NIH Proposal Writing Workshop

DAY 1 | 4.11.2024 | AFTERNOON SESSION

FACENTE CONSULTING
UNDERSTAND • IMPLEMENT • TELL YOUR STORY

Plan for the Afternoon

1. Importance of Preliminary Data
2. How to Choose Your Research Team
3. How to Structure the Innovation Section
4. How to Develop the Significance Section
5. Approaching Literature Review and Citations

Plan for the Afternoon

1. **Importance of Preliminary Data**
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Importance of Preliminary Data

Preliminary data can be used to:

- Provide proof of capacity to achieve your goals
- Support why you're making the hypothesis you're making/ support your hypothesis
- Demonstrate that your proposed intervention has a chance to work.
- Convince reviewers your study setting and/or population is an appropriate place to do the study

Proof that we can meet household contact investigation targets:

TB Stigma Grant

Acceptability and Feasibility of Home-Based TB Testing of Household Contacts (HHCs) Using a Portable GeneXpert Device (Medina-Marino, PI; R21EB023679). We performed home-based TB testing of HHCs using a portable GeneXpert device. Among 271 TB index patients enrolled at four clinics over 9 months, 944 HHCs were listed. A total of 440 households were visited up to 3 times to screen all listed contacts. A total 893 (94.6%) HHCs were screened; first attempt (73.2%), second (15.7%), third (5.7%) visit. At total of 170 (19%) screened positive for TB symptoms. Among those tested, 12.5% tested positive for TB.[121] This work shows proof of capacity to conduct and meet household contact investigations targets on our proposed timeline.

Proof that our proposed intervention is feasible and acceptable:

STI Screening Grant

Acceptability/Feasibility of STI testing among HIV-infected pregnant women, South Africa (Medina-Marino/ Klausner NIH R21HD084274). We enrolled 845 HIV-infected pregnant women attending ANC. Of 442 eligible women offered CT/NG/TV testing using self-collected vaginal swabs, 430 accepted screening (Acceptability= 97.3%).[111] All women had valid test results; >95% received test results within 90 min. Among the 174 women with a positive test result, 92% (n=159) received same-day treatment. *Our results demonstrate that integrating diagnostic testing for STIs into ANC services is acceptable and feasible, and that our study team has the capacity and experience to conduct the proposed study with high enrollment and implementation fidelity*.

Proof that the intervention does likely have an impact on a more upstream outcome:

STI Screening Grant

STI incidence during pregnancy and prevalence at time of delivery: Among 430 women tested and treated for CT/NG/TV at first ANC, we identified a 9.1% cumulative incidence of STIs between first ANC and delivery. Furthermore, our screening intervention decreased prevalent STIs by >50% compared to women receiving syndromic management (RR = 0.52; Intervention=11.1%, 95% CI: 7.9%–15.5%; Control=21.2%, 95% CI: 16.7%–26.6%).[112] *While a single molecular test and treatment approach may decrease prevalent STIs at delivery, it cannot identify incident STIs. Optimal, cost-effective screening algorithms are needed to identify incident infections and decrease the risk of sequel associated with STIs in pregnant women and neonates.*

Proof that this is an appropriate place to do the project:

TB and Men Grant

We will conduct our study in Buffalo City Metropolitan Health District (**BCM-HD**), Eastern Cape Province, South Africa; est. population=755,200; TB incidence= 743/ 100,000 persons, TB/HIV co-infection= 45.7%.[62] In 2015 (the most recent data available), BCM-HD had an overall TB treatment completion rate of 81.2%, with 6.7% deaths and 6.4% lost-to-care (**LTC**).[63] Study participants will be recruited from 6 Primary Health Clinics (**PHC**; **Table 1**). Though available data is not stratified by sex, a wealth of published literature from South Africa highlight the increased burden of TB amongst men, and the poorer health outcomes for men compared to women.[9,22,34,64] It is thus fair to conclude that that the indicators presented in Table 1 are likely worse for men than for women. Our study clinics were selected based on their TB head counts, key TB programmatic indicators (**Table 1**), our previous working relationship with these clinics, and in consultation with the BCM-HD. **PI Medina-Marino** also established two community advisory boards in BCM that will be leveraged to ensure engagement and support from local communities in clinic catchment areas. Ultimately, given our long-term relationship with BCM-HD and clinic managers, our standing relationship within study communities, and our large research platform in BCM, we believe the selected sites are outstanding locations in which to conduct this rigorous research study.

Proof that we have the capacity to do a good job implementing the proposed methods:

STI Screening Grant

Cost-effectiveness modeling for ANC STI interventions (Klausner; P30MH058107): In Botswana, we conducted micro-costing, including time-and-motion studies and provider interviews, to identify capital and recurrent costs of antenatal STI testing interventions, compared to syndromic management. By combining those data with population and epidemiological data from Botswana, and probabilities from the literature, we developed a decision model comparing three approaches for national scale-up of STI testing. Our model revealed that a mixed approach to scale-up, including both PoC and centralized testing, had the lowest cost per STI treated.[114] By extending our model to include health outcomes (i.e., maternal infections at delivery, low birth weight infants, and DALYs averted), our model showed that, *diagnostic testing for STIs during ANC services can be cost-effective if policy makers are informed by the WHO Gross Domestic Product / capita threshold. However, identifying the most cost-effective testing algorithms require further research. This work also shows that our study team has the capacity and experience to conduct the proposed study.*

Proof that there is a high rate of STIs in this population:

STI Screening Grant

STI incidence during pregnancy and prevalence at time of delivery (Medina-Marino/ Klausner NIH R21HD084274): Among 430 women tested and treated for CT/NG/TV at first ANC, we identified a 9.1% cumulative incidence of STIs between first ANC and delivery.

Proof that STIs does have an association with adverse birth outcomes:

STI Screening Grant

STIs are associated with adverse birth outcomes and mother-to-child-transmission (MTCT) of HIV. Untreated CT, NG and TV infections during pregnancy are associated with intrauterine growth retardation, low birth weight (LBW), preterm delivery, and premature rapture of membranes.[35-45] Infants in South Africa routinely receive chloramphenicol eye ointment at birth to prevent neonatal bacterial conjunctivitis, most often caused by untreated maternal CT or NG infection.[46] Yet the risks to infants born to HIV-infected mothers are greater than conjunctivitis. A study of HIV-infected women in Tanzania found that NG co-infection increased intrauterine HIV transmission by >450%.[2] **Our team's prior work Our team's prior work** in an NICHD HPTN 040 sub-study demonstrated that CT/NG infection increased HIV MTCT by 160% (RR=2.6, 1.1 – 5.8).[9] Prior research in non-pregnant women suggests that STIs in HIV-infected women may augment the risk of HIV transmission by increasing localized inflammatory responses and viral shedding;[47-56] treatment of those STIs reduced HIV transmission.[57,58] Our own study in HIV-infected pregnant women in South Africa documented 34.8% (of 731) with adverse birth outcomes including 17.8% with preterm delivery, 14.8% low birth weight and 4.8% stillbirth.[19]

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How to Choose Your Research Team

- It is very important to have a strong research team with an established working history.

Study Team: **Andrew Medina-Marino, PhD, (PI)** is Head of Research for the Foundation for Professional Development, and has extensive experience in HIV, TB and STIs. He is PI on 3 recently-funded NIH grants focused on STI screening, TB case finding, and HIV prevention, all in South Africa. **Joseph Daniels, PhD (PI)** is an Assistant Professor of Psychiatry & Human Behavior at Charles Drew University of Medicine and Science. He is a behavioral scientist with expertise in HIV and men's health, qualitative methods, and treatment adherence. He has lived and worked in South Africa, where his research focused on MSM, HIV, and TB. **Drs. Medina-Marino and Daniels** have been collaborating since 2016, and have investigated decision making around STI test result disclosure and partner treatment uptake during pregnancy,[60] and men's health behaviors relating to engagement in TB care. **Gavin George, PhD (co-I)**, is Program Lead for Health Systems Strengthening at the Health Economics and HIV and AIDS Research Division, University of KwaZulu-Natal. He is an economist with expertise in DCE design and analysis. He and PI Medina-Marino recently completed a study using DCE to understand South African health care worker's employment preferences. **Milton Wainberg, MD, (co-I)** is Professor of Clinical Psychiatry at Columbia University and Director of the NIH-funded Implementation Science Global Mental Health Research and Capacity Building Hub in sub-Saharan Africa (U19MH113203), of which PI Medina-Marino is a co-investigator. He is a global leader in providing clinical care for HIV, mental health and substance use/alcohol disorders. Finally, a Scientific Advisory Committee (**SAC**) will meet bi-annually with the study team to provide strategic insights for optimal study design, implementation and dissemination (see Letters of Support). SAC members will include: 1) **Linda-Gail Bekker, MBChB, FCP, PhD**, Deputy Director of the Desmond Tutu HIV Centre, Professor of Medicine at Univ. of Cape Town; 2) **Denis Nash, PhD MPH**, Professor and Executive Director of the Institute for Implementation Science in Population Health at City University of New York; and 3) **Grant Theron PhD,** Associate Professor, National Research Foundation's Centre of Excellence in Biomedical Tuberculosis Research, Stellenbosch University, and expert in diagnostics implementation and the South African TB care cascade.[20]

STI Screening R21

The expertise of your team also matters a lot.

Initial R21 study team description:

C.3. The Research Team. **Jeffrey Klausner, MD, MPH** (UCLA Co-PI): Dr. Klausner is an infectious disease epidemiologist and Professor of Medicine and Public Health in the UCLA Division of Infectious Diseases, School of Medicine and the Department of Epidemiology, School of Public Health. This study builds on more than 20 years of prior STI screening and treatment studies in San Francisco, South Africa and Peru. As Director of STD Prevention and Control Services in San Francisco, 1998-2009, Dr. Klausner began studies investigating the performance of molecular STI diagnostics, the role of self-specimen collection for STIs and the introduction and evaluation of population-based screening programs in schools, jails and adolescent clinics.[32-39] From 2009-2011 Dr. Klausner was Branch Chief for HIV and TB at the US Centers for Disease Control and Prevention in Pretoria, South Africa, helping lead the South African PEPFAR program for PMTCT, HIV care and treatment. In that role Dr. Klausner worked directly with national, provincial and district health authorities and local South African non-governmental organizations including FPD to support the scale-up of PMTCT services nationally. He played a key role in describing the population-based provincial rates of MTCT as part of the South African national PMTCT effectiveness evaluation.[29,40-42]Dr. Klausner is a member of the WHO STI Guidelines Committee and frequent advisor to ministries of health on HIV and STI prevention. He will have 0.20 FTE on this project, and will provide oversight of the research design, implementation, and analysis.

Andrew Medina-Marino, PhD (FPD Co-PI) is Head of FPD's Research Unit and Senior Technical Advisor for Laboratory and Disease Surveillance Systems Strengthening activities. Previously, Dr. Medina-Marino was Laboratory Branch Chief for CDC-South Africa. In this capacity, he supported and advised the South African National Institute for Communicable Diseases (NICD) National Health Laboratory Service (NHLS), South Africa's national pathology service provider, on the expansion of laboratory based surveillance programs. He also worked directly with NHLS and the National Department of Health to develop national point-of-care policy and guidelines. As a Molecular Biologist, Dr. Medina-Marino helped identify a key cell receptor that facilitates NG adherence and invasion.[43] Dr. Medina-Marino has worked extensively with the Tshwane District Dept. of Health and the staff at the two clinics that will serve as study sites. For this project he will provide direct oversight for the South African-based study team, including study nurses who will have direct contact with patient-participants and data managers. In his role as Co-PI he will devote 0.20 FTE and will oversee and ensure quality of all in-country study implementation efforts.

Joy Ikechi Ebonwu, MPH (Co-Investigator): Ms. Ebonwu is a STI Epidemiologist with FPD. Prior to working for FPD Ms. Ebonwu was an epidemiologist with the Centre for HIV and STIs at the National Institute for Communicable Diseases within the National Health Laboratory Service in South Africa. Ms. Ebonwu is currently assisting in the development and implementation of the first national sentinel STI etiological surveillance project. She has also worked as a laboratory supervisor at National Health Laboratory Service Mycobacteriology referral laboratory in Braamfontein, Johannesburg and has spent considerable time performing diagnostic procedures at the STI Research Laboratory at George Mukhari Hospital in Pretoria. Ms. Ebonwu is a graduate of the South African Field Epidemiology and Laboratory Training Program and has a Master of Public Health from the University of Pretoria and a Master of Medical Microbiology from the University of Witwatersrand in Johannesburg. For this project, Ms. Ebonwu will provide coordination and oversight of all specimen collection, and laboratory processing of all study specimens at both study sites.

Xiaoyan Wang, PhD (Co-Investigator): Dr. Wang is an Assistant Professor within the Statistics Core of the UCLA Department of Medicine. She has extensive experience with biostatistics in the design and analysis of large-scale cohort, cross-sectional and intervention studies. She will be responsible for all statistical analyses for this project.

James McIntyre, MBChB (Consultant): Dr. McIntyre is an OB/GYN physician-scientist and internationally-recognized expert on HIV MTCT. He is the executive director of the Anova Health Institute, and the international vice-chair of the NIH-funded International Material Paediatric and Adolescent AIDS Clinical Trials Network (IMPAACT). He regularly serves as a consultant on these issues to the WHO, UNAIDS, and UNICEF. He will provide approximately 2 hours of consultation each month for both years of this project.

STI Screening R21

The expertise of your team also matters a lot.

Initial R21 study team description:

2. Investigator(s):

Reviewer 3

Strengths

- Dr. Klausner is an internationally recognized expert in STIs and HIV.
- Dr. Medina-Marino has been the Laboratory Branch Chief for CDC-South Africa and experience within PEPFAR focusing on strengthening public health laboratory systems and disease surveillance programs for HIV/AIDS, TB and opportunistic infections.
- Study has OB/GYN consultant.

Weaknesses

- Inclusion of an implementation scientist would have strengthened the team.

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TB Stigma R01

The evidence that your team has a substantial collaborative working history also matters a lot.

Initial R01 study team description:

Research Team: Our team has extensive expertise in epidemiology and biostatistics, HIV and TB, quantitative and qualitative approaches to stigma, TB case finding and the care cascade, measurement, health behavior, and statistical and multilevel modeling. We have deep experience conducting TB and HIV research in South Africa. **Andrew Medina-Marino, PhD**, (co-PI) is Head of Research for the Foundation for Professional Development, and has extensive research experience in TB, HIV, and STIs. He is PI on 3 recently funded NIH grants focused on STI screening (R21HD084274), TB case finding (R21EB023679), and HIV prevention (1R01MH114648), all in South Africa and with a focus on particular steps in the care cascades. He is an expert field epidemiologist and was twice deployed by *Médecins Sans Frontières* to lead their community-based case investigation and contact tracing team in Liberia during the 2014-2016 Ebola outbreak in West Africa. **Aaron Kipp, PhD**, (co-PI) is an epidemiologist and Assistant Professor at Vanderbilt University with expertise in measures of HIV and TB-related stigma, as well as other patient-reported psychosocial measures. His international research has focused on how stigma impacts access and utilization of TB and HIV treatment and retention in care. **Drs. Medina-Marino and Kipp** have collaborated for over a year to validate stigma measures in multiple South African languages and distinct socio-cultural communities, all in preparation for this proposed study. They are currently co-mentoring an MPH student and developing publications emanating from their recent work. For this study, Dr. Medina-Marino will provide administrative oversight for the grant and will be responsible for directing all in-country study implementation and data collection activities, while Dr. Kipp will oversee all aspects of study design and data analysis. They will be jointly responsible for results dissemination.

This study will also benefit from key co-investigators. Specifically, **Amrita Daftary, PhD, MPH**, (co-I) is an expert in qualitative methods and conducting social and behavioral research in HIV and TB with a focus on the social determinants of TB and HIV health care seeking, particularly the role of stigma. She will be responsible for all qualitative components (Aim 4) of this study. **Kristopher Preacher, PhD**, (co-I) is a nationally-recognized quantitative psychologist specializing in highly relevant multilevel statistical methods. For this study, he will be responsible for the multilevel statistical analysis components of Aims 1 and 2. **Cari van Schalkwyk, MComm**, (co-I) is a research biostatistician at the South African Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), with expertise in biostatistical and mathematical modeling of HIV incidence and TB prevalence and transmission. She will be responsible for database development and management, and data analysis with Dr. Preacher.

TB Stigma R01

The evidence that your team has a substantial history also

Initial R01 stu

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Reviewer 2

2. Investigator(s):

Strengths

- The Co-PIs and other senior investigators have complementary expertise in relevant areas for the proposed research (epidemiology, biostats, HIV and TB, mixed methods for studying stigma, TB care continuum, multi-level statistical modeling)
- The Co-PIs are both epidemiologists, but the other senior investigators help to round out the team with social behavioral scientists (with both quant and qual expertise) and biostatisticians included.
- Multiple-PI plan is appropriate, with Medina-Marino covering the admin oversight, oversight of in-country study implementation and data collection, and Kipp overseeing aspects of study design and data analysis.

Weaknesses

- Brief collaborative history between the two PIs

TB Stigma R01

The evidence that your team has a substantial collaborative working history also matters a lot.

Resubmission:

Drs. Medina-Marino and Kipp have collaborated for two years on validating stigma measures in multiple South African languages, presented study findings at the recent 2018 5th South African TB conference, and co-mentored an MPH student. For this study, Dr. Medina-Marino will provide administrative oversight for the grant and will be responsible for directing all in-country study implementation and data collection activities. Dr. Kipp will oversee all aspects of study design and data analysis. They will be jointly responsible for result dissemination.

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FROM THIS MORNING:

Three Key Science Docs

SPECIFIC AIMS + RESEARCH STRATEGY + BIBLIOGRAPHY & REFERENCES CITED

- 1 page
- Summarizes the importance and focus of proposal

- Usually 6 (R21) or 12 (R01) pages
- Describes in detail the significance, innovation, and approach of proposal

- No page limit
- References for most of the application

U.S. Letter size paper; 11-inch font minimum for main text; 0.5" empty margin minimum

FROM THIS MORNING:

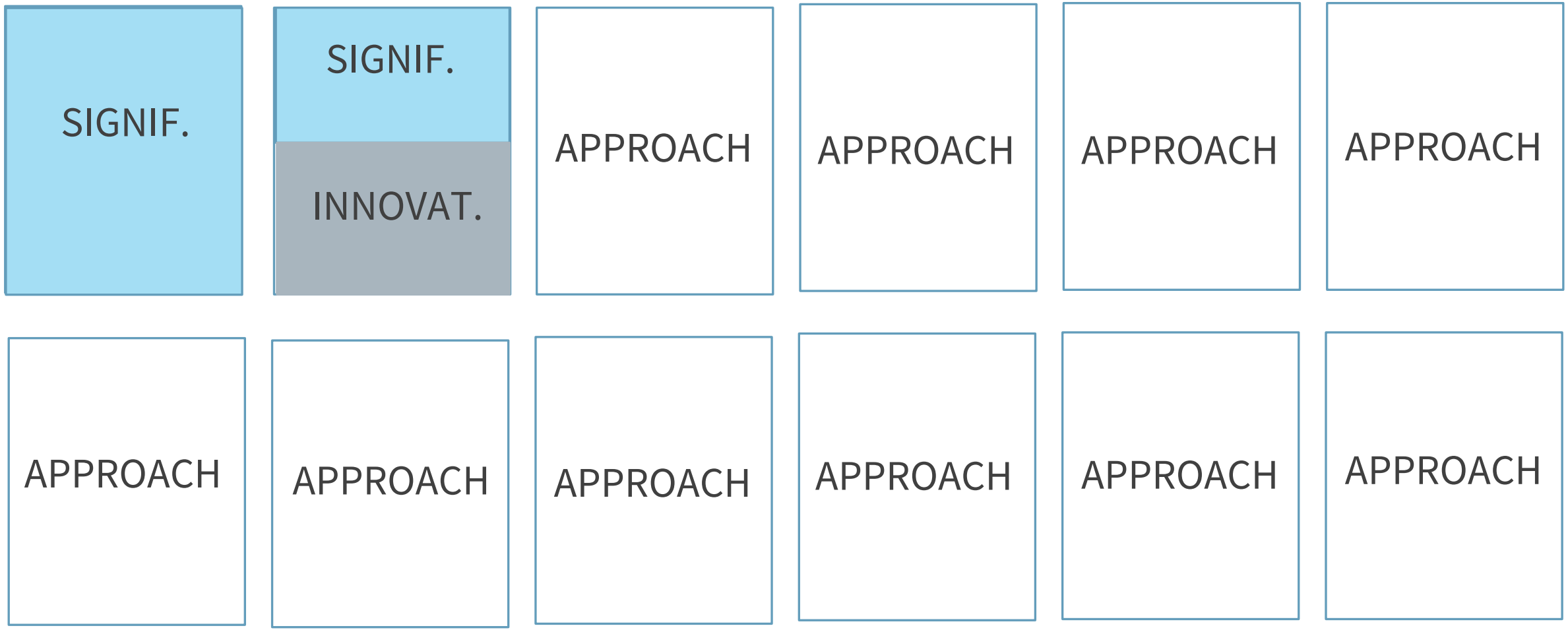
Three Key Science Docs

SPECIFIC AIMS	RESEARCH STRATEGY	BIBLIOGRAPHY & REFERENCES CITED
• 1 page • Summarizes the importance and focus of proposal	• Usually 6 (R21) or 12 (R01) pages • Describes in detail the **significance**, **innovation**, and **approach** of proposal	• No page limit • References for most of the application

U.S. Letter size paper; 11-inch font minimum for main text; 0.5" empty margin minimum

RESEARCH STRATEGY

Relative lengths of each section (12 page R01)



RESEARCH STRATEGY

Relative lengths of each section (6 page R21)

Writing the INNOVATION Section

There is a fine line between an innovation and a study strength. A study strength is not actually an innovation!

Innovation: Purpose

What is unique or novel about your study?

<u>Some key areas of innovation</u>:

A. New research question/hypothesis not yet studied
B. New application of existing/old method
C. Including/expanding an area of research to a new or understudied population (by subgroup, geography, etc.)

***Make each area of innovation a topic sentence that can be fleshed out with 2-3 additional sentences.

Innovation: Example

Unstudied question/hypothesis

New Technology for the Early Detection of TB. *This pilot study is designed to determine the acceptability and feasibility of routinizing TB testing of household contacts using the PoC GeneXpert® Omni System [Cepheid, Sunnyvale, CA] and the FDA-cleared, commercially available MTB/RIF molecular assay [Xpert MTB/RIF, Cepheid, Sunnyvale, CA]; MTB/Rif is a highly sensitive and specific assay that provides detection and differentiation of drug sensitive and rifampicin resistant TB.24 The GeneXpert® Omni System (Figure 1) is a new, mobile diagnostic platform designed to function in resource-constrained environments such as those proposed here, and requires no daily maintenance or biohazardous waste management. The platform functions well in resource-constrained environments and with variable to no power supply; a supplemental rechargeable battery provides freedom to operate for up to 2-days of testing. GeneXpert® is approved for use directly on raw sputum and results are available within 2 hours.24 This study will be the first to evaluate the use of this new tool for home-based PoC testing as part of TB contact investigation.*

3. Innovation:

Strengths

- The rapid diagnostic assay constitutes a highly innovative and significant approach to community based screening for tuberculosis. Although this is one step in the tuberculosis care cascade, it is a key barrier to effective case finding.
- Although the epidemiological approaches are standard, the investigation of the new assay in a high burden setting of tuberculosis transmission is novel.

Omni System [Cepheid, Sunnyvale, CA] and the FDA-cleared, commercially available MTB/RIF molecular assay [Xpert MTB/RIF, Cepheid, Sunnyvale, CA]; MTB/Rif is a highly sensitive and specific

3. Innovation:

Strengths

- The study is innovative because it will examine the feasibility and acceptability of using routing testing of household contact with the new Genexpert Omni system.
- This study would be the first to test the use of this new tool in point-of-care testing as part of the TB contact investigation.

tool for home-based PoC testing as part of TB contact investigation.

Innovation: Example

New application of an existing/old method

Apply Novel Intersectional Methods. *While intersectionality is often viewed as a framework, that mainly utilizes qualitative methods, traditional regression methods (e.g., interaction terms, multi-level) do capture elements of intersectionality.*[97] *However, adapted or novel quantitative methods are needed to better analyze intersectionality.*[85,98-100] *One method is multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA),*[100-102] *which combines demographics such as age, gender, and race into mutually exclusive strata termed intersectional strata. These represent the macro-level environment within which multiple identities intersect to impact health experiences. It partitions heterogeneity into between- and within-strata variance, where larger between-strata variance suggests more influence from the macro-level environment. To date, MAIHDA has been applied to chronic conditions using large datasets from European registries to create intersectional strata based on demographics.*[103-106] *However, there is concern about proper interpretation of model parameters and that MAIHDA has not been sufficiently tested.*[107,108] *Our study presents a unique opportunity to explore and compare novel methods like MAIHDA in the context of traditional intersectional methods (multi-level, interaction, qualitative).*

Innovation: Example

3. Innovation:

Strengths

- The NIRM-TB Care Cascade intervention is well-conceptualized as a basis to inform intervention development.
- The intersectional stigma framework provides an integral model to examine the interrelationships among key influencing factors in international contexts (e.g., TB stigma, HIV, social determinants of health, and TB outcomes).
- The proposed study employs novel methods (e.g., MAIHDA) in combination with traditional intersectional methods which poses strong implications for innovative scalable prevention interventions.

about proper interpretation of model parameters and that MAIHDA has not been sufficiently tested.[107,108] Our study presents a unique opportunity to explore and compare novel methods like MAIHDA in the context of traditional intersectional methods (multi-level, interaction, qualitative).

Innovation: Example

Including diverse/unstudied groups

Considerable attention has been focused on identifying and intervening upon the unique barriers to TB care and optimal treatment outcomes experienced by those co-infected with HIV, mobile populations, prisoners and miners, pregnant women and children, urban populations and healthcare workers.[6,51–59] *However, little attention is paid to the unique challenges men face accessing and remaining in care, or to developing targeted interventions to improve men's TB outcomes.*[7,60]

Innovation: Example

Including diverse/unstudied groups

3. Innovation:

Strengths

- Scant attention has been given to the unique challenges of access to care, retention in care, and targeted interventions to improve men's TB outcomes.
- First study to explore men's unique experiences in accessing TB care, explore treatment experiences, and understand men's preferences related to the development of male-centered interventions.
- Explores unique methodology for providing care to men with TB.

Weaknesses

- No score driving weaknesses noted.

Innovation: Example

Including diverse/unstudied groups

Since 1990, Eastern Cape Province has ranked last among South Africa's nine provinces in its Human Development Index score.[19,20] Eastern Cape has the second highest HIV prevalence (25.2%; 95% CI: 19.8%-31.5%),[3] the highest TB incidence (1236 per 100,000 persons; 95% CI: 945-1526),[21,22] and some of the poorest outcome metrics for HIV, TB, mental health, maternal-child health and health service delivery in South Africa.[10,16–18] Even with these facts, most research support, capacity, implementation, donor funding and infrastructure continues to flow to the well-established, historically advantaged institutions in Durban (KwaZulu-Natal Province), Johannesburg (Gauteng Province) and Cape Town (Western Cape Province). In fact, since 1993, 99.7% of all NIH funded projects awarded directly to South African institutions (N=1019) went to institutions in the Durban, Johannesburg, and Cape Town regions; none have gone to institutions in Eastern Cape.[23] …Of note, since 1993, only 8 (0.79%) of NIH's 1019 funded projects awarded directly to South African institutions have gone to HDIs, and none have been awarded to institutions outside of Durban, Johannesburg or Cape Town.[23] To address some of these inequities, in 2017 the world-renowned Desmond Tutu Health Foundation (DTHF) established a research program in Eastern Cape Province to support research infrastructure, capacity and output from Eastern Cape by collaborating with and capacitating local institutions.

Innovation: Example

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Strengths

- The focus on capacity building and professional training in HDIs in a low-income, high HIV prevalence area is a definite plus.

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Plan for the Afternoon

1. Importance of Preliminary Data
2. How to Choose Your Research Team
3. How to Structure the Innovation Section
4. **How to Develop the Significance Section**
5. Approaching Literature Review and Citations

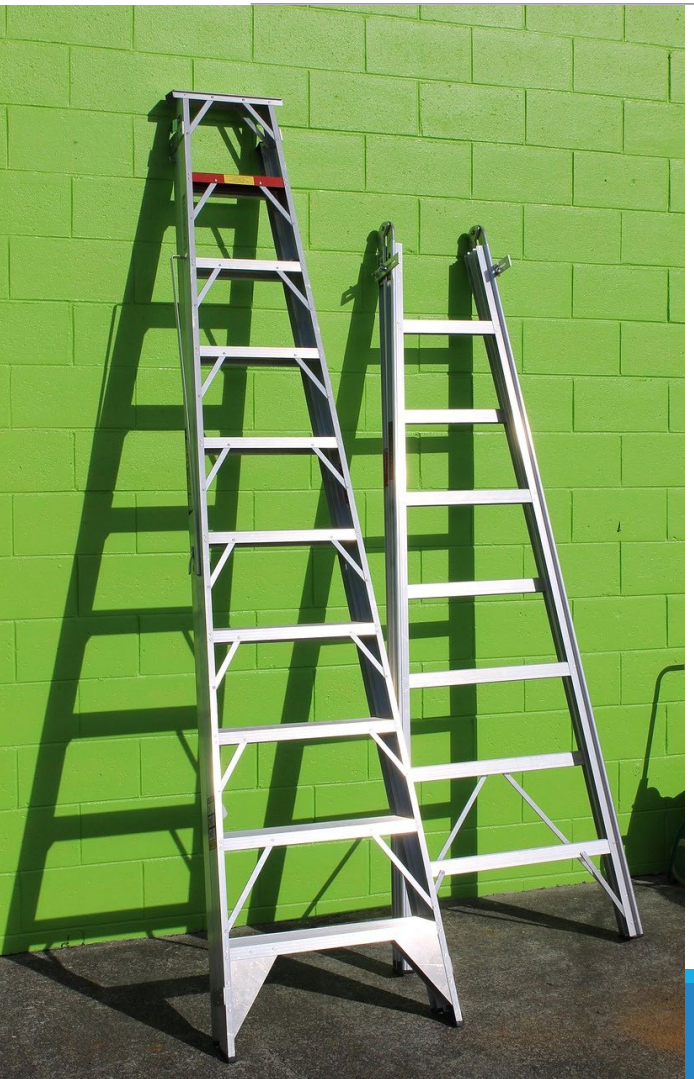
Significance: *Purpose*

- Why is your research topic important and warranted?
- Framed by scientific background/context (with citations!)
- ***Build a narrative

"…the reviewer should be engrossed in an unfolding story that leaves him/her eager to know the next stops in the plot. Your experimental plan should be the logical approach to continue the story, addressing questions raised naturally by the plot so far."

- Otto Yang, *Guide to Effective Grantwriting*

Significance: Building an Argument Ladder



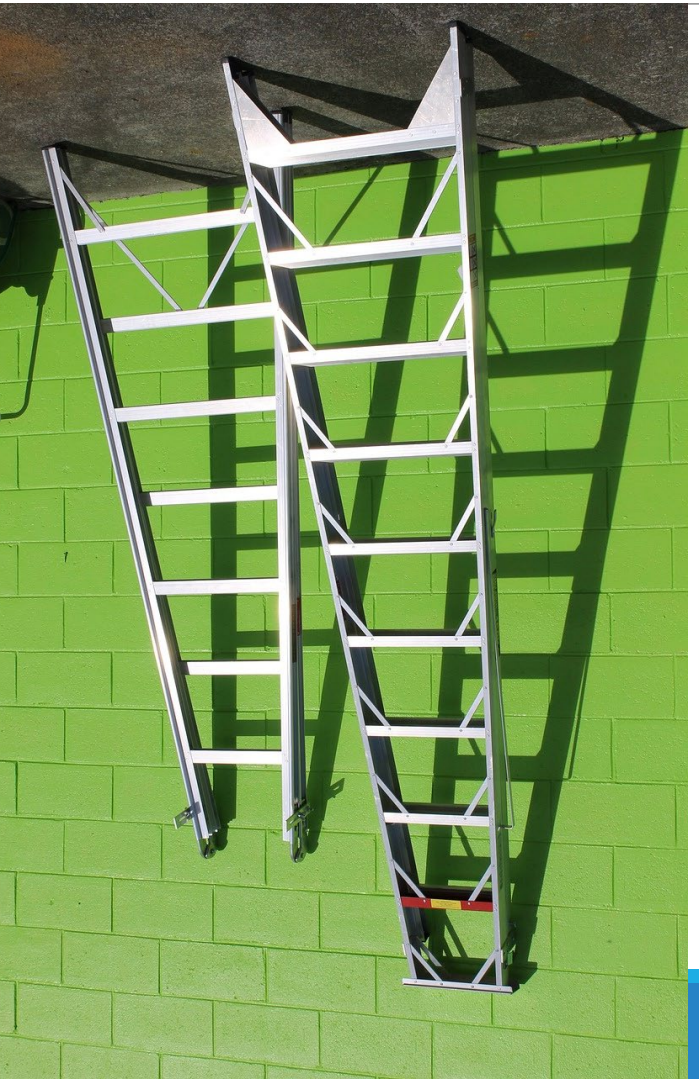
BROAD

BOTTOM RUNG

SPECIFIC

TOP RUNG

Significance: Building an Argument Ladder



BROAD
BOTTOM RUNG

1. Syphilis is a reemerging global health problem.
2. Shortages of penicillin—current recommended treatment—are a global health threat.
3. Penicillin allergy is common.
4. Existing penicillin alternatives are inadequate.
5. Cefixime has promise as a syphilis treatment, but we lack large-scale data on its efficacy.
6. Understanding treatment response, especially in vulnerable groups, is key to optimizing treatment.

SPECIFIC
TOP RUNG

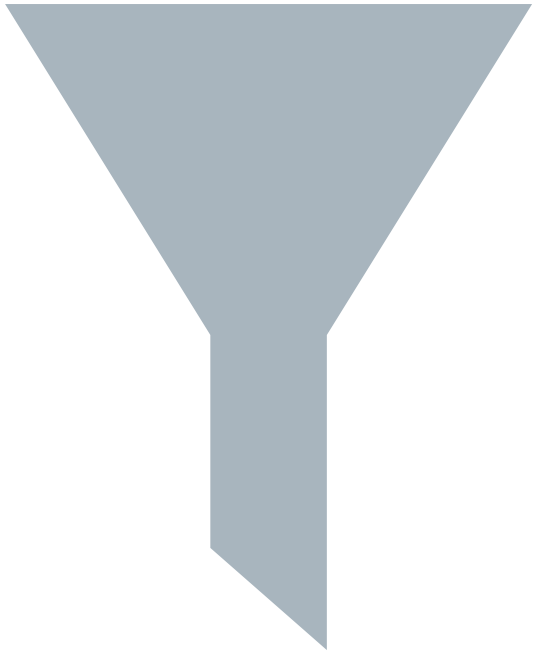
Significance: *Building the Rungs*

- Go back to your Specific Aims Page!

SPECIFIC AIMS FORMULA

Zooming back out to the big picture:

BROAD



SPECIFIC

1 **State of the ISSUE (1-2 paragraphs):**

a) Description of broad issue & its importance
b) Description of sub-issue and its importance
c) What are the critical research gaps?

2 **Where YOUR WORK fits in (1 paragraph):**

a) Your team's prior work in this area
b) How your study will bridge gaps described

3 **AIMS (list + 1-2 sentences for each aim)**

4 **IMPACT of your work (1-3 sentences)**

Significance: *Building the Rungs*

- Go back to your Specific Aims Page!
- **Each key point you came up with for #1, #2, and #4 for the Specific Aims formula should now be rungs of your ladder**
- If you really have more space, you can add more rungs, but don't overdo it

<u>One of the most common pitfalls in development of Research Strategy pages is spending too much time/space on the Significance section and not enough on the Approach section!</u>

Significance: *Turning the Rungs into Text*

Aims formula #	Topic sentence	Further points (3-6 sentences total for each rung!)
1 (issue)	Syphilis is a reemerging global health problem.	• Describe incidence globally • Describe health complications • Describe disproportionately impacted groups
1 (issue)	Shortages of penicillin—current recommended treatment—are a global health threat.	• Describe data on shortages • Describe impact of shortages on syphilis incidence
1 (issue)	Penicillin allergy is common.	• Describe data on penicillin allergy • Describe impact of penicillin allergy on syphilis incidence
1 (issue)	Existing penicillin alternatives are inadequate.	• Describe alternatives and their limitations • Describe impact of penicillin allergy on syphilis outcomes
2 (gaps)	Cefixime has promise as a syphilis treatment but we lack large-scale data on its efficacy.	• Describe why it is promising (already exists/is safe; biological mechanisms; any prior studies) • Describe lack of large-scale data
4 (impact)	Understanding treatment response, especially in vulnerable groups, is key to optimizing treatment	• Describe data on treatment failure among subgroups (e.g. PLWH)

Significance: Some final tips

- Adjust your language to reviewers (most of whom will be in the U.S.)
- Keep it concise - *leave room for the Approach section!*
- Check the clarity of your narrative:
  - Are you using and citing evidence from reliable, recent academic sources to back up your claims? *(We will talk more about this next.)*
  - If you read just the topic sentences, is there a clear justification of the importance of your research?

Practice!

Think of your own research interest and try to create an argument ladder of your own Significance section's topic sentences.

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THE BIG PICTURE:

NIH proposals need to be well-cited!

- **A lot of citations -** common to have ~50-100 in a six page proposal
  - Shows that you know your field and the context of your research well

RESEARCH STRATEGY
A. SIGNIFICANCE

There are 37 citations just in the first few paragraphs here!

Missed TB cases are a critical global health problem. In 2013, WHO estimated that 3.3 million cases of TB had been missed (undiagnosed or with a significant delay in diagnosis or treatment).[1] Reasons for low case detection include 1) insufficient diagnostic sensitivity to detect TB,[10-14] especially in those co-infected with HIV, 2) structural barriers such as poor access to health services and testing,[15-17] 3) an individual's healthcare seeking behaviors,[18,19] and 4) system-level issues such as the failure of the health system to screen TB symptomatic individuals.[3,20-22] Ongoing research by our group demonstrates that missed opportunities to screen for TB in primary and community health clinics significantly contribute to missing TB cases in South Africa. Significant efforts have been made in the past decade to diminish these barriers, with a concomitant increase in global case notification rates.[1,23,24] However, the benefits have mainly flowed to TB cases passively presenting to the health system,[23,24] suggesting additional efforts are needed to improve early case detection.

Active case finding and household contact investigations have the potential to greatly expand and improve early case detection,[4,25,26] and are key global[27] and local[7] strategies that contribute to decreasing the number of "missing" TB cases. While population-wide mass screening has been discouraged due to its uncertain impact, high costs, and poor sustainability[28], there is renewed interest in this strategy for early case detection.[29] However, while systematic screening of household contacts is a cost-effective,[30] high-yield intervention for the detection of TB,[31-34] there exist significant limitations that impact its effectiveness.

Low uptake of community-to-clinic referrals for testing is a significant barrier to diagnosis and treatment of secondary TB cases screened during household contact investigations (HCI). In South Africa, recent studies have found the prevalence of TB in HHCs to be as high as 6,075 per 100,000 population,[25] and 3,624 per 100,000 in HHCs of patients with MDR and XDR TB.[35] Unfortunately, low uptake of referrals for clinical assessment and testing by HHCs screened during HCIs is a major weakness of contact investigations in high-burden countries,[36,37] and directly contributes to the 3.3 million global missing cases of TB. In theory, by bringing diagnostic services into the community and integrating them with household contact investigations, many barriers

THE BIG PICTURE:

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  - Shows that you know your field and the context of your research well
- **Good quality citations that are most relevant to your claims**
  - Primarily peer-reviewed journal articles within past five years (older articles sometimes okay, depending on field and research question)
  - Authoritative government reports/data can be included as makes sense (e.g., statistics on HIV prevalence in given region), but should not be majority → you are grounding your work in the research field
  - No Wikipedia, non-authoritative websites, etc.

Getting ready to cite

- **Use a reference manager that your whole team has access to**
  - Zotero is a good free option
  - https://www.zotero.org/support/quick_start_guide
- **Use a standard citation format (NIH Specific Format)**
  - Include the PMCID#, where available (required for papers co-authored by applicant)
  - Note: Interim research products have specific citation requirements

Citations: Tips & Tricks

- **For research proposals, citations are continuous across the Aims, Research Strategy and other sections (e.g., Human Subjects/Clinical Trials)**
  - Although these sections will be separated when submitting your proposal, keeping them together in one Word document until your proposal is final will make citations much easier
- Note: Biosketch citations (discussed tomorrow) are not part of this

Citations: Tips & Tricks

- **Add citations as you go, through your reference manager**
  - Much more efficient and saves you a crunch at the end
  - But don’t worry about formatting the “Bibliography and References Cited” section until the proposal is totally ready

Finalizing the “Bibliography and References Cited”

- **When your proposal is final:**
  - Copy just the references cited list that your reference manager generated to a new Word doc
  - Clean the references list to correct any mistakes made by the reference manager (e.g., missing pieces, weird formatting)
  - Save document as “Final References_clean” in Word
- Note: No page limit on the final Bibliography and References Cited

WHAT WE'VE DONE THIS AFTERNOON

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