

The effect of ‘superspreaders’ on the transmission of *M. tuberculosis* among household contacts in Kampala, Uganda

1. Background

Tuberculosis (TB) remains a major public health problem globally. An estimated 1.7 billion people around the world are currently infected with *M. tuberculosis* (1). In 2017, 10.0 million people developed the disease and TB caused approximately 1.6 million deaths (1). A recent paper by Handel and colleagues that analyzed six different cohorts worldwide revealed evidence for the presence of ‘superspreaders’ who may be responsible for the majority of incident TB cases (2). Much work has been done in the identification of individuals who may be at high risk for TB infection. However, in resource limited countries, identifying potential superspreaders may be more cost-effective and lead to a decrease of transmission (2). We propose to study the effect of superspreaders on the transmission of TB among household contacts in Uganda.

2. Methods

We will use data collected as part of the Kawempe Community Health Study (KCHS). The data collection took place in the Kawempe division of Kampala, the capital of Uganda, from 2002 through 2012. During this time, 872 index cases of pulmonary TB and their household contacts were enrolled in this prospective longitudinal cohort study. The exposure in this study will be the presence of a superspreader in the household. In this analysis, a superspreader will be defined as a male index TB case between the ages of 15 and 45 with a positive sputum smear (evidence of infectiousness) and an abnormal chest x-ray. The quantitative outcome of interest will be the percentage of persons in each household who became infected with TB. These persons fall into two categories: Those who develop latent TB infection (LTBI) and those who develop active TB disease (converters).

In order to build a propensity score, we used 5 household covariates that could represent potential environmental factors that affect transmission of TB. We also included 41 index cases characteristics that could represent host factors that affect transmission of disease.

We included appropriate graphical and numerical data summaries across households exposed to superspreaders and household not exposed to superspreaders, followed by propensity score matching (caliper matching without replacement) and potential weighting methods to address selection bias. For outcomes analysis, our primary tool was a linear regression on propensity-matched pairs.

3. Results

Using 1:1 caliper matching without replacement and based on acceptable Rubin’s rules results, we were able to obtain good covariate balance between our two household groups. Our analysis revealed that, on average, households exposed to a superspreader had 4.95 (95%

CI -0.99 to 10.77) more percentage points of LTBI when compared to households not exposed to a superspreader. On the other hand, households exposed to superspreaders had 0.54 (95% CI -4.71 – 3.64) less percentage points of converters when compared to households not exposed to a superspreader. Since both of these estimates cross zero, the results were not statistically significant.

4. Conclusions

Our results did not reveal an association between exposure to superspreaders and the rate of TB infection as measured by the percentage of household members with LTBI or active TB disease. Future work will need to continue refining the superspreader phenotype and include pathogen characteristics in order to fully understand the interplay of the factors involved in disease transmission.

- (1) Global tuberculosis report, 2018. World Health Organization.
http://www.who.int/tb/publications/global_report/en/
- (2) Handel A, Martinez L, Sekandi JN, et al. Evidence for supercoughers in an analysis of six tuberculosis cohorts from China, Peru, The Gambia and Uganda. *Int J Tuberc Lung Dis* 2019;23(12):1286-1292.

The effect of 'superspreaders' on the transmission of *M. tuberculosis* among household contacts in Kampala, Uganda

JESUS GUTIERREZ

JXG754@CASE.EDU

APRIL 30TH 2020



Uganda-CWRU Research Collaboration: 1988-2018
Celebrating 30 years of excellence

Tuberculosis Overview



- Caused by *Mycobacterium tuberculosis* (Mtb)
- Prevalence
 - 2 million deaths and 9 million new cases per year.
 - Top cause of death due to infectious disease globally
- Transmitted through the air
- If untreated, TB disease has a mortality rate of 50%
- Global financial cost estimated at \$1 trillion in the next 10 years.

The Concept of 'Superspreaders'

- The 20/80 rule
- Examples in different infectious diseases have been documented
 - Typhoid fever, measles, rubella, HIV, Ebola, SARS, covid-19
- Events are shaped by host, pathogen, and environmental factors

Is there evidence of a 'Superspreader' effect in the transmission of *Mycobacterium tuberculosis*?

Estimated new tuberculosis cases in 2015



Source: WHO

Ugandan Household contact study

- Study enrollment 1995-1999, 2002-2012, and 2014-present
- Identify culture-confirmed index pulmonary TB cases at TB clinic
 - Enroll household members
 - Clinical and epidemiological evaluation
 - Blood samples taken for immunological and genetic analyses
 - Two year follow-up – clinical work-up, including tuberculin skin test (TST) **every 3 months**



Methods

- **Exposure:** Index case classified as a ‘superspreader’ – someone with high lung capacity and high infectivity
 - Defined as male, ages 15-45, with a positive smear test and abnormal chest x-ray.
- **Outcomes:** rate of infection within the household
 - Primary: Percentage of household members who developed latent TB infection (LTBI)
 - Secondary: Percentage of household members who developed active TB disease (Converters)

Covariates associated with index case

- **Demographics:** age, marital status
- **Symptoms:** Cough, cough duration, chest pain, dyspnea, dyspnea duration, fever, fever duration, hemoptysis, headache, malaise, myalgia, nausea, abdominal pain, adenopathy, loss of appetite, arthralgia, back pain, bone pain, confusion, diarrhea, dizziness, vision problems, pruritus
- **Signs:** Productive sputum, duration of productive sputum, purulent sputum, rash, rigors, night sweats, vomiting, weight loss, BCG scar, TST positivity
- **CXR:** bilateral disease, upper lung, lower lung, fibrosis, cavitory disease, miliary disease, adenopathy, effusion, thickening
- **Lab:** smear positivity, culture positivity
- **Comorbidities:** HTN, DM, HIV, kidney disease, cancer
- **Severity of disease:** Bandim TB score

Covariates associated with household

- Number of household members
- Number of household members per room
- Number of windows used during the day
- Cooking method – outside household vs. inside household
- Euclidean distance from nearest health center (Km)

Unadjusted Table One

	Superspreader	Control	<i>p</i> -value
n (872 total)	124	748	
Persons per household	4.01 (2.41)	3.69 (1.75)	0.151
Cooking Method			0.015*
Inside	97 (78.2)	557 (74.9)	
Outside	15 (12.1)	151 (20.3)	
Other	12 (9.7)	36 (4.8)	
Distance from health center (km)	2.96 (1.63)	3.01 (1.70)	0.790
Bandim TB score	6.43 (2.12)	5.92 (2.12)	0.013*
Chest pain			0.047*
Present	84 (68.3)	508 (67.9)	
Absent	38 (30.9)	240 (32.1)	
Bilateral findings in CXR			0.013*
Right	33 (26.8)	184 (24.6)	
Left	15 (12.2)	158 (21.2)	
Both	74 (60.2)	369 (49.4)	
Culture positivity			0.021*
Yes	121 (97.6)	745 (99.6)	
No	3 (2.4)	3 (0.4)	

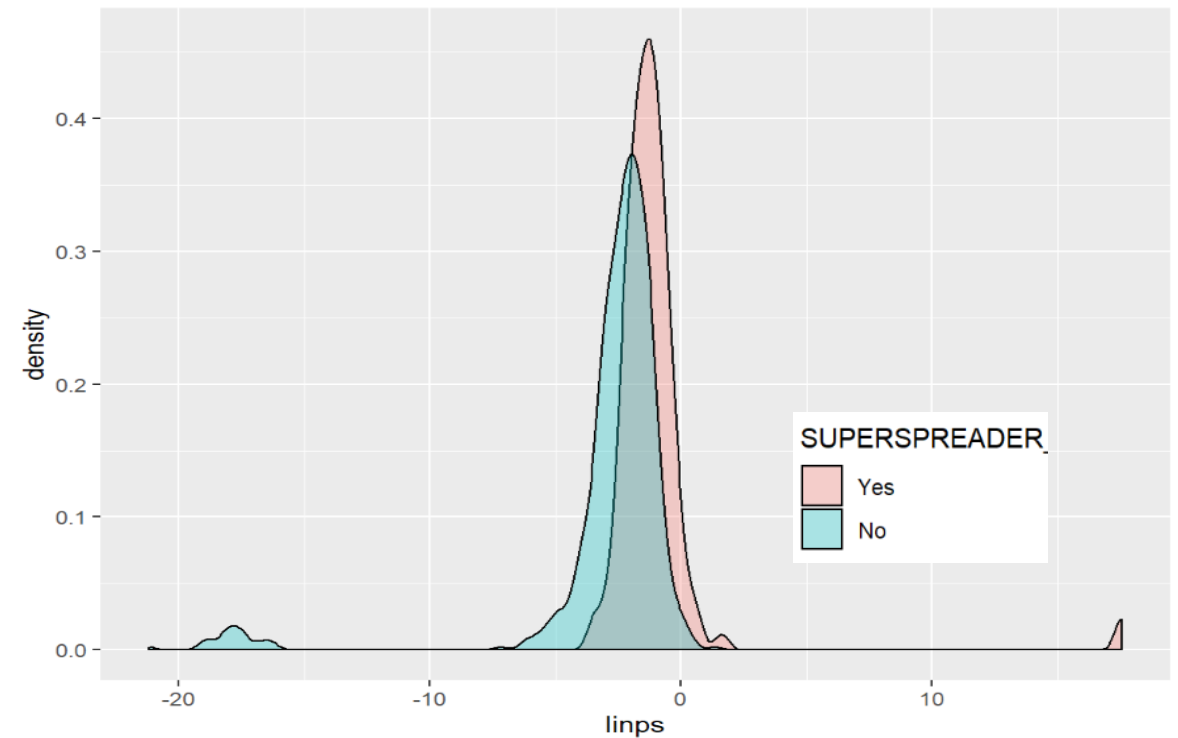
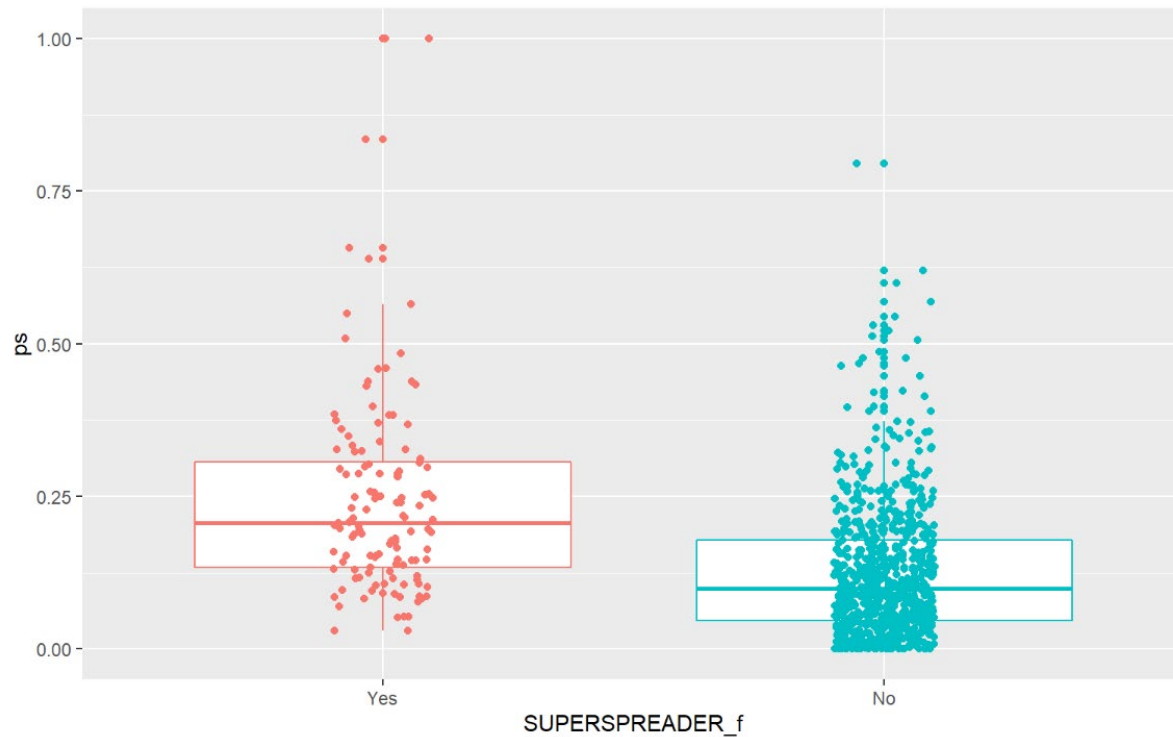
* Denotes statistically significant results at $p < 0.05$ level (standard deviation) or (percentages)

Analysis

- Propensity score model
- Matching:
 - 1:1 Greedy matching without replacement
 - 1:1 Greedy matching with replacement
 - 1:1 Caliper matching without replacement
- Propensity Score weighting

Propensity Score Model

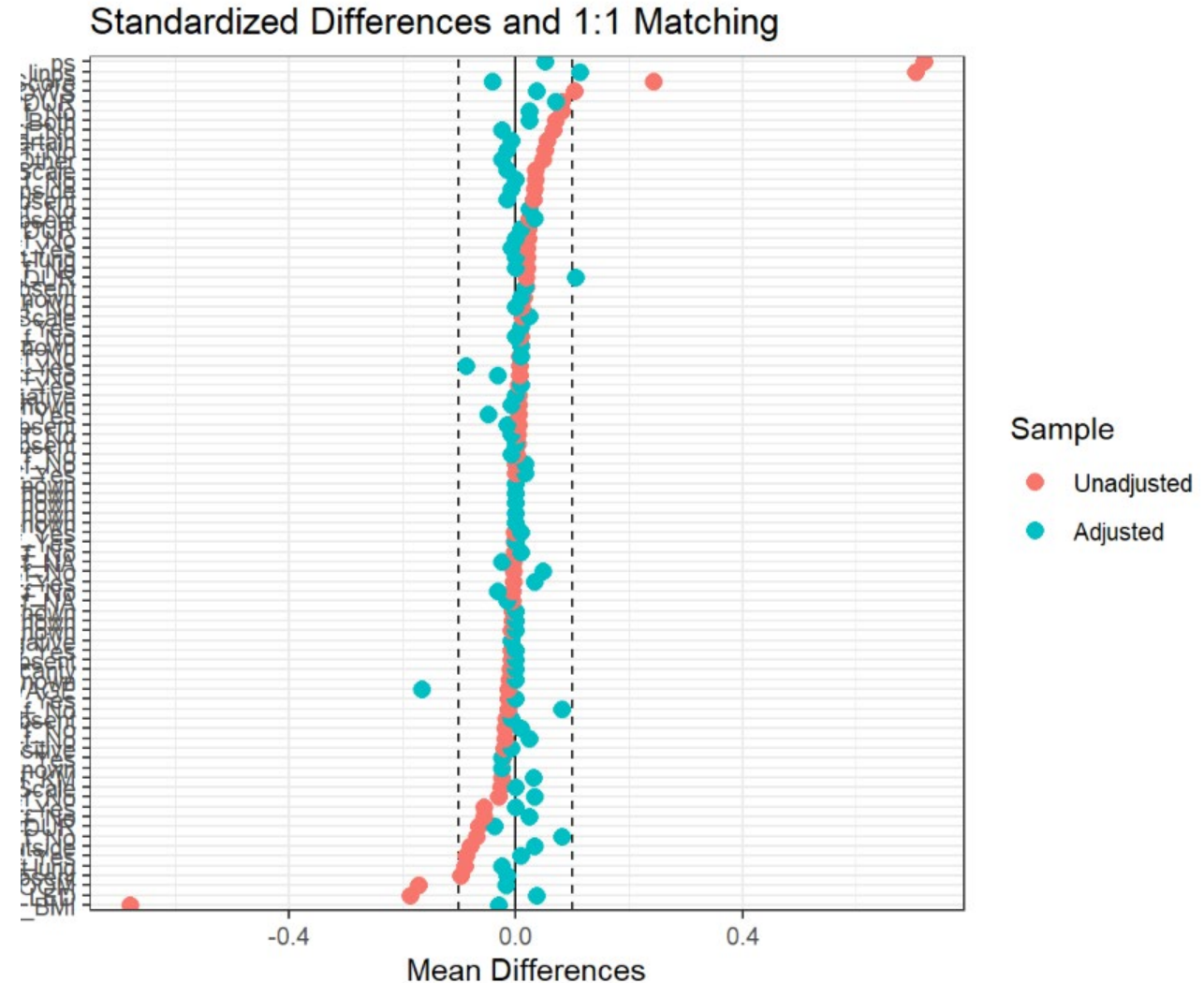
- Included 46 covariates
- Superspreaders: 0.03 – 1.00 Control: 0.00 – 0.80



1:1 Greedy Matching w/o Replacement

- 124 Matches:
 - 124 Superspreaders and 124 controls.
- Dropped 624 controls

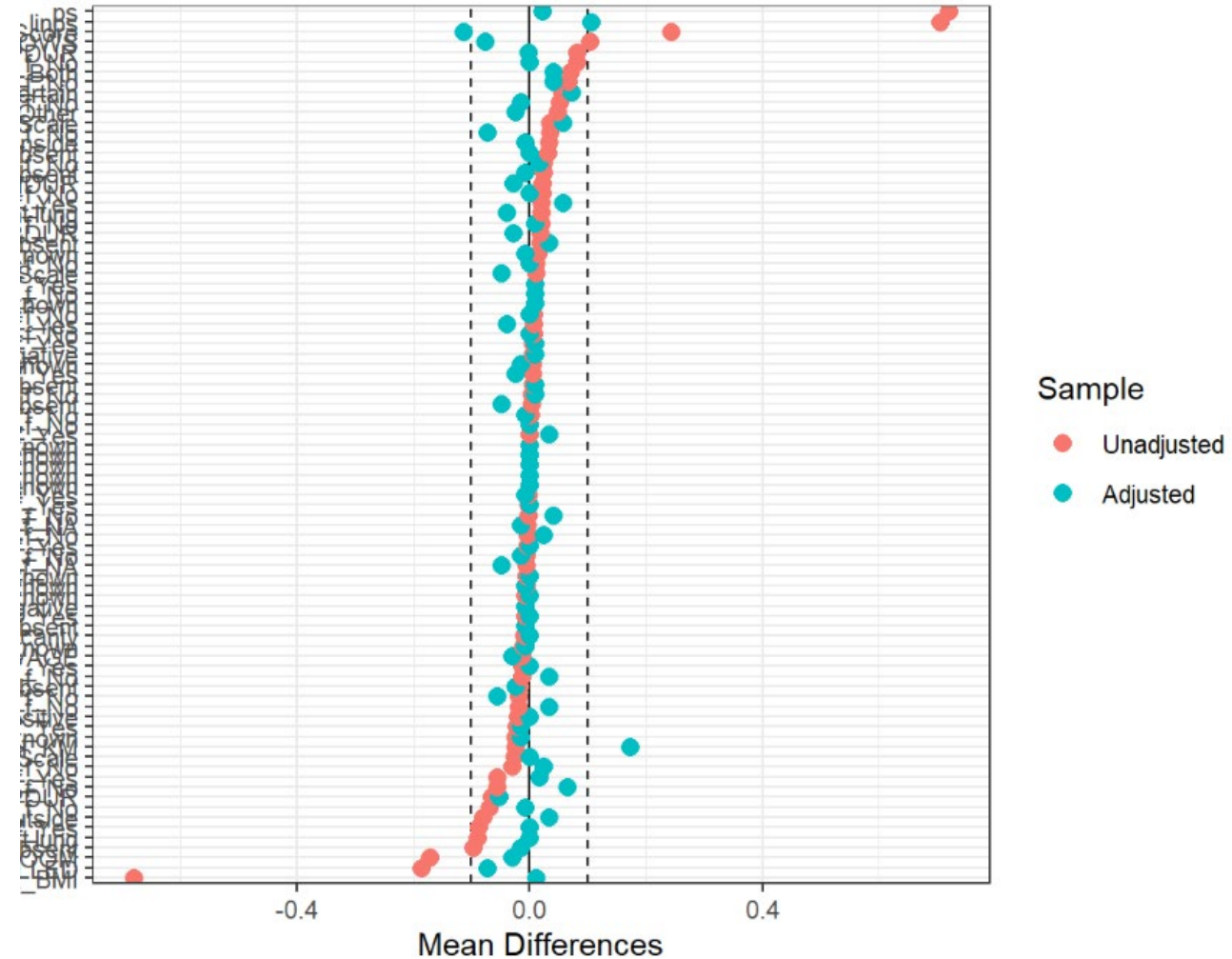
	Unadjusted	Match 1
Rubin's Rule 1	58.4	15.2
Rubin's Rule 2	0.68	9.28



1:1 Greedy Matching w/ Replacement

- 124 Matches:
 - 124 Superspreaders and 106 controls.
- Dropped 642 controls

	Unadjust.	Match 1	Match 2
RR1	58.38	15.24	13.96
RR2	0.68	9.28	8.23

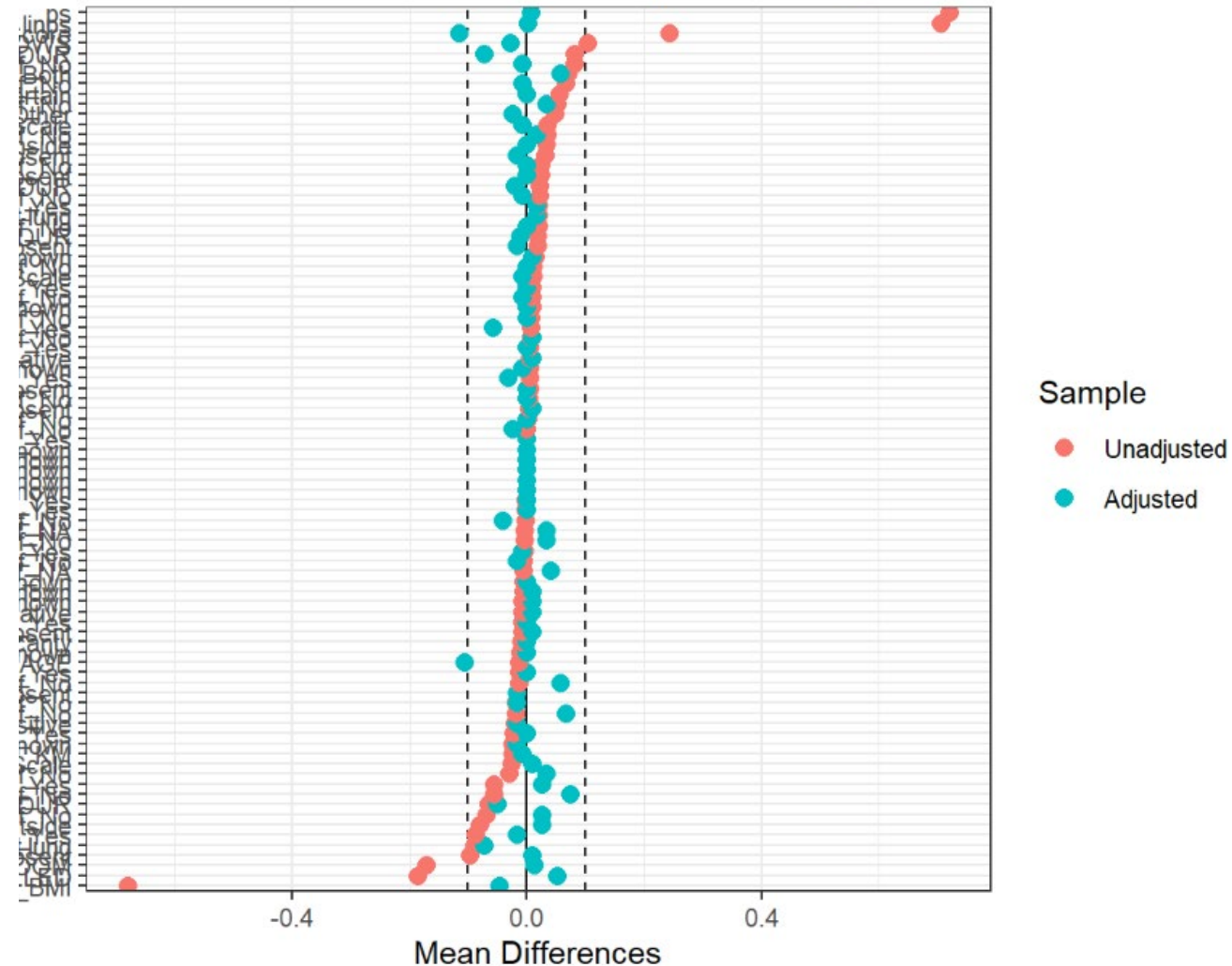


1:1 Caliper Matching w/o Replacement

- 122 Matches:
 - 122 Superspreaders and 122 controls.
- Dropped 2 Superspreaders and 626 controls

	Unadjust.	Match 1	Match 2	Match 3
RR1	58.38	15.24	13.96	0.64
RR2	0.68	9.28	8.23	1.04

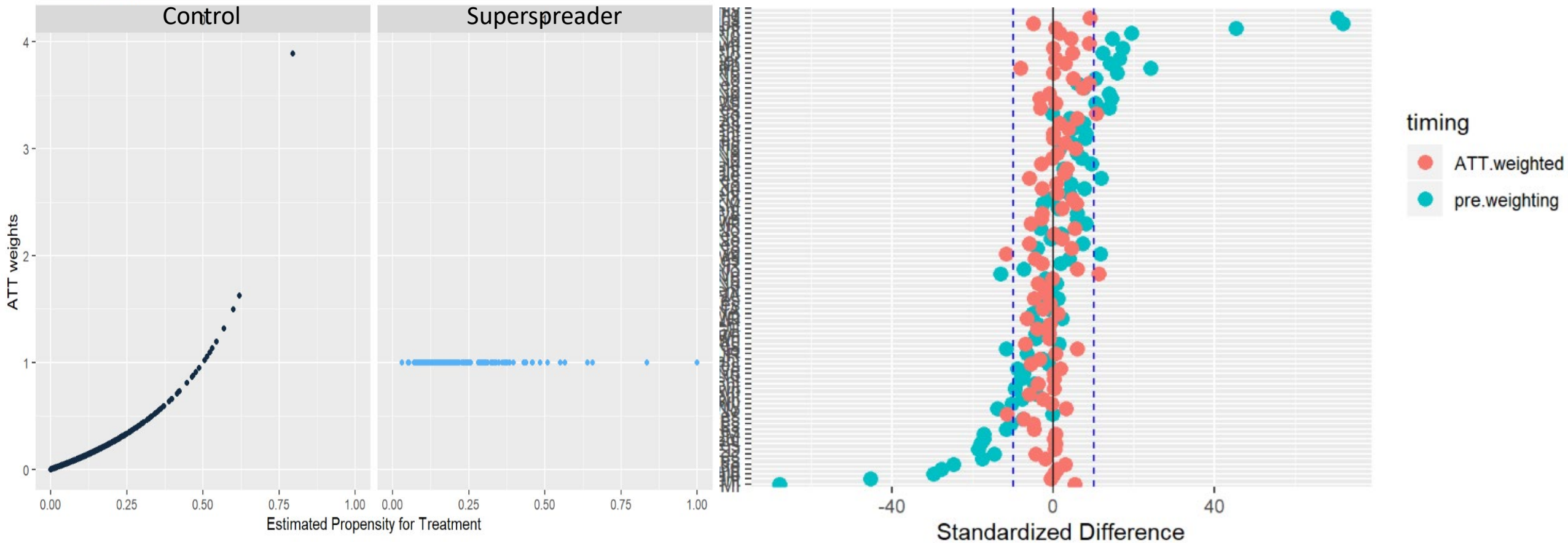
Standardized Differences and Caliper Matching



ATT Weighting

	Unadjust.	Match 1	Match 2	Match 3	ATT Wt.
RR1	58.38	15.24	13.96	0.64	70.60
RR2	0.68	9.28	8.23	1.04	0.68

ATT weighting structure



Results

- Primary Outcome: Percentage of household contacts within a household who develop LTBI

	Estimate	95% CI
Unadjusted	3.99	-0.50 – 8.47
1:1 Caliper Matching	4.95	-0.99 – 10.77

- Secondary Outcome: Percentage of household contacts within a household who develop active TB disease

	Estimate	95% CI
Unadjusted	0.74	-2.20 – 3.70
1:1 Caliper Matching	-0.54	-4.71 – 3.64

Conclusion

No evidence that being exposed to a 'Superspreader' within a household is associated with a higher transmission rate of *M. tuberculosis*.

Statistical Considerations

- Instability of outcomes
 - May consider combining primary and secondary outcomes
 - Transforming them into binary outcomes
- Refining definition of 'Superspreaders'
 - Composite variable
 - May need to include women with different characteristics
- Future studies will need to include pathogen covariates that were not available

Acknowledgements

Collaborators

- W. Henry Boom
- Tom Hawn
- Scott Williams
- Bill Scott
- Chetan Seshadri
- Galit Alter
- Sarah Fortune



Ugandan Co-Investigators

- Harriet Mayanja-Kizza
- Ezekiel Mupere
- Moses Joloba

Ugandan team

- Mary Nsereko
- Ronald Kiyemba
- Hussein Kisingo
- Joy Beseke
- Sophie Nalukwago
- Home visitors
- Counselors
- Nurses
- Immunology lab

CWRU-TBRU Data team:

- LaShaunda Malone
- Bonnie Thiel
- Keith Chervenak

Stein lab:

- Rob Igo
- *Noemi Hall*
- *Ningning Ma*
- Penny Benchek
- Michael McHenry
- Jesús Gutierrez

Funding

- NIH
- BMGF



Questions?
