

# Fall 2018 Cycle UCSF-RAP Application Cover Page **SAMPLE**

	Investigator	Series	Rank	Degree(s)	School / Department
PI1	Oldenburg, Catherine <catherine.oldenburg@ucsf.edu>	In Residence	Assistant Professor	PhD, MCR/MPH/MS	UCSF Medicine /

**Grant Mechanism:** Pilot for Junior Investigators in Basic and Clinical/Translational Sciences

**Project Title:** Azithromycin as adjunctive therapy for the treatment of uncomplicated severe acute malnutrition

**Submission Version:** New Submission

**Budget Requested:** \$40,000

**Co-Investigators:** Kelly, J. Daniel / O'Brien, Kieran

**Mentor:** Thomas Lietman

## Abstract

Severe acute malnutrition (SAM) affects nearly 19 million preschool children annually, the vast majority of whom are in sub-Saharan Africa. Children with SAM may have asymptomatic infection at the time of admission to the nutritional program, but due to immune system suppression the infection often goes undiagnosed. The World Health Organization therefore recommends treatment of children with uncomplicated SAM treated as outpatients with a broad-spectrum antibiotic, typically amoxicillin. Resistance to amoxicillin is near-ubiquitous for some pathogens in some settings in sub-Saharan Africa, and a recent randomized controlled trial in Niger demonstrated no benefit for recovery with the use of amoxicillin versus placebo. Azithromycin, which is uncommonly used for routine treatment of children in rural sub-Saharan Africa, has recently been shown in a randomized controlled trial to prevent all-cause child mortality at the community level when used as biannual mass drug administration compared to placebo. For children with SAM, azithromycin may offer benefits over amoxicillin, including the long half-life of a single 20 mg/kg dose, and less community resistance to macrolides. We propose a pilot individually randomized controlled trial to test the efficacy of administration of an adjunctive dose of azithromycin compared to a 7-day course of amoxicillin (current standard of care) in children with uncomplicated SAM being treated as outpatients in a rural region of Niger with a high burden of disease. The primary outcome will be nutritional recovery at 8 weeks after admission to the nutritional program, and we will additionally evaluate effects on malaria and longitudinal growth. We hypothesize that children randomized to receive azithromycin will have increased probability of nutritional recovery at 8 weeks compared to those receiving the standard of care.

Budget Details		PI1 Details	
<b>Budget includes a travel component:</b>	no	<b>Gender:</b>	Female
<b>Project involves payments to international organizations/research expenses in other countries:</b>	yes	<b>Race:</b>	White
<b>Project potentially involves subjects from special category populations:</b>	yes	<b>Ethnicity:</b>	Hispanic or Latino
<b>IRB/IACUC/STEM CELL Approvals</b>		<b>Time spent in Research:</b>	75-100%
		<b>Time spent in Clinic:</b>	0
<b>Project involves human subjects:</b>		<b>Current K awardee?:</b>	no
		<b>Received funding from a RAP Funding Agency in the past three years?:</b>	no
<b>Project involves human stem cells:</b>	no		
<b>Project involves animal subjects:</b>	No, Not Applicable		

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**2. Project Title**

Azithromycin as adjunctive therapy for the treatment of uncomplicated severe acute malnutrition

### 3. PROPOSAL

#### A. SPECIFIC AIMS

**Severe acute malnutrition (SAM) affects nearly 19 million children under the age of 5 annually.**<sup>1</sup> Children with SAM often bear a large burden of infectious disease.<sup>2</sup> Since malnutrition can suppress the immune system, children with SAM and co-existing infection are often asymptomatic. As a result, the World Health Organization (WHO) has recommended routine treatment of children with SAM with a broad-spectrum antibiotic as adjunctive therapy to standard treatment with ready-to-use therapeutic food (RUTF). However, the evidence for this recommendation is mixed, with one large randomized controlled trial of amoxicillin in Malawi showing a benefit<sup>3</sup> and one in Niger showing no benefit for nutritional recovery.<sup>4</sup>

**Mass azithromycin distribution has been shown to reduce all-cause mortality at the community level.**<sup>5</sup> In Niger, Tanzania, and Malawi, mortality was reduced by nearly 14% in communities randomized to biannual mass single-dose azithromycin distribution to preschool children. The largest effects were seen in Niger, with nearly 1 in 5 deaths averted. Children with SAM have 9 times the risk of all-cause mortality compared to their well-nourished peers, and an increased risk of infectious mortality.<sup>6</sup> For children with SAM, azithromycin may be an attractive alternative to amoxicillin. A single dose of azithromycin utilizing trachoma-based dosing (20 mg/kg)<sup>7,8</sup> has a long half-life, and thus dosing could occur during outpatient visits and not rely on caregiver administration. Furthermore, while amoxicillin and cotrimoxazole are the most commonly used antibiotics for treatment of childhood infections in communities with a high burden of SAM, the use of azithromycin is uncommon. Treatment with an uncommonly used antibiotic may be beneficial as there may be less antibiotic resistance to macrolides, which may increase its efficacy.

**We propose a pilot randomized controlled trial to test the efficacy of administration of adjunctive azithromycin as part of routine outpatient care for uncomplicated SAM in children aged 6-59 months.** We propose to randomize children presenting to nutritional programs in Niger to one of two arms: 1) a 7-day course of twice-daily amoxicillin (current standard of care) or 2) a single dose of azithromycin. We propose the following specific aims:

**SPECIFIC AIM 1: Determine the effect of azithromycin on nutritional recovery in children with uncomplicated SAM.** *We hypothesize that children randomized to receive azithromycin will have increased nutritional recovery 8 weeks after admission to the nutritional program compared to children receiving amoxicillin.*

**SPECIFIC AIM 2: Determine the effect of azithromycin on malaria incidence among children with uncomplicated SAM.** *We hypothesize that children randomized to receive azithromycin will have reduced risk of malaria at 8 weeks compared to children randomized to amoxicillin.*

#### B. BACKGROUND AND SIGNIFICANCE

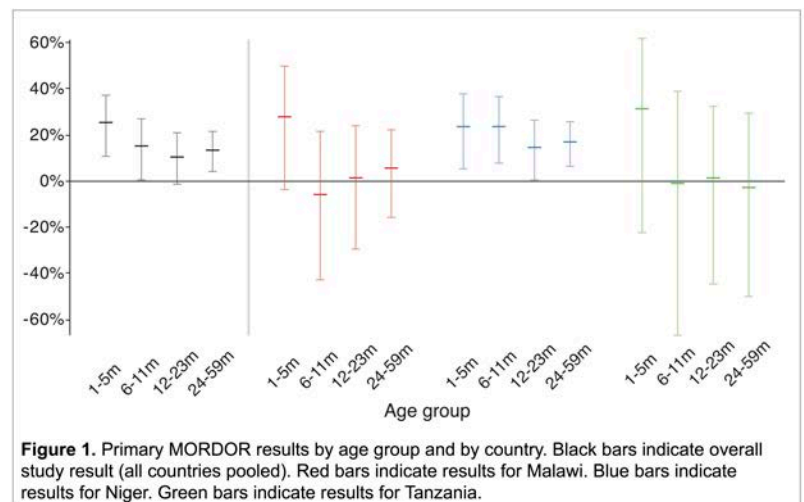
**The role of amoxicillin as adjunctive therapy for children with uncomplicated severe acute malnutrition (SAM) is unclear.** Current WHO guidelines recommend a routine 7-day dose of amoxicillin for children with uncomplicated SAM treated on an outpatient basis. Children with SAM face greater risk of infectious mortality compared to their well-nourished peers. Suppression of the immune system via malnutrition may mask clinical symptoms of infection, and thus routine treatment is recommended. However, the evidence base for this recommendation is minimal. Two studies of amoxicillin as adjunctive therapy for SAM found mixed results.<sup>3,4</sup> In Malawi, routine amoxicillin led to increased nutritional recovery and decreased mortality.<sup>3</sup> In Niger, there was no effect of routine amoxicillin on either nutritional recovery or mortality.<sup>4</sup> Importantly, the Malawi study population had a high prevalence of both kwashiorkor and HIV, whereas the prevalence of both nutritional edema and HIV are very low in Niger, and children with kwashiorkor were excluded in the Niger study. A pooled analysis of the two studies found no benefit of amoxicillin for recovery.<sup>9</sup> A third study of daily cotrimoxazole among children recovering from complicated SAM additionally found no benefit for nutritional recovery or mortality.<sup>10</sup> Given the existing mixed evidence, the superiority of amoxicillin for outcomes for children with SAM has not been proven, and whether there are alternative antibiotics that may have benefits beyond any seen with amoxicillin remains unknown.

**Azithromycin distribution in trachoma control programs has been shown to reduce the prevalence of several important childhood infectious diseases.** Mass azithromycin distribution reduces all-cause and infectious child mortality<sup>5,11-13</sup>, and some studies have indicated it may reduce the prevalence of diarrhea<sup>14</sup>, respiratory infection<sup>15</sup>, and malaria.<sup>16-18</sup> These infections are major causes of child mortality in Niger, and children with SAM are particularly susceptible.<sup>2</sup>

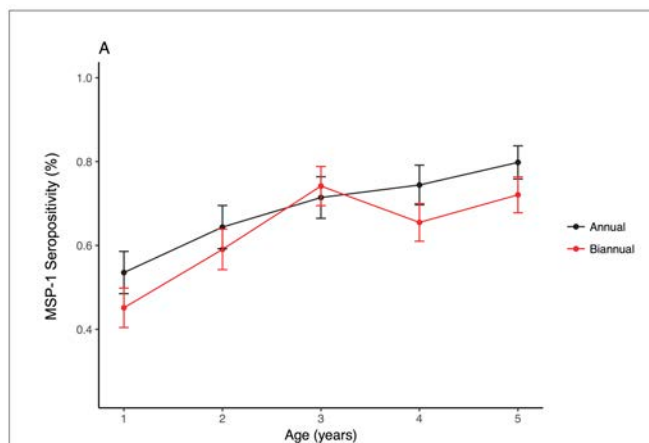
**Azithromycin as adjunctive therapy may offer several advantages over amoxicillin or co-trimoxazole.** First, a single dose of azithromycin has a long half-life, and thus dosing could occur during outpatient visits and would not rely on caregiver dosing. Second, amoxicillin and co-trimoxazole are much more commonly used for routine treatment in many regions of sub-Saharan Africa than macrolides, and baseline resistance to these antibiotic classes tend to be much higher.<sup>19</sup> Adjunctive therapy with azithromycin may be preferable, given overall reduced exposure compared to other classes.<sup>20</sup> Third, recent evidence from a randomized controlled trial in Niger indicated a substantial reduction in mortality with the use of a single dose of azithromycin in children without established infection. Given that children with uncomplicated SAM by definition do not have an established infection, the rationale for antibiotic use may be similar for that among children in the general population who are receiving presumptive treatment. As children with malnutrition are at particularly high risk of mortality, this subgroup of the population may stand to see greater benefits from a similar antibiotic regimen that has been shown to be efficacious in the general population.

### C. PRELIMINARY STUDIES

**A recent cluster-randomized trial demonstrated that mass azithromycin distribution reduces all-cause mortality at the community level.**<sup>5</sup> In Niger, Tanzania, and Malawi, mortality was reduced by nearly 14% in communities randomized to biannual mass single-dose azithromycin distribution to children 1-59 months in the MORDOR trial (*Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance*; **Figure 1**). The largest effects were seen in Niger, with nearly 1 in 5 deaths averted. In communities in Ethiopia receiving mass azithromycin for trachoma control, a significant reduction in child mortality was observed compared to communities not receiving azithromycin.<sup>13</sup> In Niger, childhood infectious mortality was lower in communities receiving biannual versus annual mass azithromycin.<sup>12</sup> A pooled analysis of these studies indicates an overall benefit across studies for all-cause mortality (Oldenburg et al, in preparation). *These studies demonstrate that mass azithromycin distribution significantly reduces all-cause and infectious child mortality, and demonstrates our team's experience with using azithromycin in child health programs.*



**In Burkina Faso, a 5-day course of amoxicillin led to significantly improved weight gain relative to placebo.**<sup>26</sup> We randomized a population-based sample of children to a course of amoxicillin, azithromycin, cotrimoxazole, or placebo and measured weight gain outcomes one month after the last antibiotic dose. Children who were randomized to amoxicillin gained approximately 300 g more over the one-month period compared to children who were randomized to placebo. There was no difference in weight gain in azithromycin or cotrimoxazole-treated children compared to placebo. These results indicate that amoxicillin may have a greater effect on weight gain than azithromycin, however this study was conducted among healthy children and the sample size was small (N=31 per arm). *This study suggests that amoxicillin may lead to greater weight gain than other antibiotic classes, but larger studies designed specifically for children with SAM are required to fully evaluate this hypothesis.*

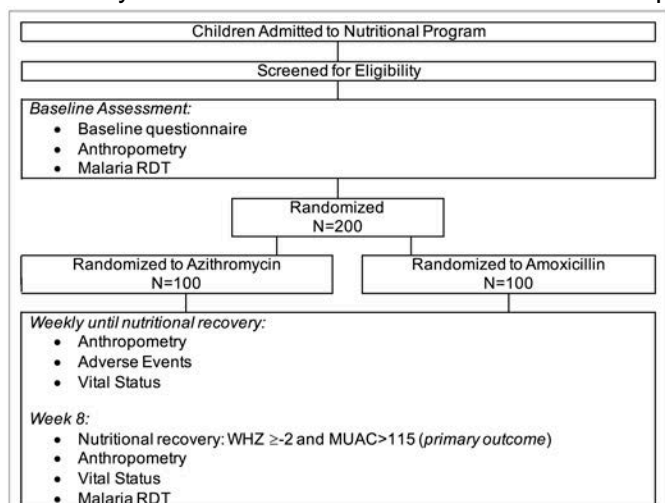


**Figure 2.** Age-seroprevalence curve for antibody positivity to MSP-1 in annual (black) and biannual (red) mass azithromycin distribution for trachoma control in Niger.

shown.<sup>18</sup> In Niger, serologic results have indicated there may be a small reduction in malaria incidence in communities receiving biannual compared to annual mass azithromycin distribution (Oldenburg et al, in preparation, Figure 2). Azithromycin therefore may be beneficial for prevention of malaria in children with SAM, which may contribute to improved nutritional response or reduced mortality. *These studies demonstrate that there may be additional benefits of treatment with azithromycin that are not conferred by amoxicillin, which does not have antimalarial activity.*

#### D. DESIGN AND METHODS

**General Study Design.** This randomized controlled trial is designed to determine the effect of azithromycin as part of the management of uncomplicated SAM in children aged 6-59 months on nutritional recovery (Figure 3). We will randomize children presenting to nutritional programs at health centers in Niger to a single dose of oral azithromycin or a short course of oral amoxicillin upon admission into the program. Apart from the



**Figure 3.** Flow diagram of study procedures

**In children with SAM, the burden of malaria is high.** In Niger, the malnutrition and malaria seasons overlap, and children with SAM are often also affected by malaria.<sup>21</sup> In a randomized controlled trial of children aged 6-59 months randomized to amoxicillin or placebo for adjunctive treatment of uncomplicated SAM in Niger, we demonstrated that 55% of participants had a positive rapid diagnostic test (RDT) at baseline and incidence of positive RDT plus fever was 12.1 cases per 100 child-months.<sup>22</sup> In contrast to amoxicillin, which has no activity against *Plasmodium falciparum*, azithromycin has modest activity against malaria by inhibiting the plasmodial apicoplast.<sup>17,23,24</sup> Azithromycin has been used successfully for prevention of malaria in pregnant women.<sup>25</sup> In studies of mass azithromycin distribution for trachoma control, a short-term reduction in malaria prevalence has been

administration of antibiotics, all children will receive standard outpatient treatment for uncomplicated SAM as specified in the guidelines of the government of Niger. Enrolled children will be followed weekly until nutritional recovery. All enrolled children will return for a final study visit at 8 weeks following enrollment. Anthropometry, vital status, and malaria infection status will be collected at each follow-up visit. Nutritional recovery over the 8-week study period (primary outcome) will be compared by arm.

**Study Area.** The trial will be conducted at four Centres de Santé Intégrés (CSI) in the Dosso District in Niger that run outpatient nutritional programs for children presenting with SAM. CSIs are government-run integrated health centers linked to and overseen by district hospitals. In this area, the burden of malnutrition increases between harvest seasons from June to December. During this

time, CSIs in Dosso see approximately 15-20 cases of SAM each week.

**Eligibility criteria for enrollment sites.** Sites must be located in the Dosso District in Niger and have seen more than 200 cases of SAM in 2017. Of the 42 potential CSIs in Dosso, 17 had available data on the number of cases of SAM seen in 2017, and 4 meet all eligibility criteria: Garantche Dey, Kigoudou Koira, Laccouroussou, and Mangue Koira.

**Eligibility criteria for individuals.** Eligible individuals are children with SAM who present to an eligible enrollment site during the study period and meet all of the following criteria:

- Age 6-59 months

- Weight-for-height z-score (WHZ) < -3 SD or mid-upper arm circumference (MUAC) < 115 mm
- No nutritional edema
- Weight ≥ 3.8 kg
- Primary residence within catchment area of enrollment site
- Available for full 8-week study
- Has not been admitted to a nutritional program for the treatment of SAM in the 3 preceding months
- No antibiotic use in past 7 days
- No clinical complications requiring antibiotic treatment
- No clinical complications requiring inpatient treatment
- No congenital abnormality or chronic debilitating illness that reduce likelihood of SAM treatment benefit
- No allergy to macrolides/azalides
- Sufficient appetite according to a feeding test with ready-to-use therapeutic food (RUTF)
- Appropriate written informed consent from at least one parent or guardian

Of note, nutritional edema is very uncommon in this study area (<1% of cases that report to the nutritional program). Given evidence from previous studies that indicates that there may be heterogeneity in the effect of amoxicillin on nutritional recovery in children with or without nutritional edema<sup>3,4</sup>, we have chosen to exclude children with nutritional edema from this study as meaningful inferences would not be possible in the subgroup with nutritional edema.

**Randomization.** Children meeting the inclusion criteria will be enrolled by local trained study personnel. At enrollment, children will be assigned a study identification number using the next unassigned number on a list identification numbers assigned to the site. Enrolled children will then undergo a baseline assessment, including data collection on demographics and socioeconomic status, anthropometry, and a malaria rapid diagnostic test (RDT). After completion of the baseline assessment, children will be randomized to receive either a single dose of directly observed oral azithromycin or a 7-day course of oral amoxicillin.

The randomization sequence will be generated by the study biostatistician using R (R Foundation for Statistical Programming, Vienna, Austria). Children will be randomized in a 1:1 fashion to a single dose of azithromycin or a short course of oral amoxicillin. The randomization sequence will be linked to the study identification numbers. Randomized study arm assignments will be placed in sealed, opaque envelopes labeled with study identification numbers. After enrollment and completion of the baseline assessment, a CSI nurse trained for the study will open the envelope to determine the allocation, and will administer the study medication indicated. Only the study nurse administering treatment will have access to the envelopes.

**Interventions.** Children will be randomized to receive either:

- 1) azithromycin (20 mg/kg up to 1 g, single directly observed dose, oral suspension), or
- 2) amoxicillin (50-100 mg/kg, first dose directly observed, split into 2 daily doses for 7 days, oral dispersible tablets)

Except for antibiotics, all children will receive standard outpatient treatment for uncomplicated SAM which includes RUTF (170 kcal per kilogram per day; Plumpy'Nut, Nutriset), a dose of albendazole for children aged 12-59 months, vitamin A if not already received as part of a mass treatment program, any vaccinations which the child is missing, and weekly follow-up visits until recovery.

**Masking.** Given the difference in dosing schedules and appearance of the antibiotics, UCSF investigators, participants and study personnel administering treatment will not be masked to treatment assignment. The Niger investigator will be masked. Outcome assessors will be masked to treatment assignment. This will be accomplished by assigning one CSI nurse to administer treatment and a separate masked study team member to perform outcome assessments, including anthropometry, malaria RDT, and vital status updates.

**Study Procedures and Follow-up.** After screening for eligibility in the nutritional program and the study, the caregiver of each child will complete a baseline assessment. Each child will have anthropometric measurements taken, a clinical examination, and an RDT-based malaria test. Any child testing positive for malaria at any time point will receive artemisinin-based combination therapy (Coartem, Novartis, Switzerland). In this region of Niger, children are followed weekly for at least 3 weeks after admission to the nutritional

program. Anthropometry and vital status will be collected at each regular weekly follow-up visit until discharge from the nutritional program. A final study visit for all children, regardless of whether or not they have been discharged, will occur at 8 weeks after admission to the nutritional program. Nutritional recovery by this time point will constitute the primary outcome for the trial. Additional secondary outcomes will include malaria, weight gain, and adverse events. Outcome definition and measurement is detailed in the next section.

### Outcomes.

- **Nutritional recovery by 8 weeks (Primary, Specific Aim 1).** Nutritional recovery is defined as WHZ  $\geq -2$  on two consecutive visits with MUAC  $\geq 115$ mm, no acute complication or edema for the past 7 days.
- **Malaria (Specific Aim 2).** An HRP2-based RDT for malaria (SD Bioline Malaria Antigen P.f, Standard Diagnostics, Inc, Republic of Korea) will be conducted at baseline and week 8 to determine malaria infection status, defined as positive or negative. Axillary temperature will also be collected.
- **Weight gain over 8 weeks.** Weight will be measured at all follow-up time points and weight gain will be defined as grams per kilogram per day (g/kg/day).
- **Mortality by 8 weeks.** Vital status will be assessed at all follow-up time points and mortality will be defined as death during the study period. Date of death will be recorded. A verbal autopsy will be conducted for all deaths during the study.
- **Adverse events.** Screening for adverse events will occur at each follow-up time point.
- **Time to recovery.** Time from enrollment to nutritional recovery (defined above) will be calculated in days by subtracting the date of enrollment from the date of nutritional recovery.
- **Nonresponse at 8 weeks.** Nonresponse will be documented if a child does not meet the criteria for nutritional recovery at 8 weeks.
- **Transfer to inpatient care.** The occurrence, date, and reason for transfer from outpatient to inpatient treatment will be recorded.
- **Clinical signs of infection.** At all follow-up time points, clinical signs of infection will be recorded, including care-giver reported experience of fever, diarrhea, vomiting, and respiratory infection/cough and clinical diagnoses made at by site personnel
- **HAZ.** Height or length will be measured at all follow-up time points and height-for-age z-scores will be calculated.
- **MUAC.** Mid-upper arm circumference will be measured at all follow-up time points.
- **WAZ.** Weight will be measured at all follow-up time points and weight-for-age z-scores will be calculated.
- **WHZ.** Weight and height, assessed at all follow-up time points, will be used to calculate weight-for-height z-scores.

**Sample Size Considerations.** For Specific Aim 1, inclusion of 200 children (100 randomized to each arm) will provide 80% power to detect an 18 percentage point increase in the proportion of children achieving nutritional recovery in the azithromycin arm compared to the amoxicillin arm at an alpha of 0.05. We assumed that 66% of children in the oral amoxicillin arm would achieve nutritional recovery and a loss to follow-up of 10%. Assumptions for this calculation were based on nutritional recovery reported in the amoxicillin arm of a trial of routine amoxicillin for uncomplicated SAM in Niger.<sup>5</sup> For Specific Aim 2, inclusion of 200 children (100 randomized to each arm) will provide 80% power to detect a 20.5 percentage point decrease in malaria infection in children receiving azithromycin compared to children receiving amoxicillin at an alpha of 0.05. We assumed a prevalence of malaria of 55% in the amoxicillin arm and loss to follow-up of 10%. Assumptions for this calculation were based on the prevalence of malaria in children receiving amoxicillin in the Niger trial of routine amoxicillin for uncomplicated SAM in Niger.<sup>5</sup>

**Statistical Methods: Primary Outcome.** For Specific Aim 1, the primary analysis will compare nutritional recovery by 8 weeks from baseline by arm. We will use log-binomial regression for this analysis to estimate the risk ratio. If the log-binomial model fails to converge, we will use a modified Poisson model instead. For Specific Aim 2, the primary analysis will compare malaria infection status at 8 weeks. As in Specific Aim 1, we will use log-binomial regression to estimate the risk ratio and modified Poisson regression if the log-binomial model fails to converge.

**Statistical Methods: Secondary Outcomes.** Time to event outcomes will be assessed visually using Kaplan-Meier curves and compared by arm using the log-rank test. Binary outcomes will be analyzed using modified

Poisson regression for rare outcomes or log-binomial regression for common outcomes. Anthropometric assessments will be analyzed using linear mixed models to account for correlation between repeated measures and allow for use of data collected at all time points in one model. For anthropometric assessments, z-scores will be calculated based on the 2006 WHO Child Growth Standards. Anthropometric z-scores will be analyzed as continuous variables and secondary analyses will explore categorization. All analyses will be intention-to-treat. A significance level of 0.05 will be used for inference and 95% confidence intervals will be reported for all effect estimates. All analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria). For all models, model diagnostics will be conducted to assess appropriate fit.

**Timeline.** We estimate that each site will receive 15-20 cases of uncomplicated SAM each week during the malnutrition season and that we will be able to enroll at least half of these cases. With four enrollment sites, we anticipate completing enrollment in 6 weeks, and completing follow-up 8 weeks after the final enrollment. Allowing for a window of +2 weeks, data collection for the study can be completed in 16 weeks.

Tasks	Status	Pre grant	6/2019	7/2019	8/2019	9/2019	10/2019 12/2019
<b>Study Preparation</b>							
Finalize protocol and database	Completed	↔					
Obtain UCSF IRB approval	Completed	↔					
Obtain Niger Ethical committee approval	Submitted	↔					
Identify and orient enrollment sites	Completed	↔					
Prepare randomization	Completed	↔					
<b>Study Implementation</b>							
Train study personnel	Not started		↔				
Enrollment and follow-up	Not started			↔			
<b>Analyze and Disseminate Results</b>	Not started						↔

## E. CAREER GOALS

I am an infectious disease epidemiologist with training and experience in a broad range of epidemiologic methods, including both observational studies and randomized controlled trials. During my doctoral training, my work focused primarily on treatment and prevention of HIV infection in adult populations.<sup>27-31</sup> Since joining the Proctor Foundation at UCSF, my work has focused on infectious diseases of childhood, including trachoma<sup>32,33</sup>, malaria<sup>22,34</sup>, and the role of antibiotics in child health and survival.<sup>26</sup> With Dr. Tom Lietman, I am currently co-Principal Investigator of several randomized controlled trials, including: 1) evaluating the effect of targeted azithromycin distribution for trachoma control in Ethiopia, 2) evaluating targeted azithromycin to young infants at their 6-week postnatal or 8-week vaccine visit for survival in Burkina Faso, and 3) evaluating the safety and efficacy of azithromycin during the neonatal period for survival. My career goals include building my expertise in interventions for pediatric infectious disease and to establish myself as an independent investigator in global child health. The proposed project would advance my career goals by providing critical experience and preliminary data for an R01-level NIH application.

## F. MENTORING PLAN

Dr. Tom Lietman will serve as my mentor on this proposal. I have worked with Dr. Lietman since 2009, and together we have co-authored 48 publications. Dr. Lietman was the Principal Investigator of the MORDOR trial, and has extensive experience with studies of azithromycin for child health and in randomized controlled trials. I will regularly meet with Dr. Lietman throughout the course of this study, including the design, implementation, and analysis phases. My office is co-located with Dr. Lietman's, and we will meet at least weekly to discuss the progress of the project. Dr. Lietman will provide critical input to ensure that the project is meeting its goals. I am also working with other experts in the field, including Dr. Christine Stewart at UC Davis and Dr. Phil Rosenthal at UCSF. Dr. Stewart is a nutritional epidemiologist and Dr. Rosenthal is an infectious disease physician and malaria epidemiologist. Drs. Stewart and Rosenthal will provide critical content expertise for the project for study design and measurement of outcomes, monitoring of the study, and interpretation of results. I will consult with Drs. Stewart and Rosenthal before the beginning of the study, at least quarterly during the course of the study, and during the analysis and dissemination phase.



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- 27 Oldenburg CE, Seage G, Tanser F, *et al.* Antiretroviral therapy and mortality in rural South Africa: A comparison of causal modeling approaches. *American Journal of Epidemiology* 2018; **In press**.
- 28 Oldenburg CE, Ortblad KF, Chanda M, *et al.* Zambian Peer Educators for HIV Self-Testing (ZEST) Study: Rationale and design of a cluster randomized trial of HIV self-testing among female sex workers in Zambia. *BMJ Open* 2017; **20**: e014780.
- 29 Chanda MM, Ortblad KF, Mwale M, *et al.* HIV self-testing among female sex workers in Zambia: A cluster randomized controlled trial. *PLoS Medicine* 2017; **14**: e1002442.
- 30 Oldenburg C, Barnighausen T, Tanser F, *et al.* Antiretroviral therapy to prevent HIV acquisition in serodiscordant couples in a hyperendemic community in rural South Africa. *clinical infectious diseases* 2016; **63**: 548–54.
- 31 Oldenburg CE, Bor J, Harling G, *et al.* Impact of early antiretroviral therapy eligibility on HIV acquisition. *AIDS* 2018; **32**: 635–43.
- 32 Oldenburg CE, Amza A, Kadri B, *et al.* Comparison of Mass Azithromycin Coverage Targets of Children in Niger: A Cluster-Randomized Trachoma Trial. *American Journal of Tropical Medicine and Hygiene* 2018; **98**: 389–95.
- 33 Amza A, Kadri B, Nassirou B, *et al.* Effectiveness of expanding annual mass azithromycin distribution treatment coverage for trachoma in Niger: a cluster randomised trial. *Br J Ophthalmol* 2017; : bjophthalmol–2017–310916–8.
- 34 Oldenburg CE, Amza A, Kadri B, *et al.* Annual Versus Biannual Mass Azithromycin Distribution and Malaria Parasitemia During the Peak Transmission Season Among Children in Niger. *The Pediatric Infectious Disease Journal* 2017; : 1–20.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 00/00/2019	THROUGH 00/00/2020
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List PERSONNEL (*Applicant organization only*)

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested (*omit cents*) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Catherine Oldenburg	PD/PI	0.6			X,XXX	X,XXX	X,XXX	X,XXX
SUBTOTALS →						X,XXX	X,XXX	X,XXX

CONSULTANT COSTS

EQUIPMENT (*Itemize*)SUPPLIES (*Itemize by category*)

Azithromycin (\$500)

500

TRAVEL

INPATIENT CARE COSTS

OUTPATIENT CARE COSTS

ALTERATIONS AND RENOVATIONS (*Itemize by category*)OTHER EXPENSES (*Itemize by category*)

UCSF Data Network Recharge (\$564)

Niger study approvals (\$1,500)

Study team training (\$4,500)

Study team transportation (\$2,500)

Study team fees (\$20,863)

29,927

CONSORTIUM/CONTRACTUAL COSTS

DIRECT COSTS

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (*Item 7a, Face Page*)

\$ 40,000

CONSORTIUM/CONTRACTUAL COSTS

FACILITIES AND ADMINISTRATIVE COSTS

0

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD

\$ 40,000

## **BUDGET JUSTIFICATION**

### **University of California, San Francisco**

**Salaries:** Pursuant to University of California (UC) policy, salaries in the initial budget period are based on current published UC salary scales and include University mandated range adjustments and merit increases scheduled to occur before the proposed project start date.

**Fringe Benefits:** Fringe benefits are based on campus budget projections, consistent with guidance from the University of California, San Francisco (UCSF) Office of Sponsored Research. Fringe benefits include health and life insurance, social security, Medicare, dental plan, vision, unemployment insurance, non-industrial disability insurance, worker's compensation insurance, and retirement.

## **KEY PERSONNEL**

**Catherine E. Oldenburg, ScD, MPH, Principal Investigator (0.6 calendar months).** For the proposed trial, Dr. Oldenburg will be responsible for the oversight and coordination of the implementation of the trial. This includes functions such as maintaining up-to-date study protocols, obtaining human research approvals from Institutional Review Boards, conducting the training and certification of all study personnel, monitoring study progress, and organizing periodic study monitoring visits.

**Kieran O'Brien, MPH, Co-Investigator (2.4 calendar months, WOS).** Ms. O'Brien is an epidemiologist and doctoral candidate in epidemiology at the Francis I. Proctor Foundation at UCSF and the University of California, Berkeley. She will work closely with Dr. Oldenburg on all aspects of trial design, implementation, and analysis. Ms. O'Brien speaks French and has previously lived and worked in Francophone West Africa.

**J. Daniel Kelly, MD, MPH, Co-Investigator (0.6 calendar months, WOS).** Dr. Kelly is a board-certified infectious diseases physician who will serve as the medical monitor for the trial. Dr. Kelly has previously run treatment programs for acute malnutrition treatment in Sierra Leone, and has worked extensively in Sierra Leone and Liberia on Ebola.

## **MATERIALS AND SUPPLIES**

**Azithromycin (\$500).** Azithromycin oral suspension will be purchased in Niamey, Niger. In Niamey, azithromycin will cost approximately \$5 per dose for each of 100 children randomized to the azithromycin arm.

## **OTHER EXPENSES**

**UCSF Data Network Recharge (\$564):** Effective November 1, 2009 the Chancellor's Executive Committee approved a UCSF data network services recharge. The recharge provides funding for critical equipment in support of the campus network. Effective 7/1/18 - 6/30/19, the funding model for data network service includes a UCSF-wide per capita recharge of \$47/month/FTE.

Per review and agreement by our cognizant federal agency, UCSF data network costs are an allowable direct expense.

**Niger study approvals (\$1,500).** Submission of an application to the Niger ethical committee involves an application submission fee (\$1,000) and presentation costs (\$250), including preparation of the presentation and transportation to the meeting. In addition to approval from the national ethical committee, approval must be obtained from local District and CSI-level leaders, each of which involves organizing a presentation meeting and arranging for refreshments and transportation for all attendees (\$250).

**Study team training (\$4,500).** Training costs include training materials (\$500), room rentals (\$1,400), refreshments (\$100), transportation reimbursements for trainees (\$500), and per diems for trainees (\$2,000).

**Study team transportation (\$2,500).** Transportation costs include transportation for the local Niger investigator and study supervisors to visit each CSI regularly, within initial weekly visits to each CSI for monitoring followed by bi-monthly visits after the first 4 weeks.

**Study team fees (\$20,863).** The study will support, in full or in part, the salaries of 4 study team members to collect data at each site (\$10,243), 8 CSI nurses to administer treatment (\$3,100), community health workers to screen for severe acute malnutrition in the community and monitor follow-up (\$3,500), study supervisors to visit the study teams regularly (\$3,000), and a Niger investigator to provide local oversight of the trial during implementation and monitoring (\$1,020).

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Oldenburg, Catherine Elizabeth

eRA COMMONS USER NAME (credential, e.g., agency login): catherineo

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Carnegie Mellon University, Pittsburgh, PA	B.S.	05/2005	Biological Sciences
Boston University School of Public Health, Boston, MA	M.P.H.	05/2009	International Health; Epidemiology
Harvard T.H. Chan School of Public Health, Boston, MA	Sc.D.	05/2016	Epidemiology
University of California, San Francisco, San Francisco, CA	Postdoctoral Fellowship	06/2017	Infectious Disease Epidemiology; Biostatistics

**A. Personal Statement**

I am an infectious disease epidemiologist and assistant professor in the Departments of Ophthalmology and Epidemiology & Biostatistics at the University of California, San Francisco, and will serve as Principal Investigator on this proposal. My training is in infectious disease epidemiology and global health, and my work specifically focuses on individual and cluster randomized trials of interventions to reduce infectious disease burden and improve survival in children. I currently serve as the Principal Investigator of the National Eye Institute-funded Kebele Elimination of Trachoma for Ocular Health trial, a cluster randomized trial of azithromycin-based strategies for trachoma elimination in Amhara, Ethiopia. I am co-Principal Investigator on three large randomized controlled trial of mass azithromycin distribution for the prevention of child, infant, and neonatal mortality in Nouna, Burkina Faso, funded by the Bill and Melinda Gates Foundation. I am also a co-investigator on the Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance-2 (MORDOR 2) study, a longer-term continuation study of the MORDOR study that demonstrated a reduction in all-cause child mortality following biannual mass azithromycin distribution in Niger. Previously with partners at the Centre de Recherche en Sante de Nouna (CRSN) in Burkina Faso, I served as the Principal Investigator for a pilot randomized controlled trial of the effect of antibiotic distribution on intestinal and nasopharyngeal microbiome and resistome in children aged 6-59 months and short-term growth changes. We are currently processing the swabs that were collected as part of this trial, and expect results to be ready next year. As Principal Investigator on the proposed project, I will apply my training and experience with international studies and infectious disease epidemiology on the design, oversight, and analysis of the study in close collaboration with partners at UCSF and in Niger.

**B. Positions and Honors****Positions and Employment**

2005-2007 Staff Research Associate, University of California, Berkeley  
 2009-2012 Research Coordinator, University of California, San Francisco  
 2012-2015 Graduate Research Assistant, The Fenway Institute, Boston, MA

2017- Assistant Professor, University of California, San Francisco

### **Other Experience and Professional Memberships**

2017 - Member, American Society of Tropical Medicine and Hygiene  
2010 - Member, Society for Clinical Trials  
2012 - Member, American Public Health Association  
2014 - Member, International AIDS Society

### **Honors**

2008 Ken James Travel Scholarship, Boston University School of Public Health  
2014 Distinction, Epidemiologic Methods Doctoral Qualifying Examination  
2014 Travel Scholarship, HIV Research for Prevention Meeting, Cape Town, South Africa  
2015 Teaching Assistant Award, Department of Epidemiology, Harvard School of Public Health  
2016 Young Investigator Scholarship, Conference on Retroviruses and Opportunistic Infections  
2017 NIH Pediatric Loan Repayment Program Awardee, National Eye Institute  
2018 Research to Prevent Blindness Career Development Award

### **C. Contributions to Science**

My full bibliography lists 119 publications in peer-reviewed journals primarily in the field of infectious disease epidemiology and clinical trials. My work focuses on randomized controlled trial and quasi-experimental methods for the evaluation of treatment and prevention interventions for infectious disease globally. Specifically, my current work is focused on infectious diseases of childhood, the intersection between infectious disease burden and nutrition, and its contribution to mortality. My current projects focus on the role of antibiotics for reducing infectious burden and improving survival, including azithromycin for trachoma control in Ethiopia and mortality reduction in Niger and Burkina Faso.

**1. Interventions for child health, including infectious disease and nutrition.** I am currently involved in several studies of antibiotics for child health, including studies of azithromycin for prevention of child mortality in Niger and Burkina Faso, and amoxicillin for severe acute malnutrition in Niger. With colleagues at Harvard and MSF, we demonstrated that malaria infection in children with severe acute malnutrition led to decreased height gain over a 3-month period. With colleagues in Burkina Faso, we demonstrated that increased dietary diversity is significantly associated with improved nutritional status in preschool children and that antibiotics improve short-term weight gain. I am also currently involved in several cluster-randomized trials of azithromycin for trachoma control in Ethiopia and Niger. With colleagues in Niger and UCSF, we demonstrated that expanding azithromycin treatment coverage to 90% from the World Health Organization-recommended 80% did not lead to significantly reduced ocular chlamydia infection in mesoendemic communities. However, an expanded mass azithromycin treatment target reduced ocular chlamydia prevalence more quickly in a biannual treatment strategy targeted only to children. This work has provided important evidence of alternative antibiotic strategies for trachoma control. We have also investigated spillover benefits of mass azithromycin into other infectious diseases, including malaria.

- a. A Sié, C Dah, L Ouermi, C Tapsoba, P Zabre, T Bärnighausen, AM Arzika, E Lebas, BM Snyder, TC Porco, JD Keenan, CE Oldenburg. (2018). Effect of antibiotics on short-term growth among children in Burkina Faso: a randomized trial. *Am J Trop Med Hyg*. 2018 Jul 16. Epub ahead of print.
- b. Oldenburg, C.E., Guerin, P.J., Berthé, F., Grais, R.F., Isanaka, S. Malaria and nutritional status among children with severe acute malnutrition in Niger: a prospective cohort study. *Clin Infect Dis*. 2018 Mar 7. Epub ahead of print.
- c. Oldenburg, C.E., Amza, A., Kadri, B., Nassirou, B., Cotter, S.Y., Stoller, N.E., West, S.K., Bailey, R.L., Porco, T.C., Gaynor, B.D., Keenan, J.D., Lietman, T.M. (2018). Comparison of mass azithromycin coverage targets of children in Niger: A cluster randomized trachoma trial. *Am J Trop Med Hyg*. 98(2):389-395.
- d. Oldenburg, C.E., Amza, A., Kadri, B., Nassirou, B., Cotter, S.Y., Stoller, N.E., West, S.K., Bailey, R.L., Porco, T.C., Keenan, J.D., Lietman, T.M., Gaynor, B.D. (2017). Annual versus biannual mass azithromycin distribution and malaria parasitemia during the peak transmission season among children in Niger. *Pediatr Infect Dis J*. 37(6): 506-510.

- e. Amza, A., Kadri, B., Nassirou, B., Cotter, S.Y., Stoller, N.E., West, S.K., Bailey, R.L., Porco, T.C., Gaynor, B.D., Keenan, J.D., Lietman, T.M., Oldenburg, C.E. (2017). Effectiveness of expanding annual mass azithromycin distribution treatment coverage for trachoma in Niger: A cluster randomized trial. *Br J Ophthalmol.* 102(5): 680-686.

**2. Infectious disease epidemiology.** I have been involved in multiple observational studies the epidemiology of infectious disease. In India, I was involved in studies of antimicrobial resistance in bacterial and fungal keratitis. In these studies, we characterized the relationship between infection with a resistant organism and clinical outcome. Recently, with colleagues at UCSF, I conducted a systematic review of antimicrobial resistance, which demonstrated that

- a. KS O'Brien, PM Emerson, PJ Hooper, AL Reingold, EG Dennis, JD Keenan, TM Lietman, CE Oldenburg. (2018). Antimicrobial resistance following mass azithromycin distribution for trachoma control: a systematic review. *Lancet Infect Dis.* In press.
- b. CE Oldenburg, P Lalitha, M Srinivasan, R Rajaraman, M Ravindran, J Mascarenhas, DS Borkar, KJ Ray, ME Zegans, SD McLeod, TC Porco, TM Lietman, NR Acharya. (2013). Emerging moxifloxacin resistance in *Pseudomonas aeruginosa* keratitis isolates in South India. *Ophthalmic Epidemiology.* 20(3):155-8.
- c. CE Oldenburg, P Lalitha, M Srinivasan, P Manikandan, MJ Bharathi, R Rajaraman, M Ravindran, J Mascarenhas, N Nardone, KJ Ray, DV Glidden, NR Acharya, TM Lietman. (2013). Moxifloxacin susceptibility mediates the relationship between causative organism and clinical outcome in bacterial keratitis. *Invest Ophthalmol Vis Sci.* 54(2): 1522-6.

**3. Antiretroviral and HIV testing prevention strategies for HIV.** My doctoral work focused on antiretroviral therapy (ART)-based HIV prevention strategies, including treatment as prevention (TasP), post-exposure prophylaxis (PEP), and pre-exposure prophylaxis (PrEP), and HIV testing interventions. In rural South Africa, we demonstrated a 77% reduction in HIV acquisition with the introduction of ART into serodiscordant couples in a population-based setting. Using a quasi-experimental study design, we demonstrated that immediate eligibility for ART reduced household-level HIV acquisition by approximately 50%. A randomized controlled trial in Zambia demonstrated that HIV self-testing is acceptable, accessible, and safe for female sex workers, which led to country-level policy adoption related to HIV self-testing.

- a. Oldenburg, C.E., Bor, J., Harling, G., Tanser, F., Mutevedzi, T., Shahmanesh, M., Seage, G.R., De Gruttola, V., Mimiaga, M.J., Mayer, K.H., Pillay, D., Bärnighausen, T. (2018). Impact of early antiretroviral therapy eligibility on HIV acquisition: Household-level evidence from rural South Africa. *AIDS.* Epub ahead of print.
- b. Oldenburg, C.E., Chanda, M.M., Ortblad, K.F., Mwale, M., Chongo, S., Kamungoma, N., Kanchele, C., Fullem, A., Moe, C., Barresi, L.G., Harling, G.D., Bärnighausen, T. (2018). Effect of HIV self-testing on the number of sexual partners among female sex workers in Zambia: A randomized controlled trial. *AIDS.* 32(5): 635-643.
- c. Chanda, M.M., Ortblad, K.F., Mwale, M., Chongo, S., Kanchele, C., Kamungoma, N., Fullem, A., Dunn, C., Barresi, L.G., Harling, G., Bärnighausen, T., Oldenburg, C.E. (2017). HIV self-testing among female sex workers in Zambia: A cluster randomized controlled trial. *PLOS Medicine.* 14(11):e1002442.
- d. Oldenburg, C.E., Bärnighausen, T., Tanser, F., Iwuji, C.C., DeGruttola V., Seage, G.R., Mimiaga, M.J., Mayer, K.H., Pillay, D., Harling G. (2016). Antiretroviral therapy to prevent HIV acquisition in serodiscordant couples in a hyperendemic community in rural South Africa. *Clin Infect Dis.* 63(4), 548-54.

**4. Development of interventions for prevention and treatment of infectious diseases.** I have been involved in the development of interventions for the prevention and treatment of several infectious diseases using quantitative and mixed methods approaches. This work has included mixed methods formative work for the development of a sanitation intervention for trachoma prevention, which is currently being tested in a full-scale cluster randomized trial, as well as the development of HIV prevention interventions in Southeast Asia and the United States.

- a. Aiemjoy, K.A., Stoller, N.E., Gebresillasie, S., Shiferaw, A., Tadesse, Z., Sewent, T., Ayele, B., Chanyalew, M., Aragie, S., Callahan, K., Stewart A., Emerson, P.M., Lietman, T.M., Keenan, J.D.,



- Oldenburg, C.E. (2017). Is using a latrine a “strange thing to do”? A mixed method study of sanitation preference and behaviors in rural Ethiopia. *Am J Trop Med Hyg.* 96(1):65-73.
- b. Oldenburg, C.E., Le, B., Toan, T., Thien, D.D., Huyen, H., Friedman, M.R., Stall, R., Colby, D. (2016). HIV pre-exposure prophylaxis indications and readiness among HIV-uninfected transgender women in Ho Chi Minh City, Vietnam. *AIDS Behav.* 20(Suppl 3):365-370.
  - c. Stack, C., Oldenburg, C.E., Mimiaga, M.J., Krakower, D., Novak, D., Egan, J., Stall, R., Safren, S.A., Mayer, K.H. (2016). Sexual behavior patterns and PrEP dosing preferences in a large sample of North American men who have sex with men. *J Acquir Immune Defic Syndr.* 17(1), 94-101.

### **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/10uMWxtbQpAQp/bibliography/40460551/public/?sort=date&direction=ascending>

### **D. Additional Information: Research Support and/or Scholastic Performance**

#### **Ongoing Research Support**

Research to Prevent Blindness                      Oldenburg (PI)                      07/2018-06/2022  
 Targeted Azithromycin Strategies for Trachoma Elimination in Ethiopia  
 This is a Career Development Award designed to support alternative core group strategies for targeting azithromycin for trachoma control in Ethiopia.  
 Role: Principal Investigator

OPP1187628                      Lietman/Oldenburg/Doan/Keenan (MPIs)                      03/2018-03/2022  
 Bill and Melinda Gates Foundation  
 Azithromycin for the Prevention of Neonatal, Infant, and Child Mortality in Burkina Faso  
 This is a series of three randomized controlled trials designed to evaluate the efficacy of azithromycin for the prevention of child mortality in a rural region of Burkina Faso.  
 Role: Principal Investigator

UG1 EY028088                      Oldenburg & Lietman (MPIs)                      09/2017-06/2022  
 National Eye Institute  
 Kebele Elimination of Trachoma for Ocular Health  
 This cluster randomized trial of targeted azithromycin distribution strategies is designed to establish the effectiveness of targeting core groups for the elimination of trachoma in the presence of annual mass azithromycin distribution in Amhara, Ethiopia.  
 Role: Principal Investigator

OPP 1032340                      Lietman (PI)                      03/2018-03/2020  
 Bill and Melinda Gates Foundation  
 Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance-2 (MORDOR-2)  
 This study is a continuation study of the MORDOR study which demonstrated a significant reduction in all-cause mortality in children under 5. In this study, communities from the original Niger study are re-randomized to continuation versus discontinuation of mass azithromycin distribution, and long-term trends in antimicrobial resistance following azithromycin distribution are evaluated.  
 Role: Co-Investigator

#### **Completed Research Support**

That Man May See                      Oldenburg (PI)                      05/2017-04/2018  
 Efficacy of azithromycin for river blindness control in Liberia  
 This pilot randomized controlled trial is designed to evaluate the efficacy of azithromycin for clearance of *Wolbachia*, an endosymbiotic bacterium required for adult female onchocercal worm fertility.  
 Role: Principal Investigator

International Initiative for Impact Evaluation (3ie)      Bärnighausen (PI)      01/2016-03/2017  
A peer educator-delivered HIV self-testing intervention for female sex workers in Zambian border towns  
This cluster randomized trial is designed to elucidate the efficacy of HIV self-testing through peer educator networks for improving HIV status knowledge and HIV testing coverage among female sex workers in three transit towns in Zambia.  
Role: Co-Investigator

International Initiative for Impact Evaluation (3ie)      Bärnighausen (PI)      01/2016-03/2017  
The causal impact of HIV self-test kits on HIV testing among female sex workers in Kampala, Uganda  
This cluster randomized trial is designed to elucidate the efficacy of HIV self-testing through peer educator networks for improving HIV status knowledge and HIV testing coverage among female sex workers in Kampala, the capital city of Uganda.  
Role: Co-Investigator

T32 DA013911      Flanigan (PI)      07/2014-06/2016  
HIV and other infectious consequences of substance abuse  
Predoctoral training fellowship to support dissertation work in rural South Africa.  
Role: Trainee

T32 AI007535      Seage (PI)      09/2012-06/2014  
Epidemiology of infectious disease and biodefense  
Predoctoral training fellowship to support didactic training and development of dissertation proposal.  
Role: Trainee

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lietman, Thomas Mark

eRA COMMONS USER NAME (credential, e.g., agency login): tlietman

POSITION TITLE: Professor of Ophthalmology, Epidemiology and Biostatistics, UCSF

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Yale College	B.A.	1984	Biophysics & Biochem
Columbia University, Physicians and Surgeons	M.D.	1990	Medicine
Johns Hopkins University, Wilmer Eye Institute	Residency	1991-4	Ophthalmology
UCSF, Francis I. Proctor Foundation	Fellowship	1994-5	Cornea and Uveitis
UCSF, Department of Epidemiology & Biostatistics	Fellowship	1995-7	Mathematical Modeling

**A. Personal Statement**

Our group also has considerable experience with individual and community-randomized trials of trachoma, childhood mortality, and corneal ulcer treatment and prevention. I have served as the Principal Investigator on a number of NIH-funded clinical trials: the Steroids for Corneal Ulcer Trial (SCUT), the two Mycotic Ulcer Treatment Trials (MUTT I and MUTT II), the two Trachoma Amelioration in Northern Amhara studies (TANA and TIRET), and the Village Integrated Eye Worker trial (VIEW, in Nepal). I am multiple PI (with Dr Oldenburg) on the ongoing Ethiopian trachoma trial KITFO. In addition, I was the overall PI on the Bill and Melinda Gates Foundation-funded MORDOR I study and am one of the multiple PI (with Drs Oldenburg, Keenan, and Doan) for the MORDOR II studies (Niger and Burkina Faso). We ran the Niger arm of the BMGF-funded PRET trachoma study (PI Dr. Sheila West, Johns Hopkins), and we have worked on the BMGF-funded Neglected Tropical Disease modeling consortium (PI Deirdre Hollingsworth, Oxford University). I have had the opportunity to be the primary mentor on 5 K23 awards, two of which are still ongoing. Recently, our group has explored big data for infectious disease, including two NEI projects. Our Digital Disease Detection grant is locating pink eye epidemics in the US from web searches, electronic medical records, and social media. Our Forecasting Trachoma grant (multiple PI with Dr Porco) uses several large databases to determine if and when trachoma will be controlled worldwide. We have predicted, monitored, and assessed the clinical implications of antibiotic resistance in NIAID, NEI, and BMFG grants (including PREDICTING RESISTANCE, SCUT, MUTT, TANA, MORDOR).

**B. Positions and Honors**

1997–1998 Assistant Clinical Professor, Dept. of Ophthalmology and the F. I. Proctor Foundation, UCSF  
 1998–2003 Assistant Professor-in-Residence, Dept. of Ophthalmology and Proctor Foundation, UCSF  
 1999–2005 Director, WHO Collaborating Center for the Prevention of Blindness, Proctor Foundation  
 1999–2007 Director, Cornea & External Disease Fellowship Training Program, Proctor Foundation, UCSF  
 2003–2008 Associate Professor-in-Residence, Depts of Ophthalmology, Epidemiol and Biostats, UCSF  
 2008- Director, Proctor International Center  
 2009- Associate Director, F.I. Proctor Foundation  
 2009- Professor-in-Residence, Departments of Ophthalmology, Epidemiol and Biostats, UCSF  
 2012- Professor, Departments of Ophthalmology, Epidemiology and Biostatistics, UCSF  
 2014- Director, Francis I Proctor Foundation

## **Awards & Honors**

1987–1989	Howard Hughes Medical Institute – NIH Research Scholars Program Fellowship
1993	Herman K. Goldberg Research Award (Wilmer Eye Institute)
1994–1995	Heed Ophthalmic Fellowship
1997	NIH/NIAID Physician Scientist Award
2000	Research to Prevent Blindness, Career Development Award
2007	Mentor of the Year award, Global Health Sciences, UCSF
2007	Halie Debas Teaching Academy award
2009	Medaille d'Or du Trachoma, IOAT

## **C. Contributions to Science**

**1. Repeated mass antibiotic distributions for trachoma.** Trachoma control programs rely in large part on oral azithromycin. Our group proved in a community-randomized trial that a single mass distribution significantly lowered community prevalence of infection compared to no (delayed) treatment. Our early mathematical models suggested that repeated distributions with an imperfect antibiotic could still lead to elimination, but might require biannual distributions. In Ethiopia, we demonstrated that elimination was feasible w/ repeated treatments, and compared biannual versus biannual distributions. Our mathematical models suggested that infection could be completely eliminated while targeting only children. Trials in Ethiopia confirmed that infection decreased even in those who themselves had not received treatment, indicating a herd-like effect of repeated distributions. My role was to acquire funding and to design, analyze, and write (or co-write) each of the reports below.

- a. Lietman T, Porco T, Dawson C, Blower S. Global elimination of trachoma: how frequently should we administer mass chemotherapy? *Nature Medicine* 1999; 5(5): 572-6.
- b. Chidambaram JD, Alemayehu W, Melese M, Lakew T, Yi E, House J, Cevallos V, Zhou Z, Maxey K, Lee DC, Shapiro BL, Srinivasan M, Porco T, Whitcher JP, Gaynor BD, Lietman TM. Effect of a single mass antibiotic distribution on the prevalence of infectious trachoma. *JAMA* 2006; 295(10): 1142-6.
- c. Melese M, Alemayehu W, Lakew T, Yi E, House J, Chidambaram JD, Zhou Z, Cevallos V, Ray K, Hong KC, Porco TC, Phan I, Zaidi A, Gaynor BD, Whitcher JP, Lietman TM. Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma. *Jama* 2008; 299(7): 778-84.
- d. House JI, Ayele B, Porco TC, Zhou Z, Hong KC, Gebre T, Ray KJ, Keenan JD, Stoller NE, Whitcher JP, Gaynor BD, Emerson PM, Lietman TM. Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomised trial. *Lancet* 2009; 373(9669): 1111-8.

**2. Effects of mass azithromycin on childhood mortality and antibiotic resistance.** Mass oral azithromycin distributions may have collateral effects beyond trachoma control. Our studies in Nepal, Ethiopia, and Niger suggested possible beneficial effects on malaria and growth, as well as selection for macrolide-resistant strains of *Streptococcus pneumoniae*. The NEI-funded TANA trachoma trial in Ethiopia found that childhood mortality was significantly lower in communities randomized to azithromycin treatment as opposed to delayed treatment. Our recent BMGF-funded *large simple trial* MORDOR proved that biannual distributions of oral azithromycin in Niger, Tanzania, and Malawi reduced 1-59 month mortality by 14% compared to placebo. Mortality was most reduced 18% in Niger, and 25% overall in the 1-5-month age group. Follow-up studies demonstrated that macrolide resistance decreased substantially after treatments were discontinued. Several studies from our group have found that repeated mass oral azithromycin distributions increased the prevalence of macrolide resistance in nasopharyngeal pneumococcus. We could find no such increase in resistance to other classes of antibiotics. Antibiotic resistance decreased after mass distributions were continued. My role was to acquire funding and to design, co-analyze, and co-write each of the reports below.

- a. Keenan JD, Bailey RL, West SK, Arzika AM, Hart J, Weaver J, Kalua K, Mrango Z, Ray KJ, Cook C, Lebas E, O'Brien KS, Emerson PM, Porco TC, Lietman TM, Group MS. Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. *N Engl J Med*. 2018;378(17):1583-92.

- b. Porco TC, Gebre T, Ayele B, House J, Keenan J, Zhou Z, Hong KC, Stoller N, Ray KJ, Emerson P, Gaynor BD, Lietman TM. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. *Jama* 2009; 302(9): 962-8.
- c. Skalet AH, Cevallos V, Ayele B, Gebre T, Zhou Z, Jorgensen JH, Zerihun M, Habte D, Assefa Y, Emerson PM, Gaynor BD, Porco TC, Lietman TM, Keenan JD. Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae*: a cluster-randomized clinical trial. *PLoS Med* 2010; 7(12): e1000377.
- d. Haug S, Lakew T, Habtemariam G, Alemayehu W, Cevallos V, Zhou Z, House J, Ray K, Porco T, Rutar T, Keenan J, Lietman TM, Gaynor BD. The decline of pneumococcal resistance after cessation of mass antibiotic distributions for trachoma. *Clin Infect Dis* 2010; 51(5): 571-4.

### 3. Infectious corneal ulcer treatment and the importance of antimicrobial resistance.

Immunosuppression for bacterial corneal ulcers has been controversial since steroids were introduced in the 1950s. In a large NEI-funded RCT that was a UCSF-Aravind-Dartmouth collaboration (SCUT), we demonstrated that overall, steroids did not make much of a difference, but that in non-*Nocardia* cases and severe cases, steroids were beneficial. Steroids were particularly beneficial if given earlier in the course of infection. In a separate collaboration with Aravind, we showed that *in vitro*, fungal isolates from ulcers were more susceptible to voriconazole than natamycin. In MUTT, a large NEI-funded RCT with Aravind, we proved that this was not true *in vivo*. Topical natamycin was clearly superior to topical voriconazole. MUTT II found no benefit to the addition of oral voriconazole to topical antifungal therapy. Antibiotic resistance was found to correlate with outcome in both bacterial (SCUT) and fungal (MUTT) trials. My role was to acquire funding and to design, co-analyze, and write (or supervise) each of the reports below.

- a. Srinivasan M, Mascarenhas J, Rajaraman R, Ravindran M, Lalitha P, Glidden DV, Ray KJ, Hong KC, Oldenburg CE, Lee SM, Zegans ME, McLeod SD, Lietman TM, Acharya NR. Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT). *Arch Ophthalmol* 2012; 130(2): 143-50.
- b. Lalitha P, Prajna NV, Oldenburg CE, Srinivasan M, Krishnan T, Mascarenhas J, Vaitilingam CM, McLeod SD, Zegans ME, Porco TC, Acharya NR, Lietman TM. Organism, Minimum Inhibitory Concentration, and Outcome in a Fungal Corneal Ulcer Clinical Trial. *Cornea* 2012.
- c. Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, Raghavan A, Oldenburg CE, Ray KJ, Zegans ME, McLeod SD, Porco TC, Acharya NR, Lietman TM. The Mycotic Ulcer Treatment Trial: A Randomized Trial Comparing Natamycin vs Voriconazole. *Arch Ophthalmol* 2012: 1-8.
- d. Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): A Randomized Clinical Trial. Prajna NV, Krishnan T, Rajaraman R, Patel S, Srinivasan M, Das M, Ray KJ, O'Brien KS, Oldenburg CE, McLeod SD, Zegans ME, Porco TC, Acharya NR, Lietman TM, Rose-Nussbaumer J; Mycotic Ulcer Treatment Trial II Group. *JAMA Ophthalmol*. 2016 Dec 1;134(12):1365-1372.

### 4. Mathematical modeling of infectious disease transmission. Many of our community-randomized trachoma trials have been designed from modeling results. We demonstrated that periodic mass azithromycin treatments could eventually eliminate infectious trachoma, even without complete coverage. We estimated that biannual distributions might be required in severely affected areas (tested in TEF, TANA, and TIRET). Models predicted that children alone form a core group, and frequent targeting of this age group could lead to eventual elimination (tested in TIRET and PRET-Niger). Models also led to the hypothesis that those infected before programs started could form a core group, or those remaining infected after years of treatment could form a residual core group given the continued presence of annual distributions (tested in SWIFT and KITFO, modeling manuscript submitted). Mathematical analysis of TANA results suggested that infection would return to communities after being brought to a low level, although the return might be a little slower the lower the level of return. My role was to acquire funding and to design, analyze, and write each of the reports below.

- a. Lietman T, Porco T, Dawson C, Blower S. Global elimination of trachoma: how frequently should we administer mass chemotherapy? *Nature Medicine*. 1999;5(5):572-6.
- b. Melese M, Chidambaram JD, Alemayehu W, Lee DC, Yi EH, Cevallos V, Zhou Z, Donnellan C, Saidel M, Whitcher JP, Gaynor BD, Lietman TM. Feasibility of eliminating ocular Chlamydia trachomatis with repeat mass antibiotic treatments. *JAMA*. 2004;292(6):721-5.

- c. Lietman TM, Gebre T, Ayele B, Ray KJ, Maher MC, See CW, Emerson PM, Porco TC. The epidemiological dynamics of infectious trachoma may facilitate elimination. *Epidemics*. 2011;3(2):119-24.
- d. Ray KJ, Lietman TM, Porco TC, Keenan JD, Bailey RL, Solomon AW, Burton MJ, Harding-Esch E, Holland MJ, Mabey D. When can antibiotic treatments for trachoma be discontinued? Graduating communities in three african countries. *PLoS Negl Trop Dis*. 2009;3(6):e458.

**5. Big data and forecasting.** We have concentrated on finding epidemics and forecasting future disease from large databases, including google searches, twitter feeds, the world's trachoma data from the International Trachoma Initiative and Global Trachoma Mapping Program, and large leprosy surveys. We have shown that while short term forecasts of trachoma in individual communities or districts is difficult, the overall distribution of prevalence across communities or districts is predictable. In leprosy, we have confirmed that an exponential distribution of prevalence across geographical units is consistent with disease control. My role was to acquire funding and to design, analyze, and write (or co-write or supervise) each of the reports below.

- a. Deiner M, Lietman T, McLeod S, Chodosh J, Porco T. Eye Disease Surveillance Tools Emerging from Search and Social Media Data: A Study of Temporal Patterns of Conjunctivitis. *JAMA Ophthalmol*. 2016 Sep 1;134(9):1024-30.
- b. Liu F, Porco TC, Amza A, Kadri B, Nassirou B, West SK, Bailey RL, Keenan JD, Solomon AW, Emerson PM, Gambhir M, Lietman TM. Short-term Forecasting of the Prevalence of Trachoma: Expert Opinion, Statistical Regression, versus Transmission Models. *PLoS Negl Trop Dis*. 2015 Aug 24;9(8)
- c. Rahman SA, West SK, Mkocho H, Munoz B, Porco TC, Keenan JD, Lietman TM. The distribution of ocular Chlamydia prevalence across Tanzanian communities where trachoma is declining. *PLoS Negl Trop Dis*. 2015;9(3):e0003682.
- d. Lietman TM, Worden L, Liu F, Porco TC. The distribution of district-level leprosy incidence in India is geometric-stable, consistent with subcriticality. *Epidemics*. 2018, *in press*.

#### **D. Additional Information: Research Support and/or Scholastic Performance**

##### **Ongoing Research Support**

R01 EY024608	NIH-NEI	Lietman (PI)	02/01/2016-01/31/2020
Digital Detection of Infectious Eye Epidemics			
Mathematical modeling using big data for detection of conjunctivitis epidemics			
Role: Principal Investigator			
R01 EY025350	NIH-NEI	Lietman, Porco (MPI)	05/01/2016-04/30/2020
Forecasting Trachoma Control			
Mathematical modeling and prediction of trachoma epidemics			
Role: Principal Investigator			
UG1 EY028088	NIH-NEI	Oldenburg, Lietman (MPI)	09/30/2017-06/30/2022
Kebele Elimination of Trachoma for Ocular Health(MPIs)			
Targeting a residual core group to eliminate trachoma			
Role: Multiple Principal Investigator			
U10 EY022880	NIH-NEI	Lietman (PI)	09/30/2013-08/31/2019
Village Integrated Eye Workers trial			
A cluster-randomized trial of corneal ulcer prevention			
Role: Principal Investigator			
MORDOR II-Niger	BMGF	Lietman and Keenan (MPI)	01/01/2018-12/31/2019
Bill and Melinda Gates Foundation			
Continuation of MORDOR I in Niger for 2 additional years, allowing 4-years of resistance monitoring			

Role: Principal Investigator

MORDOR II-Burkina BMGF Lietman (MPI) 01/01/2018-12/31/2022  
Keenan, Oldenburg, Doan

Bill and Melinda Gates Foundation

3 trials to assess mass oral azithromycin distributions for neonatal, infant, and childhood mortality, monitoring for macrolide resistance in the nasopharynx and stool

Role: Principal Investigator

University of Warwick Subcontract Porco & Lietman (MPI) 10/23/2014-12/31/2019

Bill & Melinda Gates Foundation, Novartis Foundation, Task Force for Global Health

Neglected Tropical Diseases (NTD) Modeling Consortium

Mathematical modeling for 9 infectious diseases through a network of collaborations with epidemiologists, policy makers, and field experts. Our UCSF effort focuses on trachoma, leprosy, and onchocerciasis

**Completed Research Support (within past 3 years)**

MORDOR I BMGF Lietman (PI) 01/01/2013-12/31/2017

*Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance*

Bill and Melinda Gates Foundation

Multi-country trial to assess mass oral azithromycin distributions for post-neonatal childhood mortality, monitoring for macrolide resistance

Role: Principal Investigator

U10 EY018573 NIH-NEI Lietman & Acharya (PIs) 09/30/2009-08/31/2016\*

Mycotic Ulcer Treatment Trials

Two RCTs assessing treatments for fungal keratitis, and the relationship between resistance and outcome

Role: Principal Investigator

\*NCE period

U10 EY016214 NIH-NEI Lietman (PI) 09/30/2004-08/31/2015

Eliminating Trachoma with Repeat Mass Drug Treatment

A set of community-randomized trachoma trials, monitoring for pneumococcal resistance

Role: Principal Investigator

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: O'Brien, Kieran Sunanda

eRA COMMONS USER NAME (credential, e.g., agency login): OBRIENKIERAN

POSITION TITLE: Co-investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan, Ann Arbor	BA	04/2008	International Development
University of Michigan, Ann Arbor	MPH	04/2012	Epidemiology
University of California, Berkeley	PhD (in progress)	04/2019 (expected)	Epidemiology

**A. Personal Statement**

Our research team has experience with randomized controlled trials examining trachoma, mass azithromycin distributions, and the prevention and treatment of infectious keratitis in Niger, Ethiopia, India, Nepal, and the United States. I have served as a study coordinator on four NEI-funded projects: a clinical trials preparation grant for the Parasitic Ulcer Treatment Trial (PUTT), the two Mycotic Ulcer Treatment Trials (MUTT I and MUTT II), and the current Village Integrated Eye Worker trial (VIEW). In addition, I have worked on the Bill & Melinda Gates-funded MORDOR trial comparing the effect mass azithromycin to placebo on childhood mortality. I have experience designing and implementing both individual- and community-randomized trials in a variety of international settings.

**B. Positions and Honors****Positions and Employment**

2007-2010	Research Assistant, Department of Political Science, University of Michigan, Ann Arbor
2010-2012	Research Assistant, Department of Epidemiology, University of Michigan, Ann Arbor
2011-2012	Researcher, Department of Epidemiology, University of Michigan, Ann Arbor
2012-	Research Coordinator, Francis I. Proctor Foundation, University of California, San Francisco

**Honors**

2004-2008	University Honors
2010-2012	Dean's Award Scholarship

**C. Contribution to Science**

1. I have been involved in three NEI-funded individual randomized trials examining treatment of infectious keratitis, in both bacterial and fungal ulcers. The Steroids for Corneal Ulcers Trial (SCUT) examined the effect of adjunctive corticosteroids on clinical outcomes in bacterial ulcers. The Mycotic Ulcer Treatment Trial I (MUTT I) compared topical natamycin to topical voriconazole in the treatment of fungal corneal ulcers, and the Mycotic Ulcer Treatment Trial II (MUTT II) determined the effect of the addition of oral voriconazole to topical treatment on the rate of perforation in severe fungal keratitis.



- a. **O'Brien KS**, Byanju R, Kandel RP, Poudyal B, Gautam M, Gonzales JA, Porco TC, Whitcher JP, Srinivasan M, Upadhyay M, Lietman TM, Keenan JD; Village-Integrated Eye Worker Trial Group. Village-Integrated Eye Worker trial (VIEW): rationale and design of a cluster-randomized trial to prevent corneal ulcers in resource-limited settings. *BMJ Open*. 2018 Aug;8(8): e021556.
  - b. Srinivasan M, Mascarenhas J, Rajaraman R, Ravindran M, Lalitha P, **O'Brien KS**, Glidden DV, Ray KJ, Oldenburg CE, Zegans ME, Whitcher JP, McLeod SD, Porco TC, Lietman TM, Acharya NR. The steroids for corneal ulcers trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. *Am J Ophthalmol*. 2014 Feb;157(2):327-333.e3.
  - c. McClintic SM, Prajna NV, Srinivasan M, Mascarenhas J, Lalitha P, Rajaraman R, Oldenburg CE, **O'Brien KS**, Ray KJ, Acharya NR, Lietman TM, Keenan JD. Visual outcomes in treated bacterial keratitis: four years of prospective follow-up. *Invest Ophthalmol Vis Sci*. 2014 May;55(5):2935-40.
  - d. Rose-Nussbaumer J, Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Srinivasan M, Raghavan A, Oldenburg CE, **O'Brien KS**, Ray KJ, McLeod SD, Porco TC, Lietman TM, Acharya NR, Keenan JD. Vision-related quality-of-life outcomes in the Mycotic Ulcer Treatment Trial I: a randomized clinical trial. *JAMA Ophthalmol*. 2015 Jun;133(6):642-6.
  - e. Rose-Nussbaumer J, Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Srinivasan M, Raghavan A, Oldenburg CE, **O'Brien KS**, Ray KJ, McLeod SD, Acharya NR, Keenan JD, Lietman TM. Risk factors for low vision-related functioning in the Mycotic Ulcer Treatment Trial: a randomized trial comparing natamycin to voriconazole. *Br J Ophthalmol*. 2015 Nov. [Epub ahead of print]
2. My work has also involved cluster-randomized trials for trachoma and the role of the mass distribution of antibiotics in reducing childhood mortality.
    - a. **KS O'Brien**, PM Emerson, PJ Hooper, AL Reingold, EG Dennis, JD Keenan, TM Lietman, CE Oldenburg. (2018). Antimicrobial resistance following mass azithromycin distribution for trachoma control: a systematic review. *Lancet Infect Dis*. In press.
    - b. **O'Brien KS**, Amza A, Kadri B, Nassirou B, Cotter SY, Stoller NE, West SK, Bailey RL, Porco TC, Gaynor BD, Lietman TM, Oldenburg CE. Anthropometry and malaria among children in Niger: A cross-sectional study. *Am J Trop Med Hyg*. 2018 Sep;99(3):665-669.
    - c. Keenan, JD, Bailey, RL, West, SK, Arzika, AM, Hart, J, Weaver J, Kalua K, Mrango Z, Ray KJ, Cook C, Lebas E, **O'Brien KS**, Emerson, PM, Porco, TC, Lietman, TM; MORDOR Study Group. Azithromycin to reduce childhood mortality in sub-Saharan Africa. *N Engl J Med*. 2018 Apr;378(17): 1583-1592.
    - d. **O'Brien KS**, Cotter SY, Amza A, Kadri B, Nassirou B, Stoller NE, Zhou Z, West SK, Bailey RL, Keenan JD, Porco TC, Lietman TM. Childhood mortality after mass azithromycin distribution: a secondary analysis of the PRET cluster-randomized trial in Niger. *Pediatr Infect Dis J*. 2018 March 14. Epub ahead of print.
    - e. **O'Brien KS**, Blumberg S, Enanoria WT, Ackley S, Sippl-Swezey N, Lietman TM. Antibiotic use as a tragedy of the commons: a cross-sectional survey. *Comput Math Methods Med*. 2014;837929.
  3. I have also made contributions in cancer epidemiology. Specifically, I have conducted research aimed to determine the career development needs of early stage investigators working in cancer. In Ghana, I studied the role of traditional healers in cancer management and their interaction with the health care system. I also conducted research designed to enhance an incipient cancer registration system at a cancer referral hospital in Ghana.
    - a. Soliman AS, Mullan PB, **O'Brien KS**, Thaivalappil S, Chamberlain RM. Career development needs assessment in cancer prevention and control: focus on research in minority and international settings. *J Cancer Educ*. 2011 Sep;26(3):409-19
    - b. **O'Brien KS**, Soliman AS, Annan K, Lartey RN, Awuah B, Merajver SD. Traditional herbalists and cancer management in Kumasi, Ghana. *J Cancer Educ*. 2012 Jun;27(3):573-9.
    - c. **O'Brien KS**, Soliman AS, Awuah B, Jiggae E, Osei-Bonsu E, Quayson S, Adjei E, Thaivalappil SS, Abantanga F, Merajver SD. Establishing effective registration systems in resource-limited settings: cancer registration in Kumasi, Ghana. *J Registry Manag*. 2013 Summer;40(2):70-7.

## **Complete List of Published Work in My Bibliography**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1zkj2aZfgniQz/bibliography/50459692/public/?sort=date&direction=ascending>

### **D. Research Support**

U10EY018573

NIH-NEI

Lietman & Acharya (PIs) 9/30/09-8/31/14

Mycotic Ulcer Treatment Trial

An individual-randomized controlled trial to assess treatments for fungal keratitis

Role: Study Coordinator

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: J. Daniel Kelly

eRA COMMONS USER NAME (credential, e.g., agency login): DANAFRICA7

POSITION TITLE: Clinical Fellow, Division of Infectious Diseases, Department of Medicine, UCSF

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	06/2003	Chemistry
Albert Einstein College of Medicine, Bronx, NY	MD	06/2008	Medicine
Baylor College of Medicine, Houston, TX	Residency	06/2011	Internal Medicine
University of California, Berkeley, CA	MPH	06/2016	Epidemiology
Gorgas Memorial Institute	DTMH	03/2017	Tropical Medicine
University of California, San Francisco, CA	Post-doc	02/2018	Prevention Science
University of California, San Francisco, CA	Fellowship		Infectious Diseases

### A. Personal Statement

In this R01 proposal, I will be serve the role of co-investigator to provide expertise in clinical infectious diseases and antimicrobial resistance. Although I have worked with the study team on issues of antibiotic consumption and resistance, my research primarily focuses on the epidemiology and natural history of Ebola virus disease (EVD) with a particular emphasis on unrecognized Ebola virus infection. Prior to the 2013-2016 West Africa outbreak, I studied the social epidemiology of HIV and structural barriers to care in Sierra Leone. This research evolved from Wellbody Alliance, a health delivery non-profit organization in Sierra Leone that I co-founded in 2006. In August of 2014, I took a one-year leave of absence with the support of University of California, San Francisco (UCSF) to engage in the Ebola response. Over the course of the outbreak, I established an Ebola response coalition with Partners In Health, educated healthcare workers on infection prevention and control, cared for EVD patients, and co-led studies of Ebola virus diagnostics. After the outbreak, I returned to Sierra Leone to study the seroepidemiology of Ebola-affected communities in Kono District, where I had worked during the Ebola response. In 2016, I joined the U.S.-Liberian Partnership for Research on Ebola Virus (PREVAIL), the 5-year natural history of EVD survivors and close contacts, with the mentorship at UCSF and NIAID/NIH. I investigate cohorts of EVD survivors and their close contacts connected to Ebola outbreaks in Liberia, Sierra Leone, and Democratic Republic of Congo.

### B. Positions and Honors

#### Positions and Employment

07/08-06/11	Internal Medicine Resident, Baylor College of Medicine, Houston, TX
07/11-07/13	Instructor, Division of General Internal Medicine, Baylor College of Medicine, Houston, TX
07/11-07/13	Visiting Lecturer, Department of Medicine, College of Medicine and Allied Health Sciences, Freetown, Sierra Leone
07/13-09/14	Infectious Diseases Fellow, University of California, San Francisco, San Francisco, CA
07/14-11/14	Preventive Science Fellow, University of California, San Francisco, San Francisco, CA
09/14-08/15	Ebola Response, Partners In Health/Wellbody Alliance, Sierra Leone
04/15-07/15	Visiting Research Physician, Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA
08/15-02/18	Prevention Studies Fellow, University of California, San Francisco, San Francisco, CA
10/15-	Infectious Diseases Fellow, University of California, San Francisco, San Francisco, CA
08/17-	Research Associate, F.I. Proctor Foundation, San Francisco, CA

#### Other Experience and Professional Memberships

2006-2014	Wellbody Alliance, Executive Director
2013-2015	Wellbody Alliance, Strategic Advisor
2011-2014	Member, American College of Physicians
2014-2015	Wellbody Alliance/Partners In Health, Ebola Response
2015-2018	Peer Reviewer, Fulbright Commission for African Regional Research
2014-	Member, Infectious Disease Society of America

### **Honors**

2008, Albert S. Kuperman Award for Field Work in Global Health, Albert Einstein College of Medicine  
 2008, Velji Global Health Project of the Year Award, Global Health Education Consortium  
 2008, Point of Light Award, Yeshiva University  
 2009, Tiger Award, Princeton University  
 2008, Humanitarian Award, Fullah Progressive Union of Sierra Leone,  
 2011, Fulbright Scholarship, U.S. Congress  
 2015, St. Augustine Alumni Award, Malvern Preparatory School  
 2015, Clinton Global Citizen Award, The Clinton Foundation (recipient: Wellbody Alliance)  
 2015, Global Food Initiative Award, University of California, Office of the President  
 2016, Sidney MacDonald Russell Family Graduate Award, University of California, Berkeley  
 2016, Loan Repayment Program Award, NIH/NIAID  
 2018, Loan Repayment Program Award, NIH/NIAID

### **C. Contribution to Science**

**1. Epidemiology and natural history of Ebola virus infection.** I was one of the first investigators to document the seroprevalence of asymptomatic and minimally symptomatic infections during the West Africa Ebola outbreak. As an extension of this work, I was the first to describe an Ebola virus transmission chain and identify risk factors, inclusive of asymptomatic Ebola virus infections. This work contributed to re-defining Ebola survivorship. I have published and presented additional papers contributing to insights on Ebola virus transmission and the natural history of survivorship.

- **Kelly JD**, Hoff NA, Spencer D, Musene K, Bramble MS, McIlwain D, Okitundu D, Porco TC, Rutherford GW, Glymour MM, Bjornson Z, Mukadi P, Okitolonda-Wemakoy E, Nolan GP, Muyembe-Tamfum JJ, Rimoin AW. Neurological, cognitive, and psychological findings among survivors of Ebola virus disease from the 1995 Ebola outbreak in Kikwit, Democratic Republic of Congo: a cross-sectional study. *Clin Infect Dis*. 2018 Aug 10. doi: 10.1093/cid/ciy677. PMID: 30107392.
- **Kelly JD**, Barrie MB, Mesman AW, Karku S, Quiwa K, Drasher M, Slough GW, Dierberg K, Koedoyoma S, Lindan CP, Jones JH, Chamie G, Worden L, Greenhouse B, Weiser SD, Porco TC, Rutherford GW, Richardson ET. Anatomy of a hotspot: chain and seroepidemiology of Ebola virus transmission, Sukudu, Sierra Leone, 2015-16. *J Infect Dis*. 2018 Jan 9. Doi: 10.1093/infdis/jiy004. PMID: 29325149.
- **Kelly JD**, Richardson ET, Drasher M, Barrie MB, Karku S, Kamara M, Hann K, Dierberg K, Hubbard A, Lindan CP, Farmer PE, Rutherford GW, Weiser SD. Food insecurity as a risk factor for outcomes related to Ebola virus disease in Kono District, Sierra Leone: a cross-sectional study. *Am J Trop Med Hyg*. 2018 May;98(5):1484-1488. doi: 10.4269/ajtmh.17-0820. PMID: 29557329.
- Richardson ET, **Kelly JD**, Sesay O, Drasher MD, Desai IK, Frankfurter R, Farmer PE, Barrie MB. The symbolic violence of 'outbreak': A mixed methods, quasi-experimental impact evaluation of social protection on Ebola survivor wellbeing. *Soc Sci Med*. 2017 Dec;195:77-82. Doi: 10.1016/j.socscimed.2017.11.018. PMID: 29156248.

**2. Ebola virus diagnostics.** At the beginning of the West Africa Ebola outbreak, there were no point-of-care diagnostics available for clinical use. Since then, I have published and presented three field validation studies of Ebola virus diagnostics, including a lateral flow assay, an automated molecular diagnostic assay, and an EIA to describe their contribution to controlling the Ebola outbreak and advocating for use in future outbreaks.

- Broadhurst MJ, **Kelly JD**, Miller A, Semper A, Simpson A, Brooks T, Bailey D, Hula S, Nyoni W, Gropelli E, Sankoh A, Kanu S, Jalloh A, Ton Q, Sarchet N, George P, Perkins MD, Wonderly B, Murray M, Pollock NR. ReEBOV antigen rapid test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study. *Lancet*. 2015 Aug 29;386(9996):864-74. PMID: 26119838.

- Richardson ET, **Kelly JD**, Barrie MB, Mesman AW, Karku S, Quiwa K, Rutherford GW, Jones JH, Murray MB, Farmer PE. Minimally symptomatic infection in an Ebola 'hotspot': a cross-sectional serosurvey. *PLoS Negl Trop Dis*. 2016 Nov;10(11):e0005087. PMID: 27846221. PMCID: PMC5112953.
- Semper AE, Broadhurst MJ, Richards J, Foster GM, Simpson AJ, Logue CH, **Kelly JD**, Miller A, Brooks TJ, Murray M, Pollack NR. Performance of the GeneXpert Ebola assay for diagnosis of Ebola virus disease in Sierra Leone: a field evaluation study. *PLoS Medicine*. 2016 Mar 29;13(3):e1001980. Doi: 10.1371/journal.pmed.1001980. PMID: 27023868. PMCID: PMC4811569.
- **Kelly JD**. Make diagnostic centres a priority for Ebola crisis. *Nature*. 2014 Sep 11;513(7517):145. PMID: 25209763.

**3. Social epidemiology of HIV.** I published several studies identifying how stigma, social support, and homelessness were associated with poor health outcomes. These findings provide targets for interventions that may improve access to HIV care.

- **Kelly JD**, Reid MJ, Lahiff M, Tsai AC, Weiser SD. Community-Level HIV Stigma as a Driver for HIV Transmission Risk Behaviors and Sexually Transmitted Diseases in Sierra Leone: A Population-Based Study. *JAIDS*. 2017 Aug;75(4):399-407. PMID: 28406807.
- **Kelly JD**, Weiser SD, Tsai AC. Proximate context of HIV stigma and its association with HIV testing in Sierra Leone: a population-based study. *AIDS Behav*. 2016 Jan;20(1):65-70. PMID: 25771909. PMCID: PMC4570874.
- **Kelly JD**, Cohen J, Grimes B, Philip SS, Weiser SD, Riley ED. High rates of Herpes simplex virus type 2 infection in homeless women: informing public health strategies. *J Womens Health (Larchmt)*. 2016 Aug;25(8):840-5. PMID: 27243474.
- **Kelly JD**, Hartman C, Graham J, Kallen MA, Giordano TP. Social support as a predictor of success with the steps of HIV care in people newly diagnosed with HIV infection. *JANAC*. 2014 Sept-Oct;25(5):405-13. PMID: 24508174. PMCID: PMC4125558.

**4. HIV retention and adherence.** In Sierra Leone, I was the first investigator to validate the self-report adherence measure used by the Ministry of Health. I expanded this work to include HIV retention in care and was the first investigator to report the cascade of HIV care and lost to follow-up rates in Sierra Leone.

- **Kelly JD**, Hickey MD, Schlough GW, Conteh S, Sesay M, Rutherford GW, Giordano TP, Weiser SD. Understanding why HIV-infected persons disengaged from pre-ART care in Freetown, Sierra Leone: a qualitative study. *AIDS Care*. 2018 Aug 26;1-4. doi: 10.1080/09540121.2018.1515467. PMID: 30146898.
- **Kelly JD**, Schlough GW, Conteh S, Barrie MB, Kargbo B, Giordano TP. The majority of the pre-antiretroviral population who were lost to follow-up stopped their care in Freetown, Sierra Leone: a 12-month prospective cohort study starting with HIV diagnosis. *PLoS One*. 2016; 11(2):e0149584. PMID: 26901765.
- **Kelly JD**, Hubenthal EA, Empson SF, Lurton G, Barrie MB, Kargbo B, Giordano TP. Multiple self-report measures of antiretroviral adherence correlated in Sierra Leone, but did they agree? *Int J STD AIDS*. 2013 Dec;24(12):931-7. PMID: 23970613.

#### List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48331703/?sort=date&direction=descending>

#### D. Research Support

##### Ongoing Research Support

##### UCSF Global Health Sciences grant (Kelly, PI)

08/2015-07/2019

A cross-sectional seroprevalence and risk factor study of Ebola-infected persons as compared with uninfected persons in hotspots (high prevalence geographic areas) of the 2014-2015 Ebola epidemic of Sierra Leone  
-To determine asymptomatic Ebola infections rates and associated risk factors

##### UCSF Resources Allocation Program (Lietman, PI)

01/2018-12/2018

Assessing long-term ocular sequelae of Ebola virus disease survivors in Kikwit, Democratic Republic of Congo, using mobile devices

-To identify the long-term ocular sequelae of Ebola survivors in the DRC

## **Completed Research Support**

### **Wellbody Alliance (Kelly, co-PI)**

**2009-2011**

Validation of multiple self-reported measures of HIV treatment adherence in Sierra Leone  
-To determine the performance of self-reported adherence measures in this local setting

### **Fulbright Scholarship (Kelly, PI)**

**2011-2013**

Prospective study of newly diagnosed persons with HIV infection in Freetown, Sierra Leone  
-To map the cascade of HIV care and ascertain tracing outcomes of those lost to follow-up

### **Baylor College of Medicine Center for Globalization Grant (Kelly, PI)**

**2012-2013**

Text message reminders prior to HIV clinic appointments in rural Sierra Leone: a randomized controlled trial.  
-To determine the impact of text message reminders for improving HIV clinic attendance (retention in care).

### **World Health Organization TB REACH Grant (Kelly, PI)**

**2013-2014**

Contact tracing and a community-based tuberculosis program to strengthen case detection in a district with limited access to care in Sierra Leone  
-To identify additional cases of tuberculosis and improve time to diagnosis and treatment.

### **Abundance Foundation (Kelly, Co-I)**

**2014-2015**

Innovative Ebola diagnostic field testing and validation for a lateral flow antigen assay and automated molecular diagnostic assay in Sierra Leone  
-To validate the ReBOV lateral flow assay and Cepheid Ebola PCR assay

### **UC Berkeley Center for Emerging and Neglected Diseases (Kelly, PI)**

**2016-2017**

Building laboratory capacity to improve Ebola science  
-To develop a biobank in Kono District, Sierra Leone, related to Ebola research projects

### **UC Office of President Global Food Initiative (Kelly, PI)**

**08/2015-07/2018**

A pilot study of food insecurity on Ebola clinical outcomes in Sierra Leone  
-To explore the relationship between food insecurity and Ebola-related issues in a village hotspot

### **Fogarty International Center (Kelly, Co-I)**

**07/2017-07/2018**

-To develop a Global Infectious Disease Research Training Program (D43) with the long-term vision for a Master's Program in Clinical Research at the University of Liberia



FRANCIS I. PROCTOR FOUNDATION  
FOR RESEARCH IN OPHTHALMOLOGY  
UNIVERSITY OF CALIFORNIA SAN FRANCISCO

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September 12, 2018

Re: Catie Oldenburg, PhD

Dear Selection Committee,

I am delighted to provide a letter of support for Dr. Catherine (Catie) Oldenburg's application for a pilot awards for junior investigators. I am familiar with her project and can vouch for its importance in her career and for the Proctor Foundation. I've worked closely with Catie for the past 7 years, and feel comfortable assessing her accomplishments and potential—**she's an academic star**.

Catie has just finished her first year on faculty at UCSF, accomplishing more than anyone could have imagined. She has published 120 papers so far, and 27 already in 2018. She is the PI on KETFO, a large NEI trachoma RCT and co-PI on a large BMGF grant (MORDOR-II Burkina Faso). She is now performing the vast majority of the biostatistical consults for the Department of Ophthalmology, and teaching a section in the medical school epidemiology curriculum.

Catie's research focus at Proctor has been the use of mass azithromycin distributions to control trachoma and reduce childhood mortality. Her proposal for this pilot award is taking this in a new direction, and thus is an important step for her career and for our research group. Amoxicillin has been used with varying success in acute malnutrition. Azithromycin has been shown to reduce childhood mortality, and may have advantages over amoxicillin and other antibiotics. While our group has considerable experience with mass azithromycin distributions, Catie is extending the group's interest into testing the efficacy of azithromycin in malnourished children. If Catie's past productivity is any guide, multiple publications and a successful NIH grant award.

As Director of the Proctor Foundation, I can guarantee that we'll provide Catie with all the support necessary for this project to succeed. She already has built up an incredible team—this project includes Kieran O'Brien, a PhD candidate at UC Berkeley, and Ahmed Arzika, the Niger coordinator for large BMGF-funded projects. Catie also has full access to our ancillary staff and to all other Proctor faculty. Dr Travis Porco will be available for any required statistical assistance, although it should be noted that Catie has considerable skills herself.

I strongly support the application for this mentored research award, and will support the completion of this research in any way I can. The project is completely in line with our mission, and should be the catalyst for additional NIH grant support. Catie has been the most productive graduate student, post-doc, and junior faculty member that I've ever

seen. I believe that any resources that we devote to her work will be returned several fold. Please feel free to contact me with any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Tom Lietman". The signature is fluid and cursive, with the first name "Tom" and last name "Lietman" clearly distinguishable.

Thomas Lietman, MD  
Ruth Lee and Phillips Thygeson Distinguished Professor  
Departments of Ophthalmology and Epidemiology & Biostatistics  
Director, Francis I. Proctor Foundation  
University of California, San Francisco