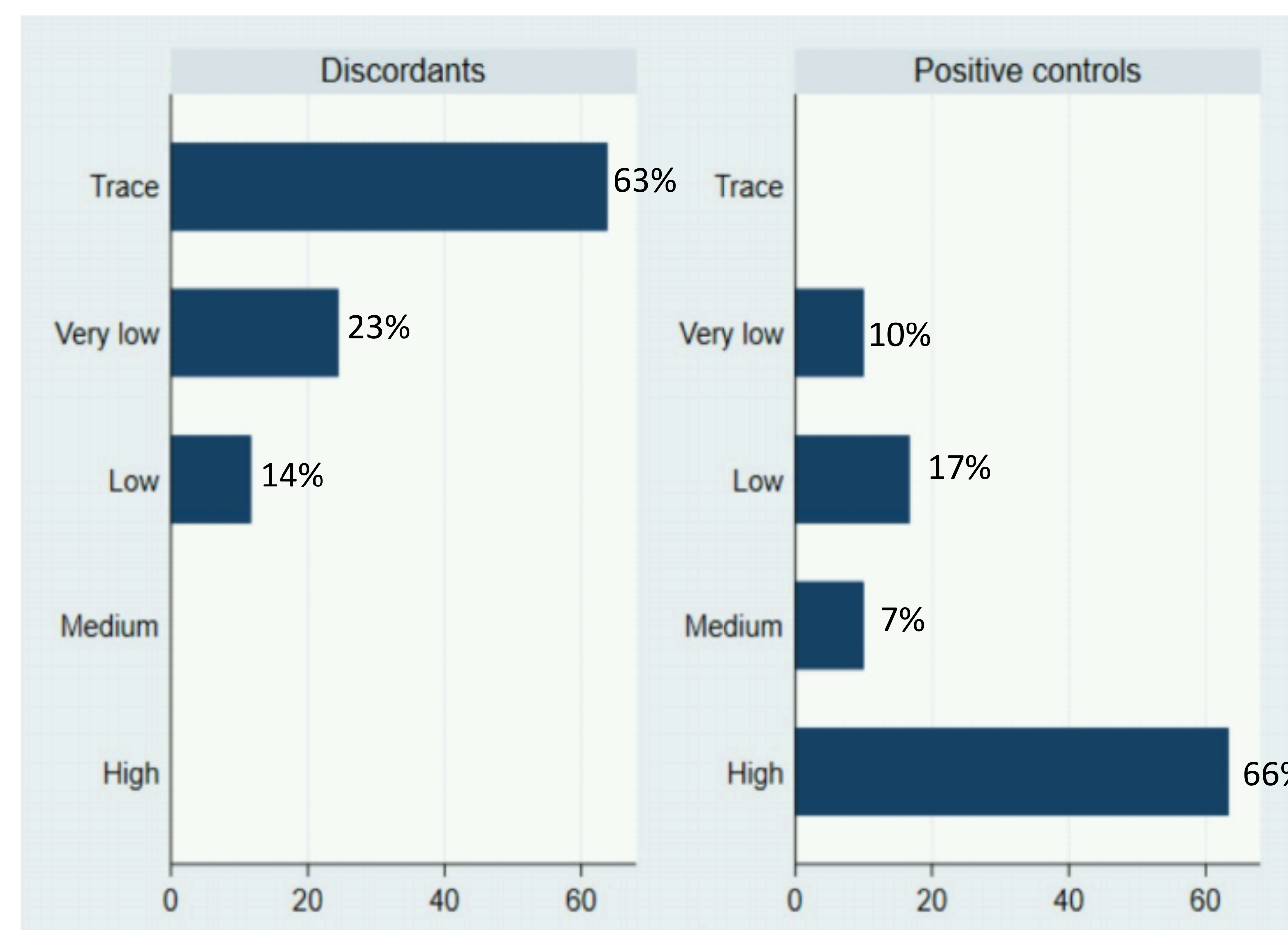
Results



There was no statistical difference regarding distribution of gender, age, enrollment site and HIV status between discordants and non-discordants

	Discordants	Neg -	Pos +
Total	94	52	29
South Africa	30 (32%)	20 (39%)	11 (37%)
Uganda	41 (44%)	10 (19%)	9 (30%)
Kenya	23 (24%)	22 (42%)	10 (33%)
Avg. Age	40	38	34
Female	39 (41%)	22 (42%)	12 (40%)
HIV + status	51 (54%)	26 (50%)	16 (53%)
Prior TB status	42 (45%)	20 (38%)	11 (27%)

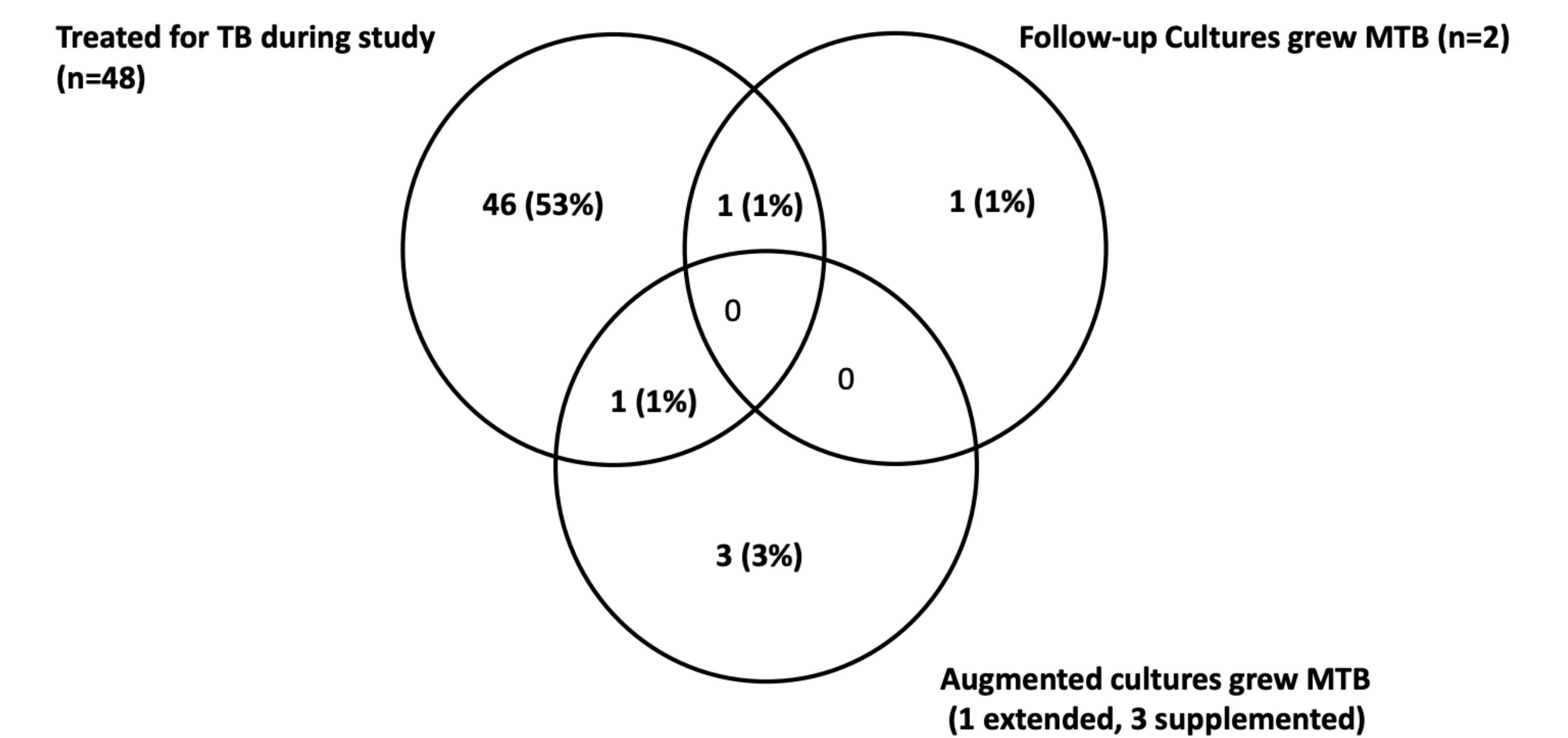
We found a predictive positive value of 65% to have a discordant result if the Ultra result was Trace or Very low



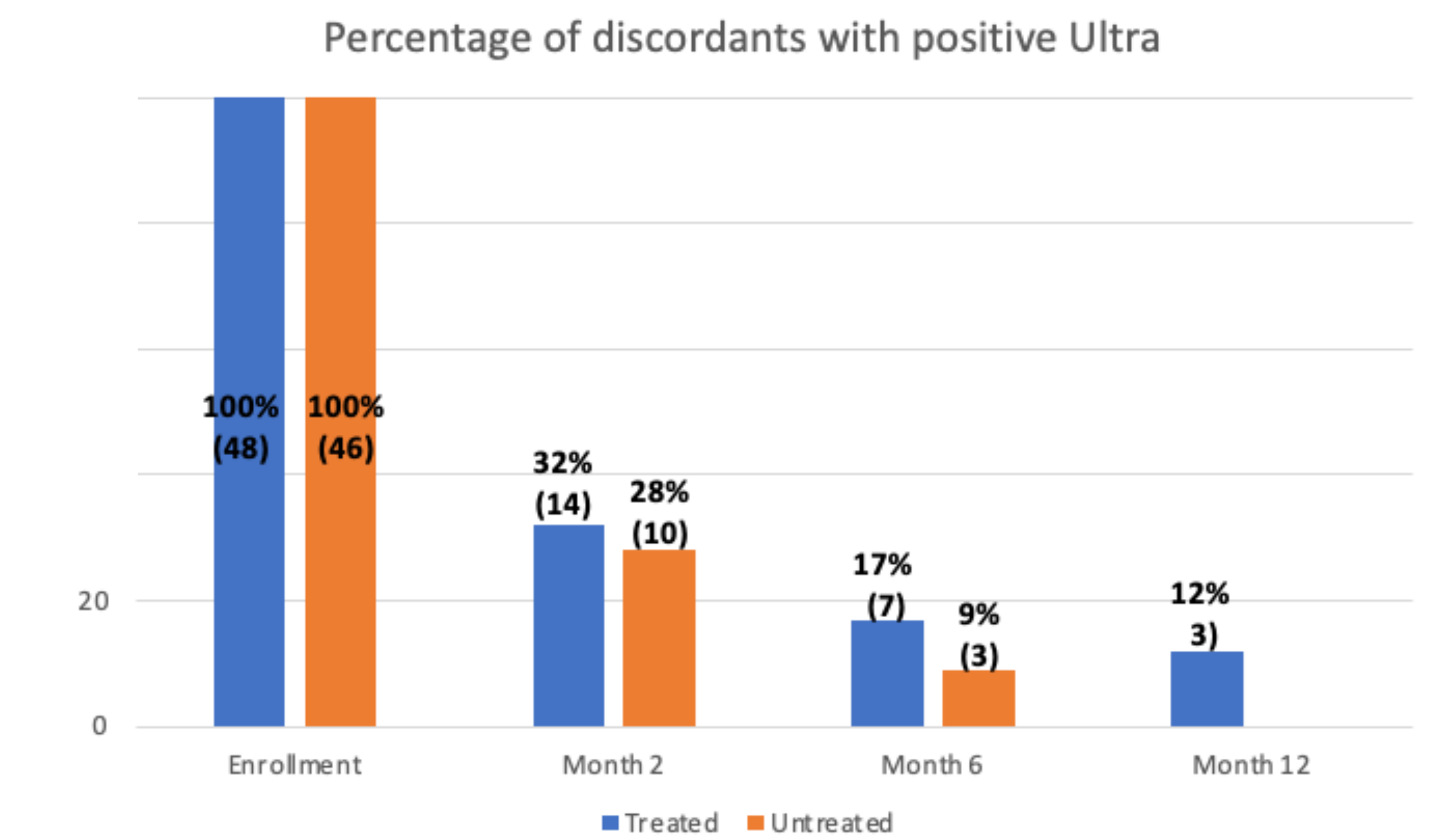
During follow up, almost half (49%) of discordants were started on TB treatment. Of the non-treated group, one participant grew MTB and 11 had persistent Ultra result that negativized during follow up without any intervention.

	Discordants	Negative controls	Positive Controls
N (total)	94	52	30
Started TB treatment during study	48	8	30
Symptoms improved or resolved with treatment (TB vs self-limiting syndrome)	46/48 (95%)	7/8 (88%)	29/30 (97%)
NO TB treatment during study	46	44	0
Symptoms improved with NO treatment (not TB vs self-limiting syndrome)	46/46 (100%)	42/44 (95%)	0

Culture follow up on non-treated discordants



Persistence of Ultra positivity on non-treated discordants



Conclusions

- We found microbiologic signals of TB during follow up of discordants (Persistent Ultra, positive TB culture, positive augmented TB culture) suggesting Ultra can identify culture-negative TB
- Ongoing evaluation of host and bacterial biomarkers from the substudy samples will help understand early or culture-negative TB