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TITLE

Mass drug administration for leprosy control in Kiribati: The COMBINE protocol

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ABSTRACT

Progress towards leprosy elimination is threatened by increasing incidence in 'hot-spot' areas where more effective control strategies are urgently required. In these areas, active case finding and leprosy prevention limited to known contacts is insufficient for control. Population-wide active case-finding together with universal prevention through mass drug administration (MDA) has been shown to be effective in 'hot-spot' areas, but is logistically challenging and expensive. Combining leprosy screening and MDA with other population-wide screening activities such as for tuberculosis (TB) may increase programme efficiency. There has been limited evaluation of the feasibility and effectiveness of combined screening and MDA interventions. The COMBINE study aims to bridge this knowledge gap.

Methods and analysis

This implementation study will assess the feasibility and effectiveness of active leprosy case-finding and treatment, combined with population-wide MDA using either single-dose rifampicin or rifamycin-containing TB preventive or curative treatment, for reducing leprosy incidence in Kiribati. The leprosy programme will run over 2022–2025 in concert with the PEARL population-wide TB screening and treatment study in South Tarawa. The primary research question is to what extent the intervention reduces the annual leprosy new case detection rate (NCDR) compared to routine screening and post exposure prophylaxis (PEP) among close contacts (baseline leprosy control activities). Comparisons will be made with 1) the pre-intervention NCDR in South Tarawa (before-after study) and 2) the NCDR in the rest of the country. Additionally, the post-intervention prevalence of leprosy obtained from a survey of a 'hot-spot' sub-population will be compared to prevalence documented during the intervention. The intervention will be implemented in collaboration with the Kiribati National Leprosy Program (NLP).

Ethics and dissemination

Approval has been obtained from relevant ethics committees. Findings will be shared with the Kiribati Ministry of Health and Medical Services, local communities and internationally through publication in peer-reviewed journals.

Strengths and limitations of this study

- Designed for both rapid and sustained reduction in leprosy prevalence using a combination of active case-finding with treatment and mass drug administration for population-wide chemoprophylaxis
- Geographically isolated island with high rates of leprosy, relatively small population and limited population mobility, facilitating proof-of-principle testing with low risk of dilution of intervention effect
- Dovetailing of existing leprosy and TB elimination activities reduces disruption to routine practice and maximises efficiency
- The absence of randomisation limits attribution of effect to the intervention; partially compensated for by employing multiple comparator assessments
- Despite the geographic isolation, the long implementation period (3 years) may allow leprosy re-infection events to occur in the community through inter-island travel

INTRODUCTION

Since the 1991 World Health Association resolution to eliminate leprosy,[1] tremendous progress has been made towards global leprosy elimination.[2] However, despite enhanced early detection and availability of effective treatment and prevention options, progress has reversed in some leprosy 'hot-spots' (regions of high leprosy endemicity).[3] National leprosy disease and disability rates have stagnated in most of the 23 leprosy global priority countries with an increase in grade-2 disability reported in 2020 for 7 of these countries, including Kiribati.[3] Global de-funding for leprosy control and health system prioritisation of diseases with more obvious and immediate clinical presentations than leprosy have exacerbated these challenges. Point prevalence surveys in leprosy endemic regions reveal many undetected cases, with major case detection and reporting gaps responsible for the 'missing millions'.[4-10] Although the relatively low incidence of childhood leprosy (6.8% of all newly detected cases) indicates that transmission has declined globally, this is not true in all areas with cases among children increasing in some countries.[3]

The ongoing leprosy disease burden in the Pacific Island nation of Kiribati is emblematic of the global situation in high burden countries. Kiribati has one of the highest leprosy incidence rates in the world and these rates are on the rise; the Ministry of Health and Medical Services (MHMS) reports a 17% increase in incidence from 2010 to 2020, with 15.9 new cases detected per 10,000 people in 2020.[3] Curative and preventive services are routinely provided by the National Leprosy Program (NLP) in line with World Health Organization (WHO) guidelines, in partnership with the Pacific Leprosy Foundation (PLF). The NLP screens contacts for leprosy and, if active leprosy is not identified, provides single-dose rifampicin for post-exposure prophylaxis (SDR-PEP) immediately and one year later. In addition, contacts are screened for signs and symptoms of leprosy annually for four more years after the initial screening. SDR-PEP was introduced in 2018 and has since been provided to 89% of all eligible leprosy contacts recorded since 2010, which amounts to screening and prophylaxis for ~9% of the total population of Kiribati (10,406 contacts). Despite these interventions, most new leprosy

cases in Kiribati are detected passively rather than by contact tracing with many presenting with advanced disease; almost half of all cases have multibacillary disease. These cases have long infectious periods before diagnosis and are an important source of transmission in the community.

To make an impact on the leprosy epidemic in Kiribati and to meet the ambitious Zero Leprosy target to halve global leprosy incidence by 2030,[11] bold new strategies are needed. Such strategies should be designed to break the chain of leprosy transmission and to reduce the risk of disease progression in highly endemic regions. One avenue for exploration is to expand the reach of active case-finding (ACF) and preventive interventions in high-risk populations. In previous studies, regions with smaller populations, but similar disease burdens to Kiribati, have benefitted from population wide ACF and mass drug administration (MDA) with SDR to reduce the risk of progression to leprosy disease in the community, irrespective of contact status.[12 13] Population-wide programmes can be very challenging to implement on a large scale because of the logistical demands of reaching whole populations, difficulties achieving acceptability and buy-in, poor access to microbial confirmation in resourced-limited settings, a lack of clinical expertise for diagnoses, and challenges in mobilising resources to support population-wide programmes. The result is that leprosy MDA for large populations (>5,000 people) is often considered unfeasible in the regions where it is most needed.

Twenty-one of the 23 leprosy priority countries also have endemic tuberculosis (TB).[3] The relatively greater funding for TB and the global movement towards expanded ACF for TB,[14-16] the shared susceptibility of *Mycobacterium leprae* and *Mycobacterium tuberculosis* to rifamycins for preventive therapy, and the similar social determinants of transmission and disease all present opportunities for leprosy control programs to leverage TB programmes for mutual gain. Where the burden of both diseases is sufficiently high, this can take the form of combined population wide ACF and MDA chemoprophylaxis activities. In South Tarawa, the PEARL study[17] provides the mechanism by which a combined intervention may be delivered

at a fraction of the cost of a separate programme. Modelling of a mass chemoprophylaxis strategy for leprosy suggests this is an effective strategy,[18] and combining mass screening and treatment for TB are expected to greatly increase efficiency and cost-effectiveness. South Tarawa was chosen for the PEARL study as it is the centre with the highest population density in Kiribati and has the highest estimated incidence of TB and leprosy.

The COMBINE study is designed to inform programmatic strategies towards leprosy elimination in the Pacific and elsewhere. We aim to assess the effectiveness, feasibility, efficiency and cost of a programme of leprosy screening and mass rifamycin-based chemoprophylaxis delivered in combination with a TB screening, treatment and prevention initiative in Kiribati.[17] We will provide evidence for practicable means of integrating leprosy control with other communicable disease programmes that can be used to effectively accelerate leprosy prevention and care in endemic regions. Many of the research questions addressed by the COMBINE study must be answered to achieve scalable and durable leprosy elimination in countries like Kiribati.

OBJECTIVES

The COMBINE study assesses the feasibility and effectiveness of leprosy screening and MDA chemoprophylaxis in a highly endemic population using a programmatic approach that:

- Investigates whether combined population-wide screening and treatment for leprosy and TB together with MDA chemoprophylaxis and ongoing SDR-PEP for contacts can achieve rapid and durable reductions in leprosy incidence;
- Evaluates the effectiveness of leprosy MDA chemoprophylaxis using a pragmatic combination of either SDR or rifamycin-based TB preventive treatment;
- Measures the cost of MDA delivery when integrated with infrastructure from an existing population-wide screening program (the PEARL study[17]);
- Documents operational strategies to feasibly integrate enhanced leprosy and TB control efforts, and to reduce leprosy associated stigma.

METHODS AND ANALYSIS

Study design

COMBINE is a pragmatic controlled non-randomised before-and-after implementation study designed to evaluate the impact of the intervention upon leprosy NCDR. The COMBINE study will leverage infrastructure created by the PEARL study to deliver population-wide leprosy ACF and chemoprophylaxis. We will deliver the intervention over 3 years, aiming to reach the entire population of South Tarawa in that time.

Setting

The Republic of Kiribati is a geographically isolated nation in the Pacific region comprising 32 atolls and one raised coral island spread over a land territory of 811 km^2 amid an ocean territory of 3.5 million km^2. The intervention site is the capital atoll of South Tarawa (population 63,439) which is the densely-populated 'transmission hot-spot' and amplifier of leprosy disease throughout the country (see **Table 1** for baseline characteristics of the study population).[19] Kiribati has only one specialised leprosy clinic which is located in South Tarawa.

Residents live in village communities on a chain of low-lying islets connected by a causeway. Visitors from 'outer islands' to the capital often stay for an extended period. Anecdotally, this pattern of travel in and out of South Tarawa is associated with clusters of TB and leprosy in outer island communities.

While diagnosis and contact-tracing practices have been improved and standardised since 2010, it is uncertain whether the upward trend in new case detection rate (NCDR) in Kiribati over the past decade is an accurate measure of worsening epidemic control or reflective of enhanced case detection. What is clear, is that child NCDR has exceeded 30% of all newly detected cases for the past 3-years (2019-2021), indicating that the background community-level leprosy transmission has outpaced the potential to control the disease burden with existing leprosy programme interventions.

Table 1. Baseline characteristics of the population and intervention group

	Intervention group *South Tarawa*	**No intervention group** *Rest of Kiribati*	**Whole of Kiribati**
Population, 2020 *	63,439	56,501	119,940
- **Females (%)**	32,981 (52.0%)	27,805 (49.2%)	60,786 (50.7%)
- **Median age (years)**	23.2	22.3	22.9
- **Average household size (people)**	6.6	4.9	5.0
- **Net migration rate (% of population)**	2%	0.7%	1.4%
Urbanisation	Majority urban; some rural	Majority rural; some urban	Mixed urban and rural
BCG coverage, 2021 (% of live births) **	2434/2525 (96.4%)	839/888 (94.5%)	3273/3413 (95.9%)
Leprosy new cases, 2020 (rate per 10,000) **	93 (14.44)	62 (11.15)	155 (12.92)
- **Child cases (%)**	18 (19.4%)	18 (29.0%)	36 (23.2%)
- **MB cases (%)**	50 (53.8%)	20 (32.3%)	70 (45.2%)
Eligible contacts 2010–2020 **	9527	2264	11,811
- **received SDR (%)**	8381 (88%)	2021 (89%)	10,402 (89%)

Selected baseline characteristics or populations in the intervention area (South Tarawa), no intervention area (rest of Kiribati) and for the whole of Kiribati. BCG – Bacille Calmette-Guerin; MB – multibacillary; SDR – single-dose rifampicin.

* *National Statistics Office, 2020 census data*

** *Ministry of Health and Medical Services, programme data*

Intervention group and recruitment

The intervention group comprises residents of South Tarawa (and the small communities of Buota and Abatao adjacent to South Tarawa) aged 3-years and above, and aged less than 3-years if they have documented household contact (relevant definitions are provided in **Box 1**) with someone who has had TB in the past 1 year, or leprosy at any time since they were born. Study participants will be identified via household and village-level lists of residents from the 2020 census, and then invited to attend screening locations using door-to-door visits at households and community-based institutions (businesses, churches, et cetera). Basic demographic, social and geographic data will be collected at enrolment by the PEARL study screening teams.

Box 1. Definitions

Case of leprosy – clinical definition classified as multibacillary (MB) or paucibacillary (PB) according to WHO criteria that has been diagnosed by the doctor of the NLP.

Household - all those using the same kitchen, including members of extended families, the Maneaba (communal hospitality shelters), and dormitories in individual locations.

Household contact - any person who has been in contact with a new leprosy case for at least 20 hours per week for at least three months during the past five years.*

**adapted from WHO definition for the Kiribati context*

Interventions

An illustration of the combined TB and leprosy interventions is provided in **Figure 1**, comparing the intervention group and standard care in the comparison group. Interventions are described in detail below. In practice, these interventions will be delivered in the setting of a combined community-based screening, diagnosis, treatment and prevention service.

Case detection, diagnosis and treatment

Screening for leprosy will be conducted by a physical examination and questionnaire (**Supplement 1**). People with presumptive leprosy will be referred to the National Leprosy Program (NLP) for expert diagnosis. Cases will be validated by a leprologist and skin biopsies from all patients with clinically diagnosed leprosy will be tested by PCR for *M. leprae* and drug resistance mutations, according to WHO guidelines.[14] Leprosy treatment will be provided by the NLP according to Kiribati national guidelines. Further details of the leprosy screening, diagnosis and treatment eligibility criteria are available in the PEARL study protocol.[17]

Contact Tracing and Post-Exposure Prophylaxis

Contact tracing and SDR-PEP will be ongoing for all index cases identified during the intervention within the study site and throughout the rest of Kiribati, as is consistent with routine practice (**Box 1**). WHO recommends that leprosy contacts should be given SDR-PEP at ≥2 years of age.[20] This has been adopted by the Kiribati NLP since 2018 and will be supported by the COMBINE study to scale-up SDR-PEP delivery throughout the intervention period, as enhanced index case detection will increase contact tracing needs. Children who are younger than 2-years and are leprosy contacts will be followed up and offered SDR-PEP by the NLP when they reach 2 years of age.

Leprosy Mass Drug Administration Chemoprophylaxis

Rifamycin-based MDA chemoprophylaxis is provided using a composite of treatments. After integrated leprosy and TB screening, participants will be commenced on treatment for TB, treatment for leprosy, or TPT using a rifamycin-based regimen, depending on the screening

outcome. For participants who are not eligible for any of those treatments, we will then offer a single dose of rifampicin according to the inclusion/exclusion criteria in **Table 2**. Considered together as in **Table 3**, all participants will be offered a rifamycin-based treatment; effectively a rifamycin-based leprosy MDA chemoprophylaxis. Detailed dosing information is provided in **Supplement 2**.

Table 2. Inclusion and exclusion criteria for single dose rifampicin

Inclusion criteria	**Exclusion criteria**
1. Enrolled in the screening intervention 2. Not eligible for any other rifamycin-based treatment 3. Aged ≥2 years 4. Informed consent. For children (<18 years) consent will be obtained from the parent or guardian, and children (≥10 years) will also provide assent.	1. History of serious liver or kidney disease. 2. Known pregnancy (SDR can be given after delivery). 3. Known allergy or severe adverse effects experienced with rifampicin use. 4. Refuses participation.

Inclusion criteria are shown for single dose rifampicin. Other treatment regimens are determined by indications and contraindications relevant to those regimens. MDA – mass drug administration; SDR – single-dose rifampicin.

Table 3. Overview of combined treatment and chemoprophylaxis

Screening outcome	**Treatment offered**	**Rifamycin component**
Leprosy	Leprosy MDT	Monthly rifampicin for 6-12 months
TB	TB treatment	Daily rifampicin for 6-12 months
RR-TB	DR-TB treatment + SDR	Single dose rifampicin
Eligible for TPT	3HP or 3RH	Weekly rifapentine or daily rifampicin for 3 months
Leprosy HHC	SDR-PEP	Rifampicin given at baseline and one year later
None of the above	SDR-MDA	Single dose of rifampicin

Screening outcomes are exhaustive but not mutually exclusive. The rifamycin component of each treatment strategy includes sufficient exposure to offer prevention for leprosy, in effect a mass drug administration of leprosy chemoprophylaxis. 3HP – 3-months of weekly rifapentine

and isoniazid; 3RH – 3-months of daily rifampicin and isoniazid; DR-TB – drug-resistant tuberculosis; HHC – household contact; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; RR-TB – rifampicin-resistant tuberculosis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – tuberculosis preventive treatment.

Community Engagement and Stigma Prevention

The objective of community engagement and mass communications is to encourage participation in the screening programme and sensitise community members to appropriate, non-stigmatising messages related to leprosy and leprosy screening. This approach is supported by the best practice statement of the Global Partnership for Zero Leprosy.[11 21] The COMBINE study supports community engagement and stigma prevention through various activities developed in concert with the PLF (who have 10 years of experience in leprosy advocacy in Kiribati) and the MHMS. These activities include:

- bi-annual advocacy activity drives which may include leprosy awareness parades, plays, signage and mass communication.
- convening of a leprosy community support group for patients diagnosed with leprosy and their close contacts/families. COMBINE nurses will assist with mentoring the community group, training in coping strategies and supporting activities.
- annual training and development workshops including all staff of the national leprosy and TB programmes with anti-stigma training for health staff delivering the COMBINE screening intervention
- job-aids and resources to support health staff and people with leprosy, for example a flipbook to aid counselling sessions between health workers and people with leprosy

Post-intervention prevalence survey

A follow-up leprosy prevalence survey will be conducted in Betio islet (~18,500 people, located within the South Tarawa intervention group) 3-4 years after the intervention there has been completed.

Outcome measures and planned analyses

The primary research question of interest is the extent to which the intervention reduces leprosy annual NCDR compared with standard routine passive case-finding and post-exposure prophylaxis of close contacts. This will be assessed 1) by comparing the post-intervention NCDR in South Tarawa (in 2025) with the pre-intervention NCDR (in 2021) and 2) by comparing the change in NCDR in South Tarawa (the intervention site) with the change in NCDR observed in the outer Kiribati islands (non-intervention sites). A supplementary analysis will examine the number of new cases detected by a house-to-house prevalence survey in Betio (~15,000 people) performed 3-4 years after initial study screening (2026), to determine the effect of the COMBINE intervention upon leprosy prevalence.

Due to the long latency of leprosy, we expect that the full effect of the intervention will only become apparent after several years have elapsed. The study sponsor, the PLF, is committed to continuing leprosy surveillance in Kiribati, enabling ongoing assessments of long-term trends in incidence beyond 2025.

Other planned analyses will examine:

1. The diagnostic yield of screening and spectrum of leprosy disease in different communities/islands in Kiribati
2. Geospatial and social relationships between leprosy cases based on Global Positioning System (GPS) co-ordinates and social contact mapping
3. Prevalence of genotypic *M. leprae* resistance to rifampicin, dapsone and clofazimine before and after the MDA programme (using PCR-based assays of skin biopsies) [22-25]

4. The costs of leprosy-only activities, TB-only activities and shared activities to inform the cost-efficiency of future combined leprosy elimination projects in the Pacific and elsewhere
5. The impact of prior exposure to rifamycins (provided as part of routine activities of the NLP and NTP) on risk of leprosy diagnosis in a high-incidence setting
6. The feasibility of combined TB and leprosy elimination efforts in the intervention site based on health service requirements (health care worker mix and person-time), together with infrastructure requirements and qualitative acceptability among decision makers and participants/communities
7. Mathematical modelling of the dynamics of leprosy incidence using 'real life' data from the COMBINE study with the aim of refining previous models[18] to improve accuracy of forecasting and decision support

Sample size

Assuming mass chemoprophylaxis coverage of 80% of the population and given a leprosy NCDR of 1600/1,000,000 for South Tarawa (the intervention group, population ~65,000) and 872 per 1,000,000 for the rest of the country (comparison group, population ~55,000), the study would provide greater than 99% power ($\alpha<0.05\%$) to detect a 50% reduction (before versus after difference) in NCDR in South Tarawa (the intervention group) and 82% power to detect a 50% reduction in South Tarawa compared with no change in the rest of the country. Predicted sample sizes were calculated using the mean number of cases observed between 2018 and 2020 and simulated number of cases observed in 2025, drawn from a Poisson distribution (10,000 replicates) according to the parameters above and assuming a population growth of 5,000 in each area.

Economic Analysis and Costing

COMBINE proposes to estimate unit costs for screening per patient, working closely with the PEARL study to perform a cost analysis of TB-only activities, leprosy-only activities and

shared activities. Accurate costing data will inform future leprosy elimination projects in the Pacific region and beyond, and will have additional benefits for subsequent planning, budgeting and modelling exercises. To enhance the application of our findings, we will seek to align costing data with existing interagency costing tools.

Data collection and monitoring

All leprosy and TB screening, chemoprophylaxis and outcome data will be captured offline on encrypted tablet devices using Research Electronic Data Capture (REDCap) surveys. Data will be uploaded and stored on a high security REDCap database server managed by the University of Sydney. This database is interoperable with the existing NLP database, and leprosy data will be shared in real time with the NLP to conduct and record contact tracing activities in the NLP database, consistent with current standard procedure.

ETHICS AND DISSEMINATION

Ethics for the COMBINE study has been obtained from the University of Sydney (project no. 2021/127) and the Kiribati Ministry of Health and Medical Services. Government support for the study to occur in collaboration with the NLP has been provided by Kiribati National Cabinet.

Participant information and counselling is provided to all prospective participants and again before treatment is offered (**Supplement 3**). Editable versions of study patient tools and a counselling flipbook are available at www.leprosy.org.nz and www.thepearlstudy.org. Informed consent is gathered verbally before participant enrolment and a signed record of consent is collected in the study REDCap database (**Supplement 4**). Verbal consent for participants attending the NLP for confirmation of diagnosis and treatment management will be obtained according to standard programme practice. Written informed consent for a skin biopsy will be taken as is usual in the clinic. This includes consent to send the specimen abroad for analysis.

The safety of treatments for TB are discussed in the PEARL study protocol. SDR is very safe, and has been used in Kiribati[18 19] and elsewhere[12 26-28] with little or no recorded side-effects. A study hotline and walk-in clinic will be available for adverse event (AE) management throughout the study period. Information on the signs and symptoms of leprosy and instructions to access the permanent leprosy clinic are provided to all participants (including those who decline to participate). Serious AEs are reported in accordance with national and University of Sydney pharmacovigilance standards. Intervention monitoring and auditing procedures will be conducted annually by the MHMS in accordance with routine practice with study reports made annually to ethics and funding bodies.

All study data will be shared with the MHMS. Reports of study progress will be made to the Kiribati community by mass communication and on the Pacific Leprosy Foundation and the PEARL study websites. Study findings will be presented at international conferences and in peer reviewed publications.

Patient Involvement Statement

This study was developed with the involvement of a reference group of I-Kiribati people affected by leprosy. This group will be involved in the COMBINE study in an ongoing basis. In particular, they will give advice concerning the practical implementation of the research, including the best ways of liaising with patients, their families and the community to ensure that communication is positive and does not contribute to stigma for people identified with leprosy and their contacts.

DISCUSSION

Innovative solutions are required to achieve progress towards leprosy elimination in Kiribati and in other areas of continuing high incidence. This is essential if we are to overcome the barriers to achieving global Zero Leprosy targets,[11] and eventually, true global leprosy elimination. As leprosy continues to require long and complex treatment programs, there is

also urgency to find novel control strategies before antibiotic resistance emerges and accelerates in high transmission populations.[29]

The proposed study design combines a robust public health intervention in response to the dual epidemics of leprosy and TB in Kiribati, along with rigorous evaluation of the intervention. Population-wide leprosy active case-finding and MDA with rifamycin-based chemoprophylaxis in a population of approximately 60,000 represents a bold step towards acceleration of leprosy control. Combining this intervention with a similar population-wide TB screening, treatment and prevention programme is an innovative health systems approach that could improve efficiency and feasibility of large-scale interventions for both diseases. If successful, this would present an important model that may be implemented in other settings.

In Kiribati (and elsewhere[12,30]), MDA chemoprophylaxis in the 1990s led to reductions in leprosy case detection but ultimately failed to produce a lasting decline in incidence in some settings. The long latency period of the disease and the absence of surrogate measures of leprosy transmission make robust short-to-medium-term outcome measures of the population-level effect of interventions particularly limited. These are challenges intrinsic to population-level leprosy research. This study is designed to address these challenges by rigorous evaluation of scaled-up interventions in combination with durable partnership for evaluation of longer-term incidence and transmission outcomes. This 'real-life' operational research design to evaluate the main intervention is accompanied by a commitment to long-term surveillance by the MHMS together with the PLF until leprosy is eliminated in Kiribati. In the shorter and medium term, improvements in the accuracy of modelling of the intervention impact (using data from the COMBINE study) will provide useful insights and interim measures of the effect of COMBINE interventions upon leprosy incidence. This will be valuable to inform programs facing similar challenges to Kiribati.

Kiribati is in a unique position, given its geographic isolation, low migration rate and limited population size, to identify and test innovative elimination strategies as proof-of-principle for leprosy control in other locations. We plan to grasp this opportunity and deliver much-needed evidence to reinvigorate attempts to eliminate this age-old scourge of humankind.

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Contributors

All authors contributed to the conceptualisation and panning of this research. All authors made important intellectual contributions to the final protocol manuscript. SC, WB and JT wrote the study proposal. MC and JH contributed equally to this paper. The funding agency played no part in any aspect of the study, nor the decision to submit this manuscript for publication.

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Competing interests' statement

Some project funding is provided by the Pacific Leprosy Foundation, which also supports consultancy work of co-authors AC and NI.

Figure 1. Overview of COMBINE study intervention

Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

REFERENCES

1. Resolution to eliminate leprosy as a public health problem by the year 2000 resolution WHA449. World Health Assembly: Geneva: 44th World Health Assembly, 1991.
2. WHO. World Health Organization leprosy elimination project: status report 2002: World Health Organization, 2003.
3. WHO. World Health Organization Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. *WklyEpidemiol Rec* 2021;96(36):421-44.
4. Urgesa K, Bobosha K, Seyoum B, et al. Evidence for hidden leprosy in a high leprosy-endemic setting, Eastern Ethiopia: The application of active case-finding and contact screening. *PLoS neglected tropical diseases* 2021;15(9):e0009640.
5. Bernardes F, Paula NAd, Leite MN, et al. Evidence of hidden leprosy in a supposedly low endemic area of Brazil. *Memórias do Instituto Oswaldo Cruz* 2017;112:822-28.
6. Smith WC, van Brakel W, Gillis T, et al. The missing millions: a threat to the elimination of leprosy. *PLoS neglected tropical diseases* 2015;9(4):e0003658.
7. de Oliveira GL, Oliveira JF, Pescarini JM, et al. Estimating underreporting of leprosy in Brazil using a Bayesian approach. *PLoS neglected tropical diseases* 2021;15(8):e0009700.
8. Frade MAC, de Paula NA, Gomes CM, et al. Unexpectedly high leprosy seroprevalence detected using a random surveillance strategy in midwestern Brazil: A comparison of ELISA and a rapid diagnostic test. *PLoS neglected tropical diseases* 2017;11(2):e0005375.
9. Mangeard-Lourme J, Singh A, Singh RK, et al. Enhanced active case-finding, identifying leprosy cases missed by recent detection campaigns in Munger District, Bihar, India. *Leprosy Review* 2017;88(4):452-62.
10. Salgado CG, Barreto JG, da Silva MB, et al. Are leprosy case numbers reliable? *The Lancet Infectious Diseases* 2018;18(2):135-37.
11. WHO. World Health Organization Towards zero leprosy. Global leprosy (Hansen's Disease) strategy 2021–2030. 2021

12. Tiwari A, Dandel S, Djupuri R, et al. Population-wide administration of single dose rifampicin for leprosy prevention in isolated communities: a three year follow-up feasibility study in Indonesia. *BMC Infect Dis* 2018;18(1):324. doi: 10.1186/s12879-018-3233-3 [published Online First: 2018/07/13]

13. Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *The American journal of tropical medicine and hygiene* 2005;72(4):443-48.

14. WHO. World Health Oorganization consolidated guidelines on tuberculosis Module 2: Screening – Systematic screening for tuberculosis diseas. *Global Tuberculosis Programme* 2021

15. WHO. Rapid communication on systematic screening for tuberculosis. 2020

16. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *N Engl J Med* 2019;381(14):1347-57. doi: 10.1056/NEJMoa1902129 [published Online First: 2019/10/03]

17. Coleman M, Hill J, Timeon E, et al. Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati: the PEARL study protocol. *BMJ Open* 2022;12(4):e055295. doi: 10.1136/bmjopen-2021-055295

18. Gilkison C, Chambers S, Blok DJ, et al. Predicting the impact of household contact and mass chemoprophylaxis on future new leprosy cases in South Tarawa, Kiribati: A modelling study. *PLoS Negl Trop Dis* 2019;13(9):e0007646. doi: 10.1371/journal.pntd.0007646 [published Online First: 2019/09/21]

19. Chambers ST, Ioteba N, Timeon E, et al. Surveillance of Leprosy in Kiribati, 1935–2017. *Emerging Infectious Diseases* 2020;26(5):833.

20. WHO. Leprosy/Hansen disease: Contact tracing and post-exposure prophylaxis. 2020

21. van Brakel WH, da Silva Pereira ZB, Barbosa JC, et al. Global Partnership for Zero Leprosy Research Agenda Working Group Subgroup on Stigma, 2019.

22. Coppola M, van den Eeden SJ, Robbins N, et al. Vaccines for leprosy and tuberculosis: opportunities for shared research, development, and application. *Frontiers in immunology* 2018;9:308.

23. Lahiri R, Adams LB. Cultivation and viability determination of Mycobacterium leprae. *International Textbook of Leprosy* 2016

24. Davis GL, Ray NA, Lahiri R, et al. Molecular assays for determining Mycobacterium leprae viability in tissues of experimentally infected mice. *PLoS neglected tropical diseases* 2013;7(8):e2404.

25. Williams DL, Torrero M, Wheeler PR, et al. Biological implications of Mycobacterium leprae gene expression during infection. *Microbial Physiology* 2004;8(1):58-72.

26. Richardus JH, Tiwari A, Barth-Jaeggi T, et al. Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme. *Lancet Glob Health* 2021;9(1):e81-e90. doi: 10.1016/s2214-109x(20)30396-x [published Online First: 2020/11/02]

27. Schoenmakers A, Mieras L, Budiawan T, et al. The State of Affairs in Post-Exposure Leprosy Prevention: A Descriptive Meta-Analysis on Immuno- and Chemo-Prophylaxis. *Res Rep Trop Med* 2020;11:97-117. doi: 10.2147/rrtm.S190300 [published Online First: 2020/10/30]

28. Feenstra SG, Pahan D, Moet FJ, et al. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Lepr Rev* 2012;83(3):292-304. [published Online First: 2013/01/30]

29. Cambau E, Saunderson P, Matsuoka M, et al. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clinical Microbiology and Infection* 2018;24(12):1305-10.

30. Nguyen LN, Cartel JL, Grosset JH. Chemoprophylaxis of leprosy in the southern Marquesas with a single 25 mg/kg dose of rifampicin. Results after 10 years. *Lepr*

Rev 2000;71 Suppl:S33-5; discussion S35-6. doi: 10.5935/0305-7518.20000064

[published Online First: 2001/02/24]

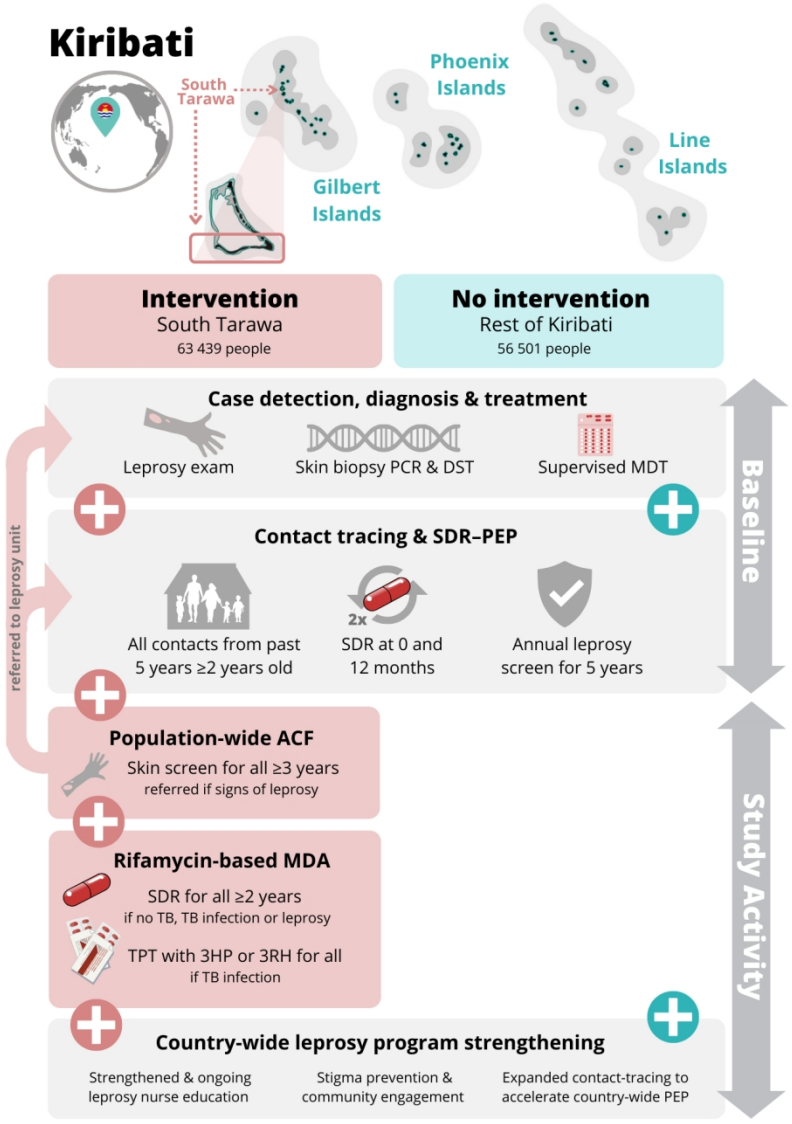


Figure 1. Overview of COMBINE study intervention. Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

536x758mm (67 x 67 DPI)

Supplementary Materials

Mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SUPPLEMENT 1. Leprosy screening Standard Operating Procedure

Population leprosy screening – general steps

1. Ask about leprosy (this may be done at a history taking station)
2. Conduct a physical check for leprosy
3. Record findings in CRF
    a. Take a photo of any examination findings
4. Refer for further evaluation if there are any findings (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)

Population leprosy screening – details

Ask (this may be done at a history taking station)

- Have you had or do you have leprosy? Have you ever been treated for leprosy?
- Are you a household contact* of someone who has had leprosy?
- Are you worried you might have leprosy? If so, why?
- Do you have any skin lesions or other abnormalities that you think could be leprosy?

Exposure

- Remove footwear and any outer layers of clothing

Areas of body to inspect

- Face including eyelashes, eyebrows, nose and mouth
- Ears
- Neck
- Arms and hands

- Legs and feet
- Lift the shirt and lower the waistband for back and upper buttocks

Looking for

- Skin lesions (pale, red, thick, raised, shiny)
    - Check if itchy, if so, don't refer to NLP (consider alternative referral if concerning)
- Skin nodules
- Altered shape of nose or ears
- Loss of eyelashes or eyebrows
- Altered shape of hand or foot
    - Check if present from birth, if so, don't refer
- Ulcers on hand or foot

Who to refer?

- People with physical examination findings consistent with leprosy
- People who are worried they might have leprosy (any reason)

How to record

- Fill the CRF
- Take a photo (good lighting, ruler or TST syringe for scale)
- Refer for further evaluation (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)
- Give referral letter if needed

* Household contact is defined according to WHO. *"Household contacts: contacts living in the same dwelling or sharing the same kitchen as the index case. These include family members but also domestic staff or aids or co-workers or others sharing the same accommodation. A family member living elsewhere should not be considered as a contact."*

SUPPLEMENT 2.

Table S1. Single dose rifampicin (SDR) chemoprophylaxis dosing.

Age/body weight	Rifampicin single dose
15 years and above	600 mg
10-14 years	450 mg
Children 6-9 years (weight ≥ 20 kg)	300 mg
Children 6-9 years (weight < 20 kg)	150 mg
Children <5 years	10-15 mg/kg

Table S2. Tuberculosis preventive treatment dosing.

S2A. 12 doses of weekly isoniazid (H) and rifapentine (P) for adults and children ≥25 kg

Weight band	HP (300mg/300mg) tablets
25-30kg (or <15ys)	2
≥30kg and ≥15ys	3

S2B. 3 months of daily dosing of child-friendly water-dispersible rifampicin (R) and isoniazid (H) tablets for children <25kg

Weight band	RH (75mg/50mg) tablets
4-7kg	1
8-11kg	2
12-15kg	3
16-25kg	4

SUPPLEMENT 3. Participant Information

PARTICIPANT INFORMATION

Finding and preventing TB and leprosy cases in Tarawa

Dear participant,

We would like to invite you (and your child if relevant) to be treated for latent or sleeping TB. This document provides information about the study, but we will also explain the study to you in person. You will have the opportunity to ask questions if there is anything that you do not understand or if you want more information. You may refuse participation and this will not be held against you or affect any future access to healthcare.

What is this study about?

TB is a disease caused by germs that are coughed into the air by someone who is ill with TB. Most people who are infected with the TB germ do not become ill and do not even know that they are infected, this is referred to as latent or 'sleeping' TB. **Sometimes sleeping TB can wake up and make you ill, which may spread the germ to others**. This research aims to treat all people with TB, those who are ill and those with sleeping TB, so that we can try to eliminate TB from Tarawa. At the same time we are also trying to eliminate leprosy from Tarawa.

This Participant Information Form tells you about the study so that you can know what it involves. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Who is conducting the study?

The study is carried out by researchers at the University of Sydney, Australia, in close collaboration with the Kiribati National TB and Leprosy Programme (NTP). The study is funded by the Australian Medical Research Future Fund and fully supported by the Kiribati Ministry of Health.

What will happen?

This study involves screening for TB (both 'sleeping TB' and illness caused by TB) and leprosy. People who are ill with TB or leprosy will be referred to the TB and Leprosy Programme for appropriate treatment. People with 'sleeping TB' will be offered TB preventive treatment (TPT) and those without any illness or TB infection will be offered leprosy preventive prophylaxis.

To check if someone is able to be given medication for sleeping TB, a study nurse will ask some personal questions. This may include questions about previous and current illnesses, medications used, drinking of alcohol or kava, and questions about pregnancy if you are a woman. Every person older than 20 years will be given a rapid test to see if they have hepatitis B infection, which is important for us to know before considering treatment for 'sleeping TB'. This test involves a finger prick to get a small drop of blood. People with risk factors will need to have a small amount of blood drawn to make sure their liver function stays healthy during the time that they are treated for sleeping TB.

How much of my time will the study take?

We will try to waste as little of you time as possible. To complete the TB and leprosy screening will require you (and your whole household) to be seen on two separate days. This is to complete all the necessary documentation and tests. It is expected that this will take about 2-3 hours of your time on each of these days. These diagnosed with sleeping TB will need to take tablets once a week for 12 weeks. Tablets will be given out at the mobile health clinic on a monthly basis and can be collected between 9am and 4pm on weekdays**.**

Who can take part in the study?

Every person older than 3 years of age living in Tarawa and Betio islet is invited to take part.

Do I have to be in the study? Can I withdraw from the study once I've started?

Taking part in this study is strongly recommended by the Kiribati Ministry of Health and Medical Services (MHMS) to get rid of TB and leprosy across Tarawa. However, participation is completely voluntary and you do not have to take part. Your decision will not affect your current or future relationship with the researchers, the Kiribati National TB and leprosy Program or the Ministry of Health.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by visiting the study clinic and speaking with a study nurse who will give you exit information and advice on how to stay healthy from TB in the future.

If you decide to withdraw from the study, we will not collect any further information from you. Information that we have already collected will be kept in our study records and may be included in the study results.

Are there any costs or risks associated with being in the study?

There are no costs associated with study participation. Mobile study clinics will be conveniently situated to be easily accessible and all study tests or treatment will be funded by the study.

If treatment for 'sleeping TB' is provided it is normal to feel a bit tired and to have bright orange urine while you are taking the tablets. Rarely people may develop some of the symptoms below, in which case it is important to inform us immediately. Rare symptoms to look out for include:

- ongoing nausea, vomiting or loss of appetite
- new rash or itchy skin
- yellowing skin or eyes
- tingling or numbness in fingers or toes
- any other symptoms of concern to you

Study nurses and doctors are available Monday to Friday, 9am to 4pm to see anyone who is feeling sick and thinks this may be due to their treatment. You may also call the 24-hour treatment hotline using the number on the back of your treatment card (TPT passport).

Are there any benefits associated with being in the study?

Yes, there are major benefits to yourself and the wider community of Tarawa, including Betio islet

- You (and your child) will get treatment for TB or leprosy if required
- You (and your child) will get treatment for sleeping TB (TPT) or to keep leprosy away
- You will help to eliminate TB and leprosy from Tarawa
- Study results will help other Pacific Island nations to eliminate TB and leprosy in the future

What if I have a complaint or any concerns about the study?

This research has been reviewed by an independent group of people called a Human Research Ethics Committee (HREC) at the University of Sydney and the Kiribati Ministry of Health and Medical Services.

If you are concerned about the way this study is being conducted please inform the study team; we want to learn and hear how we can improve things. If you wish to make a complaint to someone independent then please contact any of the people listed below.

Terotia Tabwaka Kelese, Human Resource Officer, Republic of Kiribati

Email: ttabwaka@gmail.com

or

The Manager, Ethics Administration, University of Sydney:

Telephone: +61 2 8627 8176

Email: human.ethics@sydney.edu.au

Fax: +61 2 8627 8177 (Facsimile)

Ethical Approval

This research plan (protocol) was approved by the ethics committee of the faculty of medicine and health at the University of Sydney. This helps to ensure that we do everything possible to keep you safe and to respect your rights and privacy at all times.

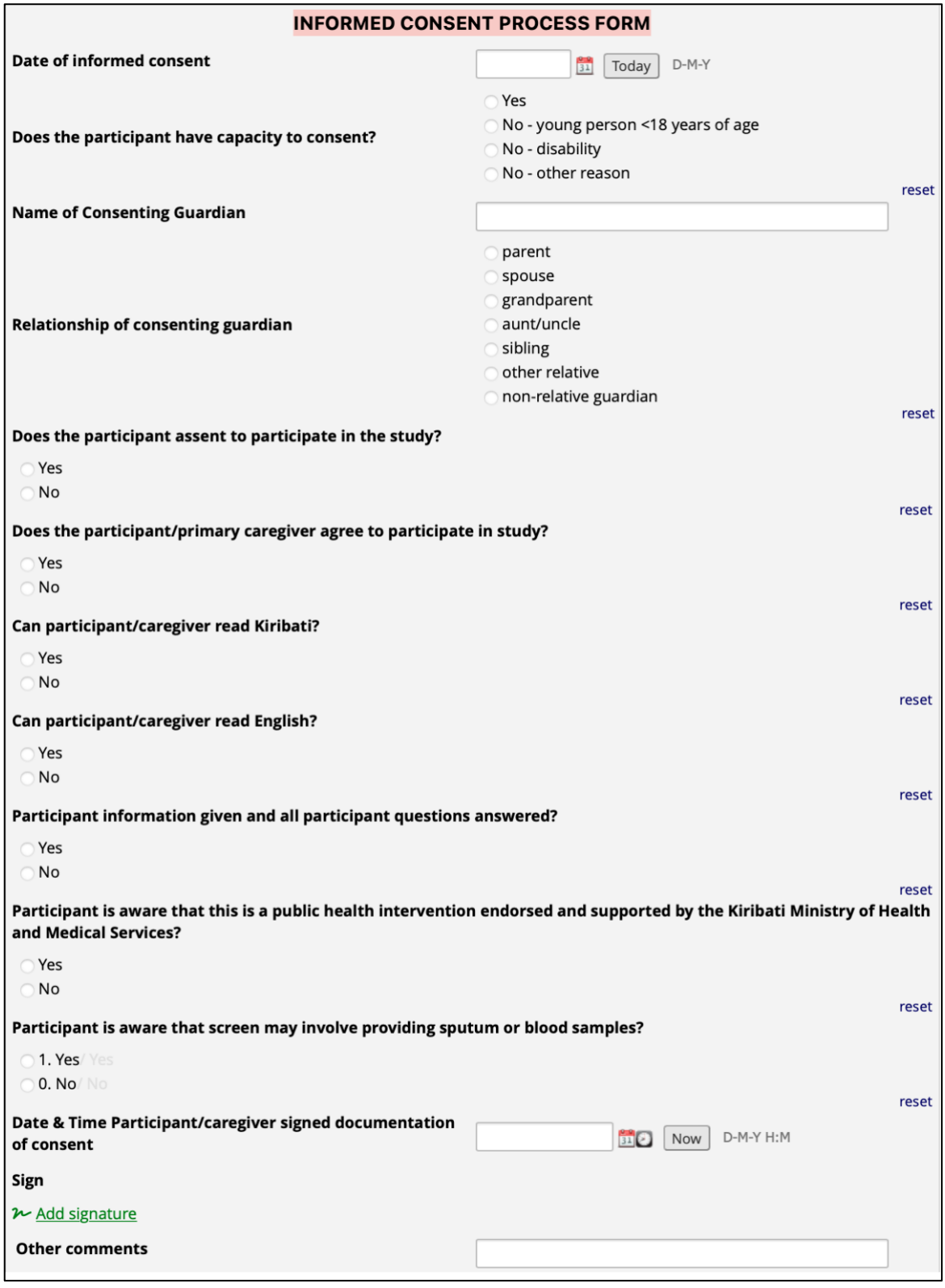
We thank you for your time and cooperation.

The PEARL Research Team with the support of the Kiribati National TB and Leprosy Control Programmes. **Further information can be found at www.thepearlstudy.org**

On behalf of the Kiribati Health Secretary

……..……

SUPPLEMENT 4. Informed Consent Form



INFORMED CONSENT PROCESS FORM

Date of informed consent Today D-M-Y

Does the participant have capacity to consent?
- Yes
- No - young person <18 years of age
- No - disability
- No - other reason

reset

Name of Consenting Guardian

Relationship of consenting guardian
- parent
- spouse
- grandparent
- aunt/uncle
- sibling
- other relative
- non-relative guardian

reset

Does the participant assent to participate in the study?
- Yes
- No

reset

Does the participant/primary caregiver agree to participate in study?
- Yes
- No

reset

Can participant/caregiver read Kiribati?
- Yes
- No

reset

Can participant/caregiver read English?
- Yes
- No

reset

Participant information given and all participant questions answered?
- Yes
- No

reset

Participant is aware that this is a public health intervention endorsed and supported by the Kiribati Ministry of Health and Medical Services?
- Yes
- No

reset

Participant is aware that screen may involve providing sputum or blood samples?
- 1. Yes / Yes
- 0. No / No

reset

Date & Time Participant/caregiver signed documentation of consent Now D-M-Y H:M

Sign

Add signature

Other comments

Mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NA not a trial
	2b	All items from the World Health Organization Trial Registration Data Set	NA not a trial
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2; 22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	13-14; table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14; figure 1; table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13; 18-19; Supplement 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-15; 18-19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-15; 18-19; S2
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA non-random
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA population-wide
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA population-wide
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA open-label
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA open-label
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18; Supplement 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18-19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4-5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19; Table 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22-23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4-5
	31b	Authorship eligibility guidelines and any intended use of professional writers	22-23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3-4
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

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TITLE

The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

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ABSTRACT

Progress towards leprosy elimination is threatened by increasing incidence in 'hot-spot' areas where more effective control strategies are urgently required. In these areas, active case finding and leprosy prevention limited to known contacts is insufficient for control. Population-wide active case-finding together with universal prevention through mass drug administration (MDA) has been shown to be effective in 'hot-spot' areas, but is logistically challenging and expensive. Combining leprosy screening and MDA with other population-wide screening activities such as for tuberculosis may increase programme efficiency. There has been limited evaluation of the feasibility and effectiveness of combined screening and MDA interventions. The COMBINE study aims to bridge this knowledge gap.

Methods and analysis

This implementation study will assess the feasibility and effectiveness of active leprosy case-finding and treatment, combined with MDA using either single-dose rifampicin or rifamycin-containing tuberculosis preventive or curative treatment, for reducing leprosy incidence in Kiribati. The leprosy programme will run over 2022–2025 in concert with population-wide tuberculosis screening-and-treatment in South Tarawa. The primary research question is to what extent the intervention reduces the annual leprosy new case detection rate (NCDR) compared to routine screening and post-exposure prophylaxis (PEP) among close contacts (baseline leprosy control activities). Comparisons will be made with 1) the pre-intervention NCDR in South Tarawa (before-after study) and 2) the NCDR in the rest of the country. Additionally, the post-intervention prevalence of leprosy obtained from a survey of a 'hot-spot' sub-population will be compared to prevalence documented during the intervention. The intervention will be implemented in collaboration with the Kiribati National Leprosy Program.

Ethics and dissemination

Approval has been obtained from the Kiribati Ministry of Health and Medical Services (MHMS), the University of Otago (H22/111) and the University of Sydney (2021/127) Human Research

Ethics Committees. Findings will be shared with the MHMS, local communities and internationally through publication.

Strengths and limitations of this study

- Designed for both rapid and sustained reduction in leprosy prevalence using a combination of active case-finding with treatment and mass drug administration for population-wide chemoprophylaxis
- Geographically isolated island with high rates of leprosy, relatively small population and limited population mobility, facilitating proof-of-principle testing with low risk of dilution of intervention effect
- Dovetailing of existing leprosy and tuberculosis elimination activities has the potential to maximise efficiency and impact, especially in settings with a high-incidence of both diseases
- The absence of randomisation limits attribution of effect to the intervention; partially compensated for by employing multiple comparator assessments
- Despite the geographic isolation, the long implementation period (3 years) may allow leprosy re-infection events to occur in the community through inter-island travel

INTRODUCTION

Since the 1991 World Health Association resolution to eliminate leprosy,[1] tremendous progress has been made towards global leprosy elimination.[2] However, despite enhanced early detection and availability of effective treatment and prevention options, progress has reversed in some leprosy 'hot-spots' (regions of high leprosy endemicity).[3] National leprosy disease and disability rates have stagnated in most of the 23 leprosy global priority countries with an increase in grade-2 disability reported in 2020 for 7 of these countries, including Kiribati.[3] Global de-funding for leprosy control and health system prioritisation of diseases with more obvious and immediate clinical presentations than leprosy have exacerbated these challenges. Point prevalence surveys in leprosy endemic regions reveal many undetected cases, with major case detection and reporting gaps responsible for the 'missing millions'.[4–10] Although the relatively low incidence of childhood leprosy (6.8% of all newly detected cases) indicates that transmission has declined globally, this is not true in all areas with cases among children increasing in some countries.[3]

The ongoing leprosy disease burden in the Pacific Island nation of Kiribati is emblematic of the global situation in high burden countries. Kiribati has one of the highest leprosy incidence rates in the world and these rates are on the rise; the Ministry of Health and Medical Services (MHMS) reports a 17% increase in incidence from 2010 to 2020, with 15.9 new cases detected per 10,000 people in 2020.[3] Curative and preventive services are routinely provided by the National Leprosy Program (NLP) in line with World Health Organization (WHO) guidelines, in partnership with the Pacific Leprosy Foundation (PLF). The NLP screens contacts for leprosy and, if active leprosy is not identified, provides single-dose rifampicin for post-exposure prophylaxis (SDR-PEP) immediately and one year later. In addition, contacts are screened for signs and symptoms of leprosy annually for four more years after the initial screening. SDR-PEP was introduced in 2018 and has since been provided to 89% of all eligible leprosy contacts recorded since 2010, which amounts to screening and prophylaxis for ~9% of the total population of Kiribati (10,406 contacts). Despite these interventions, most new leprosy

cases in Kiribati are detected passively rather than by contact tracing with many presenting with advanced disease; almost half of all cases have multibacillary disease. These cases have long infectious periods before diagnosis and are an important source of transmission in the community.

To make an impact on the leprosy epidemic in Kiribati and to meet the ambitious Zero Leprosy target to halve global leprosy incidence by 2030,[11] bold new strategies are needed. Such strategies should be designed to break the chain of leprosy transmission and to reduce the risk of disease progression in highly endemic regions. One avenue for exploration is to expand the reach of active case-finding (ACF) and preventive interventions in high-risk populations. In previous studies, regions with smaller populations, but similar disease burdens to Kiribati, have benefitted from population wide ACF and mass drug administration (MDA) with SDR to reduce the risk of progression to leprosy disease in the community, irrespective of contact status.[12-13] Population-wide programmes can be very challenging to implement on a large scale because of the logistical demands of reaching whole populations, difficulties achieving acceptability and buy-in, poor access to microbial confirmation in resourced-limited settings, a lack of clinical expertise for diagnoses, and challenges in mobilising resources to support population-wide programmes. The result is that leprosy MDA for large populations (>5,000 people) is often considered unfeasible in the regions where it is most needed.

Twenty-one of the 23 leprosy priority countries also have endemic tuberculosis (TB).[3] The relatively greater funding for TB and the global movement towards expanded ACF for TB,[14-16] the shared susceptibility of *Mycobacterium leprae* and *Mycobacterium tuberculosis* to rifamycins for preventive therapy, and the similar social determinants of transmission and disease all present opportunities for leprosy control programs to leverage TB programmes for mutual gain. Where the burden of both diseases is sufficiently high, this can take the form of combined population wide ACF and MDA chemoprophylaxis activities. In South Tarawa, the PEARL study (Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis (as

well as leprosy) in the Pacific)[17] provides the mechanism by which a combined intervention may be delivered at a fraction of the cost of a separate programme. Modelling of a mass chemoprophylaxis strategy for leprosy suggests this is an effective strategy,[18] and combining mass screening and treatment for TB are expected to greatly increase efficiency and cost-effectiveness. South Tarawa was chosen for the PEARL study as it is the centre with the highest population density in Kiribati and has the highest estimated incidence of TB and leprosy.

The COMBINE study is designed to inform programmatic strategies towards leprosy elimination in the Pacific and elsewhere. We aim to assess the effectiveness, feasibility, efficiency and cost of a programme of leprosy screening and mass rifamycin-based chemoprophylaxis delivered in combination with a TB screening, treatment and prevention initiative in Kiribati.[17] We will provide evidence for practicable means of integrating leprosy control with other communicable disease programmes that can be used to effectively accelerate leprosy prevention and care in endemic regions. Many of the research questions addressed by the COMBINE study must be answered to achieve scalable and durable leprosy elimination in countries like Kiribati.

OBJECTIVES

The COMBINE study assesses the feasibility and effectiveness of leprosy screening and MDA chemoprophylaxis in a highly endemic population using a programmatic approach that:

- Investigates whether combined population-wide screening and treatment for leprosy and TB together with MDA chemoprophylaxis and ongoing SDR-PEP for contacts can achieve rapid and durable reductions in leprosy incidence;
- Evaluates the effectiveness of leprosy MDA chemoprophylaxis using a pragmatic combination of either SDR or rifamycin-based TB preventive treatment;
- Measures the cost of MDA delivery when integrated with infrastructure from an existing population-wide screening program (the PEARL study[17]);
- Documents operational strategies to feasibly integrate enhanced leprosy and TB control efforts, and to reduce leprosy associated stigma.

METHODS AND ANALYSIS

Study design

COMBINE is a pragmatic controlled non-randomised before-and-after implementation study designed to evaluate the impact of the intervention upon leprosy NCDR. The COMBINE study will leverage infrastructure created by the PEARL study to deliver population-wide leprosy ACF and chemoprophylaxis. We will deliver the intervention over 3 years commencing November 2022 and ending November 2025, aiming to reach the entire population of South Tarawa in that time. The timeline of planned activities for the COMBINE study is illustrated in Supplementary Figure 1.

Setting

The Republic of Kiribati is a geographically isolated nation in the Pacific region comprising 32 atolls and one raised coral island spread over a land territory of 811 km^2 amid an ocean territory of 3.5 million km^2. The intervention site is the capital atoll of South Tarawa (population

63,439) which is the densely-populated 'transmission hot-spot' and amplifier of leprosy disease throughout the country (see **Table 1** for baseline characteristics of the study population).[19] Kiribati has only one specialised leprosy clinic which is located in South Tarawa. Residents live in village communities on a chain of low-lying islets connected by a causeway. Visitors from 'outer islands' to the capital often stay for an extended period. Anecdotally, this pattern of travel in and out of South Tarawa is associated with clusters of TB and leprosy in outer island communities.

While diagnosis and contact-tracing practices have been improved and standardised since 2010, it is uncertain whether the upward trend in new case detection rate (NCDR) in Kiribati over the past decade is an accurate measure of worsening epidemic control or reflective of enhanced case detection. What is clear, is that child NCDR has exceeded 30% of all newly detected cases for the past 3-years (2019-2021), indicating that the background community-level leprosy transmission has outpaced the potential to control the disease burden with existing leprosy programme interventions.

Table 1. Baseline characteristics of the population and intervention group

	Intervention group *South Tarawa*	**No intervention group** *Rest of Kiribati*	**Whole of Kiribati**
Population, 2020 *	63,439	56,501	119,940
- **Females (%)**	32,981 (52.0%)	27,805 (49.2%)	60,786 (50.7%)
- **Median age (years)**	23.2	22.3	22.9
- **Average household size (people)**	6.6	4.9	5.0
- **Net migration rate (% of population)**	2%	0.7%	1.4%
Urbanisation	Majority urban; some rural	Majority rural; some urban	Mixed urban and rural
BCG coverage, 2021 (% of live births) **	2434/2525 (96.4%)	839/888 (94.5%)	3273/3413 (95.9%)
Leprosy new cases, 2020 (rate per 10,000) **	93 (14.44)	62 (11.15)	155 (12.92)
- **Child cases (%)**	18 (19.4%)	18 (29.0%)	36 (23.2%)

- **MB cases (%)**	50 (53.8%)	20 (32.3%)	70 (45.2%)
Eligible contacts 2010–2020 **	9527	2264	11,811
- **received SDR (%)**	8381 (88%)	2021 (89%)	10,402 (89%)

Selected baseline characteristics or populations in the intervention area (South Tarawa), no intervention area (rest of Kiribati) and for the whole of Kiribati. BCG – Bacille Calmette-Guerin; MB – multibacillary; SDR – single-dose rifampicin.

* *National Statistics Office, 2020 census data*

** *Ministry of Health and Medical Services, programme data*

Intervention group and recruitment

The intervention group comprises residents of South Tarawa (and the small communities of Buota and Abatao adjacent to South Tarawa) aged 3-years and above, and aged less than 3-years if they have documented household contact (relevant definitions are provided in **Box 1**) with someone who has had TB in the past 1 year, or leprosy at any time since they were born. Study participants will be identified via household and village-level lists of residents from the 2020 census, and then invited to attend screening locations using door-to-door visits at households and community-based institutions (businesses, churches, et cetera). Basic demographic, social and geographic data will be collected at enrolment by the PEARL study screening teams.

Box 1. Definitions

Case of leprosy – clinical definition classified as multibacillary (MB) or paucibacillary (PB) according to WHO criteria that has been diagnosed by the doctor of the NLP.

Household - all those using the same kitchen, including members of extended families, the Maneaba (communal hospitality shelters), and dormitories in individual locations.

Household contact - any person who has been in contact with a new leprosy case for at least 20 hours per week for at least three months during the past five years.*

**adapted from WHO definition for the Kiribati context*

Interventions

An illustration of the combined TB and leprosy interventions is provided in **Figure 1**, comparing the intervention group and standard care in the comparison group. Interventions are described in detail below. In practice, these interventions will be delivered in the setting of a combined community-based screening, diagnosis, treatment and prevention service.

Case detection, diagnosis and treatment

Screening for leprosy will be conducted by a physical examination and questionnaire (**Supplement 1**). People with presumptive leprosy will be referred to the National Leprosy Program (NLP) for expert diagnosis. Cases will be validated by a leprologist and skin biopsies from all patients with clinically diagnosed leprosy will be tested by PCR for *M. leprae* and drug resistance mutations, according to WHO guidelines.[14] Leprosy treatment will be provided by the NLP according to Kiribati national guidelines. Further details of the leprosy screening, diagnosis and treatment eligibility criteria are available in the PEARL study protocol.[17]

Contact Tracing and Post-Exposure Prophylaxis

Contact tracing and SDR-PEP will be ongoing for all index cases identified during the intervention within the study site and throughout the rest of Kiribati, as is consistent with routine practice (**Box 1**). WHO recommends that leprosy contacts should be given SDR-PEP at ≥2 years of age.[20] This has been adopted by the Kiribati NLP since 2018 and will be supported by the COMBINE study to scale-up SDR-PEP delivery throughout the intervention period, as enhanced index case detection will increase contact tracing needs. Children who are younger than 2-years and are leprosy contacts will be followed up and offered SDR-PEP by the NLP when they reach 2 years of age.

Leprosy Mass Drug Administration Chemoprophylaxis

Rifamycin-based MDA chemoprophylaxis is provided using a composite of treatments. After integrated leprosy and TB screening, participants will be commenced on treatment for TB, treatment for leprosy, or TPT using a rifamycin-based regimen, depending on the screening outcome. For participants who are not eligible for any of those treatments, we will then offer a single dose of rifampicin according to the inclusion/exclusion criteria in **Table 2**. Considered together as in **Table 3**, all participants will be offered a rifamycin-based treatment; effectively a rifamycin-based leprosy MDA chemoprophylaxis. Detailed dosing information is provided in **Supplement 2**. SDR for PEP and MDA will be provided without baseline blood tests, consistent with the standard of care in Kiribati.

Table 2. Inclusion and exclusion criteria for single dose rifampicin

Inclusion criteria	**Exclusion criteria**
1. Enrolled in the screening intervention 2. Not eligible for any other rifamycin-based treatment 3. Aged ≥2 years 4. Informed consent. For children (<18 years) consent will be obtained from the parent or guardian, and children (≥10 years) will also provide assent.	1. History of serious liver or kidney disease. 2. Known pregnancy (SDR can be given after delivery). 3. Known allergy or severe adverse effects experienced with rifampicin use. 4. Refuses participation.

Inclusion criteria are shown for single dose rifampicin. Other treatment regimens are determined by indications and contraindications relevant to those regimens. MDA – mass drug administration; SDR – single-dose rifampicin.

Table 3. Overview of combined treatment and chemoprophylaxis

Screening outcome	**Treatment offered**	**Rifamycin component**
Leprosy	Leprosy MDT	Monthly rifampicin for 6-12 months
TB	TB treatment	Daily rifampicin for 6-12 months
RR-TB	DR-TB treatment + SDR	Single dose rifampicin

Eligible for TPT	3HP or 3RH	Weekly rifapentine or daily rifampicin for 3 months
Leprosy HHC	SDR-PEP	Rifampicin given at baseline and one year later
None of the above	SDR-MDA	Single dose of rifampicin

Screening outcomes are exhaustive but not mutually exclusive. The rifamycin component of each treatment strategy includes sufficient exposure to offer prevention for leprosy, in effect a mass drug administration of leprosy chemoprophylaxis. 3HP – 3-months of weekly rifapentine and isoniazid; 3RH – 3-months of daily rifampicin and isoniazid; DR-TB – drug-resistant tuberculosis; HHC – household contact; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; RR-TB – rifampicin-resistant tuberculosis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – tuberculosis preventive treatment.

Community Engagement and Stigma Prevention

The objective of community engagement and mass communications is to encourage participation in the screening programme and sensitise community members to appropriate, non-stigmatising messages related to leprosy and leprosy screening. This approach is supported by the best practice statement of the Global Partnership for Zero Leprosy.[11,21] The COMBINE study supports community engagement and stigma prevention through various activities developed in concert with the PLF (who have 10 years of experience in leprosy advocacy in Kiribati) and the MHMS. These activities include:

- bi-annual advocacy activity drives which may include leprosy awareness parades, plays, signage and mass communication.
- convening of a leprosy community support group for patients diagnosed with leprosy and their close contacts/families. COMBINE nurses will assist with mentoring the community group, training in coping strategies and supporting activities.

- annual training and development workshops including all staff of the national leprosy and TB programmes with anti-stigma training for health staff delivering the COMBINE screening intervention
- job-aids and resources to support health staff and people with leprosy, for example a flipbook to aid counselling sessions between health workers and people with leprosy

Post-intervention prevalence survey

A follow-up leprosy prevalence survey will be conducted in Betio islet (~18,500 people, located within the South Tarawa intervention group) 3-4 years after the intervention there has been completed.

Outcome measures and planned analyses

The primary research question of interest is the extent to which the intervention reduces leprosy annual NCDR compared with standard routine passive case-finding and post-exposure prophylaxis of close contacts. This will be assessed 1) by comparing the post-intervention NCDR in South Tarawa (in 2025) with the pre-intervention NCDR (in 2021) and 2) by comparing the change in NCDR in South Tarawa (the intervention site) with the change in NCDR observed in the outer Kiribati islands (non-intervention sites). A supplementary analysis will compare the prevalence rate of leprosy in Betio (~15,000 people) found in the initial population-wide screening intervention with the rate found from a survey in the same population performed 3-4 years later. All primary, supplementary and planned analyses will be performed using standard statistical methods, for example using Poisson regression for the NCDR outcomes and logistic regression to compare prevalence during and after the intervention.

Due to the long latency of leprosy, we expect that the full effect of the intervention will only become apparent after several years have elapsed. MHMS and PLF are committed to

continuing leprosy surveillance in Kiribati, enabling ongoing assessments of long-term trends in disease burden beyond 2025.

Other planned analyses will examine:

1. Diagnostic yield of leprosy screening using an optimised clinical examination and brief history in the setting of a community-based multi-disease screening intervention.
2. Description of the spectrum of leprosy disease in South Tarawa.
3. Description of leprosy clusters and transmission patterns using geospatial data and social contact mapping
4. The prevalence ratio of genotypic *M. leprae* resistance to rifampicin, dapsone and quinolones before and after the MDA programme (using PCR-based assays of skin biopsies) [22-25]
5. The costs of leprosy-only activities, TB-only activities and shared activities to inform the cost-efficiency of future combined leprosy elimination projects in the Pacific and elsewhere
6. The relative risk of leprosy diagnosis in participants with and without prior exposure to rifamycins (provided as part of routine activities of the NLP and NTP), prior BCG vaccination and prior TB infection and/or disease in a high-incidence setting
7. The feasibility of combined TB and leprosy elimination efforts in the intervention site assessed using a mixed methods approach: measurement of treatment coverage, description of health service requirements (health care worker mix and person-time), description of infrastructure requirements, and surveys and interviews conducted with healthcare workers, decision makers, community representatives and study participants.
8. Mathematical modelling of the dynamics of leprosy incidence using 'real life' data from the COMBINE study with the aim of refining previous models[18] to improve accuracy of forecasting and decision support

Sample size

Assuming mass chemoprophylaxis coverage of 80% of the population and given a leprosy NCDR of 1600/1,000,000 for South Tarawa (the intervention group, population ~65,000) and 872 per 1,000,000 for the rest of the country (comparison group, population ~55,000), the study would provide greater than 99% power ($\alpha \leq 0.05$) to detect a 50% reduction (before versus after difference) in NCDR in South Tarawa (the intervention group) and 82% power to detect a 50% reduction in South Tarawa compared with no change in the rest of the country. Predicted sample sizes were calculated using the mean number of cases observed between 2018 and 2020 and simulated number of cases observed in 2025, drawn from a Poisson distribution (10,000 replicates) according to the parameters above and assuming a population growth of 5,000 in each area.

Economic analysis and costing

COMBINE proposes to estimate unit costs for screening per patient, working closely with the PEARL study to perform a cost analysis of TB-only activities, leprosy-only activities and shared activities. Accurate costing data will inform future leprosy elimination projects in the Pacific region and beyond, and will have additional benefits for subsequent planning, budgeting and modelling exercises. To enhance the application of our findings, we will seek to align costing data with existing interagency costing tools.

Data collection and monitoring

All leprosy and TB screening, chemoprophylaxis and outcome data will be captured offline on encrypted tablet devices using Research Electronic Data Capture (REDCap) surveys. Data will be uploaded and stored on a high security REDCap database server managed by the University of Sydney. Leprosy case and contact management data are already archived in a comprehensive NLP database, with maintenance supported by the PLF before, during and after the study. We will contribute case and contact data from the COMBINE study to the

existing supported database through routine study procedures. Mass screening and MDA data will be available to NLP as needed and handed over to the NLP after study completion.

Post-study follow-up activities

Country-wide ACF and PEP for household contacts will continue beyond the COMBINE study as a joint-program implemented by the NLP and the PLF. We consider that the early findings of the present study will enable mobilisation of funds to deliver similar population-wide leprosy control activities in other parts of the country, as part of a 'Zero Leprosy Roadmap'. Case and contact management records are already maintained in a comprehensive database, and relevant data from the COMBINE study will be added as part of study procedures. Together with mass screening data, this will provide a rich source for future analysis of long term outcomes in the study population.

ETHICS AND DISSEMINATION

Ethical approval for the COMBINE study has been obtained from the University of Sydney (project no. 2021/127), the University of Otago (H22/111) and the Kiribati Ministry of Health and Medical Services. Government support for the study to occur in collaboration with the NLP has been provided by Kiribati National Cabinet.

Participant information and counselling is provided to all prospective participants and again before treatment is offered (**Supplement 3**). Editable versions of study patient tools and a counselling flipbook are available at www.leprosy.org.nz and www.thepearlstudy.org. Informed consent is gathered verbally before participant enrolment and a signed record of consent is collected in the study REDCap database (**Supplement 4**). Verbal consent for participants attending the NLP for confirmation of diagnosis and treatment management will be obtained according to standard programme practice. Written informed consent for a skin biopsy will be taken as is usual in the clinic. This includes consent to send the specimen abroad for analysis.

The safety of treatments for TB are discussed in the PEARL study protocol.[17] SDR is very safe, and has been used in Kiribati [18,19] and elsewhere[12, 26-28] with little or no recorded side-effectsA study hotline and walk-in clinic will be freely available for adverse event (AE) management throughout the study period. Information on the signs and symptoms of leprosy and instructions to access the permanent leprosy clinic are provided to all participants (including those who decline to participate). Serious AEs are reported in accordance with national and University of Sydney pharmacovigilance standards. Intervention monitoring and auditing procedures will be conducted annually by the MHMS in accordance with routine practice with study reports made annually to ethics and funding bodies.

All study data will be shared with the MHMS. Reports of study progress will be made to the Kiribati community by mass communication and on the Pacific Leprosy Foundation and the PEARL study websites. Study findings will be presented at international conferences and in peer reviewed publications.

Patient Involvement Statement

This study was developed with the involvement of a reference group of I-Kiribati people affected by leprosy. This group will be involved in the COMBINE study in an ongoing basis. In particular, they will give advice concerning the practical implementation of the research, including the best ways of liaising with patients, their families and the community to ensure that communication is positive and does not contribute to stigma for people identified with leprosy and their contacts.

DISCUSSION

Innovative solutions are required to achieve progress towards leprosy elimination in Kiribati and in other areas of continuing high incidence. This is essential if we are to overcome the barriers to achieving global Zero Leprosy targets,[11] and eventually, true global leprosy

elimination. As leprosy continues to require long and complex treatment programs, there is also urgency to find novel control strategies before antibiotic resistance emerges and accelerates in high transmission populations.[29]

The proposed study design combines a robust public health intervention in response to the dual epidemics of leprosy and TB in Kiribati, along with rigorous evaluation of the intervention. Population-wide leprosy active case-finding and MDA with rifamycin-based chemoprophylaxis in a population of approximately 60,000 represents a bold step towards acceleration of leprosy control. Combining this intervention with a similar population-wide TB screening, treatment and prevention programme is an innovative health systems approach that could improve efficiency and feasibility of large-scale interventions for both diseases. If successful, this would present an important model that may be implemented in other settings.

There are several limitations associated with this study protocol that may affect outcomes. First, the population wide screening and mass drug administration intervention in this study is in essence a change in health policy whereby the target population is expanded to include all residents of South Tarawa, rather than just specific contacts or groups of individuals. As with any health policy change or community-facing intervention, the impact of this new approach is dependent on the new policy reaching a large proportion of the target population and being delivered with high fidelity to the proposed design. We will take every effort to achieve high uptake and retention in care by conducting extensive community mobilisation and health communication activities. Although the outcomes of this study are defined at population level (NCDR measured before and after) and not dependent on individual level enrolment and withdrawal, we will also maintain detailed individual level records to enhance follow-up. Second, the intervention is not randomised. This will limit our ability to make inferences about causation, especially if the impact on NCDR is small. We hope that by including the rest of the country as a non-randomised 'control' group we will have some basis for comparison. Finally, the proposed combined approach to screening and prevention means that the intervention is

more time consuming to deliver and will take longer to reach the entire target population. We anticipate some level of reinfection to occur in already-screened areas of South Tarawa, while we continue to deliver the intervention across the island. Although reinfections may reduce the impact on measured NCDR, we anticipate that this would still be valuable information since we are taking a 'real world' public health approach that could serve as an example to other settings.

In Kiribati (and elsewhere [12, 30]), MDA chemoprophylaxis in the 1990s led to reductions in leprosy case detection but ultimately failed to produce a lasting decline in incidence in some settings. The long latency period of the disease and the absence of surrogate measures of leprosy transmission make robust short-to-medium-term outcome measures of the population-level effect of interventions particularly limited. These are challenges intrinsic to population-level leprosy research. This study is designed to address these challenges by rigorous evaluation of scaled-up interventions in combination with durable partnership for evaluation of longer-term incidence and transmission outcomes. This 'real-life' operational research design to evaluate the main intervention is accompanied by a commitment by the MHMS together with the PLF to deliver leprosy control activities over the longer term, until leprosy is eliminated in Kiribati (www.leprosy.org.nz); this includes surveillance, continuation of rigorous contact identification and management, and expansion of population-wide screening and mass drug administration to the rest of the country. In the shorter and medium term, improvements in the accuracy of modelling of the intervention impact (using data from the COMBINE study) will provide useful insights and interim measures of the effect of COMBINE interventions upon leprosy incidence. This will be valuable to inform programs facing similar challenges to Kiribati. The present study, along with short, medium and long term aims and commitments are currently being integrated using a 'Leprosy elimination roadmap', adapting the methods and experiences of the Global Partnership for Zero Leprosy. By embedding this study within long-term strategic partnerships, with ongoing funding and a comprehensive strategy, we hope that

the missteps of previous MDA interventions can be avoided and lasting impact can be achieved along with research outputs that will guide future interventions.[19]

Kiribati is in a unique position, given its geographic isolation, low migration rate and limited population size, to identify and test innovative elimination strategies as proof-of-principle for leprosy control in other locations. We plan to grasp this opportunity and deliver much-needed evidence to reinvigorate attempts to eliminate this age-old scourge of humankind.

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Contributors

All authors contributed to the conceptualisation and panning of this research. MC, JH, NMD, JT, JW, BMJ, WJB and STC wrote the study proposal. ET, ER, TB, NI, AC, NMD, TI, POC and PP made important intellectual contributions to the final protocol manuscript. MC and JH contributed equally to this paper. The funding agency played no part in any aspect of the study, nor the decision to submit this manuscript for publication.

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Competing interests' statement

Some project funding is provided by the Pacific Leprosy Foundation, which also supports consultancy work of co-authors AC and NI.

Figure 1. Overview of COMBINE study intervention

Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

REFERENCES

1. Resolution to eliminate leprosy as a public health problem by the year 2000 resolution WHA449. World Health Assembly: Geneva: 44th World Health Assembly, 1991.
2. WHO. World Health Organization leprosy elimination project: status report 2002: World Health Organization, 2003.
3. WHO. World Health Organization Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. *Weekly Epidemiology Record* 2021;96(36):421-44.
4. Urgesa K, Bobosha K, Seyoum B, et al. Evidence for hidden leprosy in a high leprosy-endemic setting, Eastern Ethiopia: The application of active case-finding and contact screening. *PLoS neglected tropical diseases* 2021;15(9):e0009640.
5. Bernardes F, Paula NAd, Leite MN, et al. Evidence of hidden leprosy in a supposedly low endemic area of Brazil. *Memórias do Instituto Oswaldo Cruz* 2017;112:822-28.
6. Smith WC, van Brakel W, Gillis T, et al. The missing millions: a threat to the elimination of leprosy. *PLoS neglected tropical diseases* 2015;9(4):e0003658.
7. de Oliveira GL, Oliveira JF, Pescarini JM, et al. Estimating underreporting of leprosy in Brazil using a Bayesian approach. *PLoS Neglected Tropical Diseases* 2021;15(8):e0009700.
8. Frade MAC, de Paula NA, Gomes CM, et al. Unexpectedly high leprosy seroprevalence detected using a random surveillance strategy in midwestern Brazil: A comparison of ELISA and a rapid diagnostic test. *PLoS Neglected Tropical Diseases* 2017;11(2):e0005375.
9. Mangeard-Lourme J, Singh A, Singh RK, et al. Enhanced active case-finding, identifying leprosy cases missed by recent detection campaigns in Munger District, Bihar, India. *Leprosy Review* 2017;88(4):452-62.
10. Salgado CG, Barreto JG, da Silva MB, et al. Are leprosy case numbers reliable? *The Lancet Infectious Diseases* 2018;18(2):135-37.

11. WHO. World Health Organization Towards zero leprosy. Global leprosy (Hansen's Disease) strategy 2021–2030. 2021

12. Tiwari A, Dandel S, Djupuri R, et al. Population-wide administration of single dose rifampicin for leprosy prevention in isolated communities: a three year follow-up feasibility study in Indonesia. *BMC Infectious Diseases* 2018;18(1):324. doi: 10.1186/s12879-018-3233-3 [published Online First: 2018/07/13]

13. Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *The American Journal of Tropical Medicine and Hygiene* 2005;72(4):443-48.

14. WHO. World Health Oorganization consolidated guidelines on tuberculosis Module 2: Screening – Systematic screening for tuberculosis diseas. *Global Tuberculosis Programme* 2021

15. WHO. Rapid communication on systematic screening for tuberculosis. 2020

16. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New England Journal of Medicine* 2019;381(14):1347-57. doi: 10.1056/NEJMoa1902129 [published Online First: 2019/10/03]

17. Coleman M, Hill J, Timeon E, et al. Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati: the PEARL study protocol. *BMJ Open* 2022;12(4):e055295. doi: 10.1136/bmjopen-2021-055295

18. Gilkison C, Chambers S, Blok DJ, et al. Predicting the impact of household contact and mass chemoprophylaxis on future new leprosy cases in South Tarawa, Kiribati: A modelling study. *PLoS Neglected Tropical Diseases* 2019;13(9):e0007646. doi: 10.1371/journal.pntd.0007646 [published Online First: 2019/09/21]

19. Chambers ST, Ioteba N, Timeon E, et al. Surveillance of Leprosy in Kiribati, 1935–2017. *Emerging Infectious Diseases* 2020;26(5):833.

20. WHO. Leprosy/Hansen disease: Contact tracing and post-exposure prophylaxis. 2020

21. van Brakel WH, da Silva Pereira ZB, Barbosa JC, et al. Global Partnership for Zero Leprosy Research Agenda Working Group Subgroup on Stigma, 2019.

22. Coppola M, van den Eeden SJ, Robbins N, et al. Vaccines for leprosy and tuberculosis: opportunities for shared research, development, and application. *Frontiers in Immunology* 2018;9:308.

23. Lahiri R, Adams LB. Cultivation and viability determination of Mycobacterium leprae. *International Textbook of Leprosy* 2016

24. Davis GL, Ray NA, Lahiri R, et al. Molecular assays for determining Mycobacterium leprae viability in tissues of experimentally infected mice. *PLoS Neglected Tropical Diseases* 2013;7(8):e2404.

25. Williams DL, Torrero M, Wheeler PR, et al. Biological implications of Mycobacterium leprae gene expression during infection. *Microbial Physiology* 2004;8(1):58-72.

26. Richardus JH, Tiwari A, Barth-Jaeggi T, et al. Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme. *Lancet Global Health* 2021;9(1):e81-e90. doi: 10.1016/s2214-109x(20)30396-x [published Online First: 2020/11/02]

27. Schoenmakers A, Mieras L, Budiawan T, et al. The State of Affairs in Post-Exposure Leprosy Prevention: A Descriptive Meta-Analysis on Immuno- and Chemo-Prophylaxis. *Research and Reports in Tropical Medicine* 2020;11:97-117. doi: 10.2147/rrtm.S190300 [published Online First: 2020/10/30]

28. Feenstra SG, Pahan D, Moet FJ, et al. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Leprosy Review* 2012;83(3):292-304. [published Online First: 2013/01/30]

29. Cambau E, Saunderson P, Matsuoka M, et al. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clinical Microbiology and Infection* 2018;24(12):1305-10.

30. Nguyen LN, Cartel JL, Grosset JH. Chemoprophylaxis of leprosy in the southern Marquesas with a single 25 mg/kg dose of rifampicin. Results after 10 years. *Leprosy*

Review 2000;71 Suppl:S33-5; discussion S35-6. doi: 10.5935/0305-7518.20000064

[published Online First: 2001/02/24]

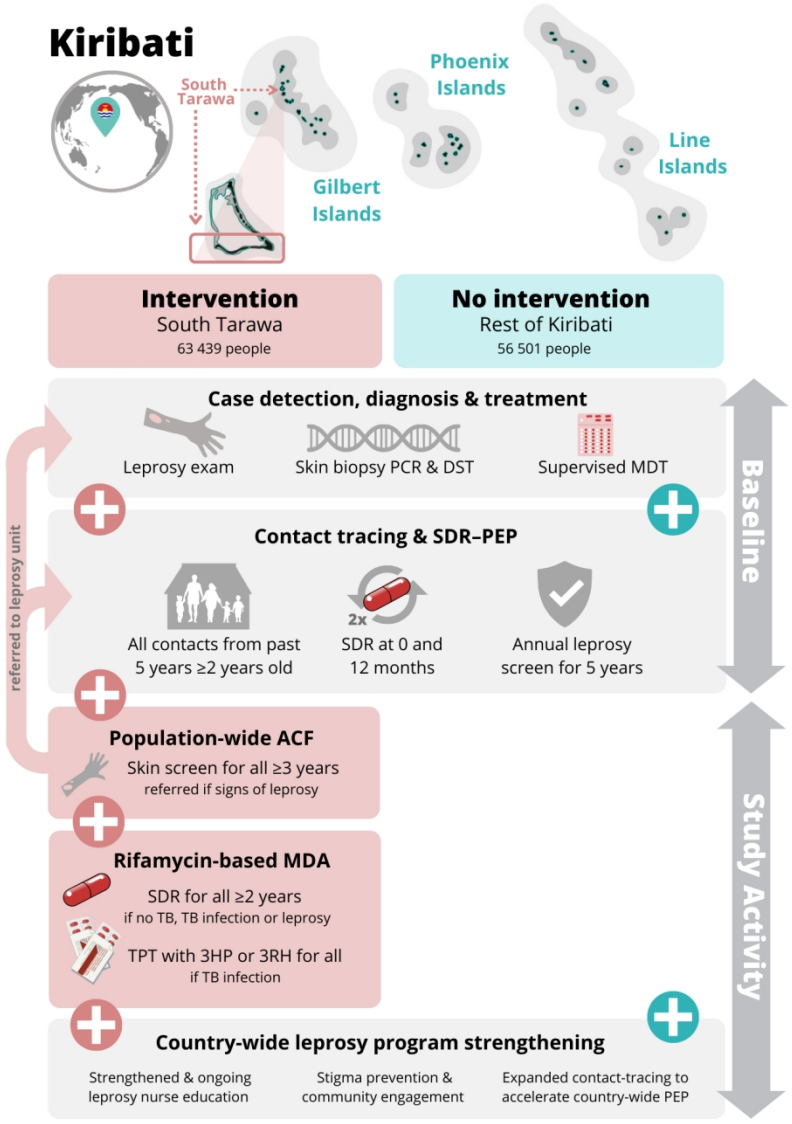


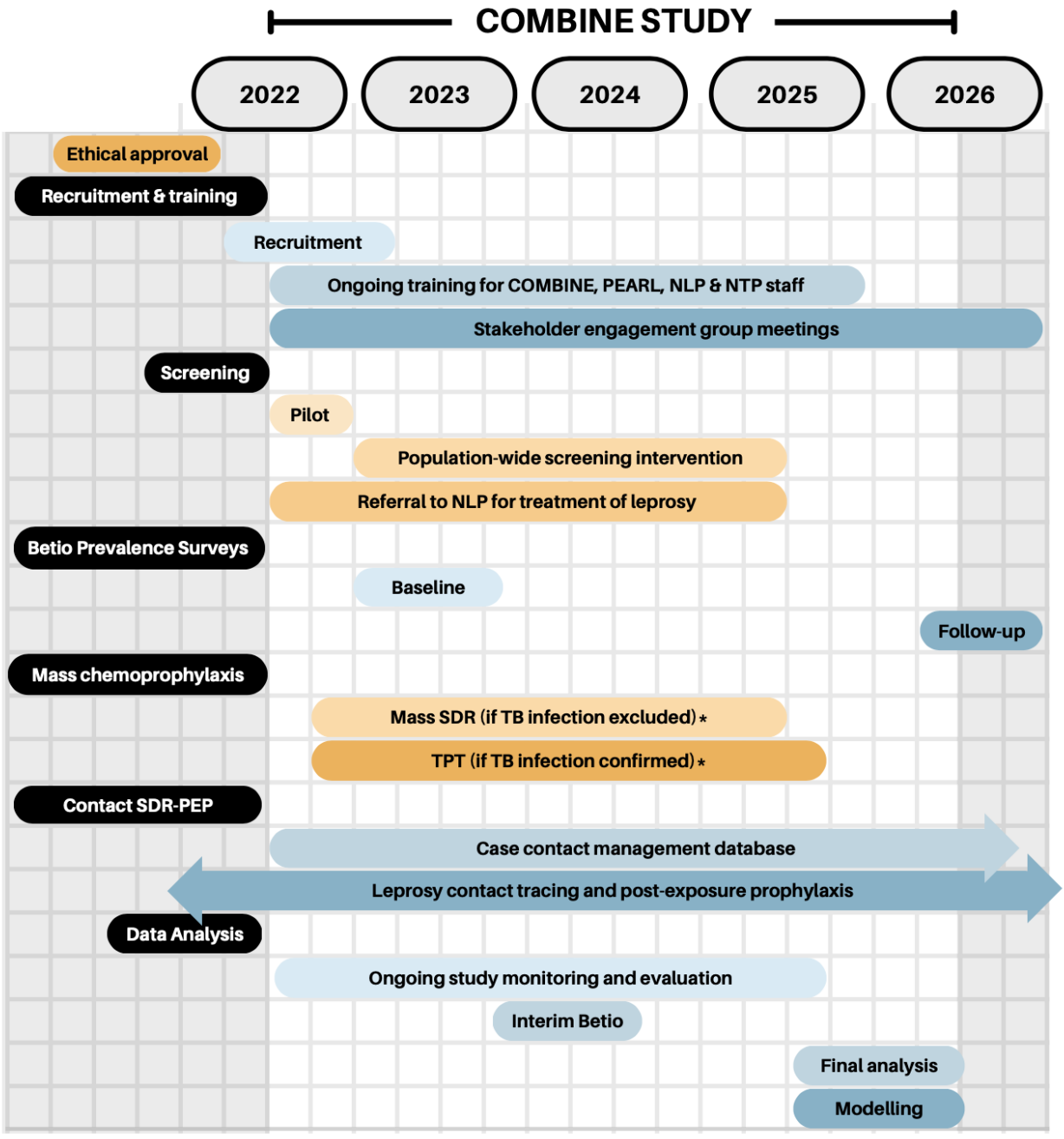
Figure 1. Overview of COMBINE study intervention. Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

536x758mm (67 x 67 DPI)

Supplementary Materials

The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SUPPLEMENTARY FIGURE 1:



Supplementary Figure 1. Timeline of COMBINE study activities

Formal COMBINE activities commenced in July 2022 and should conclude in June 2026, with data analysis and dissemination of outcomes included in this period. Left-facing arrow indicates activity which began prior to the COMBINE study. Right-facing arrows indicate activities which will continue beyond the end of the COMBINE study through NLP and PLF activities, provided adequate funding is procured. NLP – National leprosy program; NTP – National tuberculosis program; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TPT – tuberculosis preventive treatment. ***TB and leprosy disease also excluded*

SUPPLEMENT 1. Leprosy screening Standard Operating Procedure

Population leprosy screening – general steps

1. Ask about leprosy (this may be done at a history taking station)
2. Conduct a physical check for leprosy
3. Record findings in CRF
    a. Take a photo of any examination findings
4. Refer for further evaluation if there are any findings (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)

Population leprosy screening – details

Ask (this may be done at a history taking station)

- Have you had or do you have leprosy? Have you ever been treated for leprosy?
- Are you a household contact* of someone who has had leprosy?
- Are you worried you might have leprosy? If so, why?
- Do you have any skin lesions or other abnormalities that you think could be leprosy?

Exposure

- Remove footwear and any outer layers of clothing

Areas of body to inspect

- Face including eyelashes, eyebrows, nose and mouth
- Ears
- Neck
- Arms and hands
- Legs and feet
- Lift the shirt and lower the waistband for back and upper buttocks

Looking for

- Skin lesions (pale, red, thick, raised, shiny)
    - Check if itchy, if so, don't refer to NLP (consider alternative referral if concerning)
- Skin nodules
- Altered shape of nose or ears
- Loss of eyelashes or eyebrows
- Altered shape of hand or foot
    - Check if present from birth, if so, don't refer
- Ulcers on hand or foot

Who to refer?

- People with physical examination findings consistent with leprosy
- People who are worried they might have leprosy (any reason)

How to record

- Fill the CRF
- Take a photo (good lighting, ruler or TST syringe for scale)
- Refer for further evaluation (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)
- Give referral letter if needed

* Household contact is defined according to WHO. *"Household contacts: contacts living in the same dwelling or sharing the same kitchen as the index case. These include family members but also domestic staff or aids or co-workers or others sharing the same accommodation. A family member living elsewhere should not be considered as a contact."*

SUPPLEMENT 2.

Table S1. Single dose rifampicin (SDR) chemoprophylaxis dosing.

Age/body weight	Rifampicin single dose
15 years and above	600 mg
10-14 years	450 mg
Children 6-9 years (weight ≥ 20 kg)	300 mg
Children 6-9 years (weight < 20 kg)	150 mg
Children <5 years	10-15 mg/kg

Table S2. Tuberculosis preventive treatment dosing.

S2A. 12 doses of weekly isoniazid (H) and rifapentine (P) for adults and children ≥25 kg

Weight band	HP (300mg/300mg) tablets
25-30kg (or <15ys)	2
≥30kg and ≥15ys	3

S2B. 3 months of daily dosing of child-friendly water-dispersible rifampicin (R) and isoniazid (H) tablets for children <25kg

Weight band	RH (75mg/50mg) tablets
4-7kg	1
8-11kg	2
12-15kg	3
16-25kg	4

SUPPLEMENT 3. Participant Information

PARTICIPANT INFORMATION

Finding and preventing TB and leprosy cases in Tarawa

Dear participant,

We would like to invite you (and your child if relevant) to be treated for latent or sleeping TB. This document provides information about the study, but we will also explain the study to you in person. You will have the opportunity to ask questions if there is anything that you do not understand or if you want more information. You may refuse participation and this will not be held against you or affect any future access to healthcare.

What is this study about?

TB is a disease caused by germs that are coughed into the air by someone who is ill with TB. Most people who are infected with the TB germ do not become ill and do not even know that they are infected, this is referred to as latent or 'sleeping' TB. **Sometimes sleeping TB can wake up and make you ill, which may spread the germ to others**. This research aims to treat all people with TB, those who are ill and those with sleeping TB, so that we can try to eliminate TB from Tarawa. At the same time we are also trying to eliminate leprosy from Tarawa.

This Participant Information Form tells you about the study so that you can know what it involves. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Who is conducting the study?

The study is carried out by researchers at the University of Sydney, Australia, in close collaboration with the Kiribati National TB and Leprosy Programme (NTP). The study is funded by the Australian Medical Research Future Fund and fully supported by the Kiribati Ministry of Health.

What will happen?

This study involves screening for TB (both 'sleeping TB' and illness caused by TB) and leprosy. People who are ill with TB or leprosy will be referred to the TB and Leprosy Programme for appropriate treatment. People with 'sleeping TB' will be offered TB preventive treatment (TPT) and those without any illness or TB infection will be offered leprosy preventive prophylaxis.

To check if someone is able to be given medication for sleeping TB, a study nurse will ask some personal questions. This may include questions about previous and current illnesses, medications used, drinking of alcohol or kava, and questions about pregnancy if you are a woman. Every person older than 20 years will be given a rapid test to see if they have hepatitis B infection, which is important for us to know before considering treatment for 'sleeping TB'. This test involves a finger prick to get a small drop of blood. People with risk factors will need to have a small amount of blood drawn to make sure their liver function stays healthy during the time that they are treated for sleeping TB.

How much of my time will the study take?

We will try to waste as little of you time as possible. To complete the TB and leprosy screening will require you (and your whole household) to be seen on two separate days. This is to complete all the necessary documentation and tests. It is expected that this will take about 2-3 hours of your time on each of these days. These diagnosed with sleeping TB will need to take tablets once a week for 12 weeks. Tablets will be given out at the mobile health clinic on a monthly basis and can be collected between 9am and 4pm on weekdays**.**

Who can take part in the study?

Every person older than 3 years of age living in Tarawa and Betio islet is invited to take part.

Do I have to be in the study? Can I withdraw from the study once I've started?

Taking part in this study is strongly recommended by the Kiribati Ministry of Health and Medical Services (MHMS) to get rid of TB and leprosy across Tarawa. However, participation is completely voluntary and you do not have to take part. Your decision will not affect your current or future relationship with the researchers, the Kiribati National TB and leprosy Program or the Ministry of Health.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by visiting the study clinic and speaking with a study nurse who will give you exit information and advice on how to stay healthy from TB in the future.

If you decide to withdraw from the study, we will not collect any further information from you. Information that we have already collected will be kept in our study records and may be included in the study results.

Are there any costs or risks associated with being in the study?

There are no costs associated with study participation. Mobile study clinics will be conveniently situated to be easily accessible and all study tests or treatment will be funded by the study.

If treatment for 'sleeping TB' is provided it is normal to feel a bit tired and to have bright orange urine while you are taking the tablets. Rarely people may develop some of the symptoms below, in which case it is important to inform us immediately. Rare symptoms to look out for include:

- ongoing nausea, vomiting or loss of appetite
- new rash or itchy skin
- yellowing skin or eyes
- tingling or numbness in fingers or toes
- any other symptoms of concern to you

Study nurses and doctors are available Monday to Friday, 9am to 4pm to see anyone who is feeling sick and thinks this may be due to their treatment. You may also call the 24-hour treatment hotline using the number on the back of your treatment card (TPT passport).

Are there any benefits associated with being in the study?

Yes, there are major benefits to yourself and the wider community of Tarawa, including Betio islet

- You (and your child) will get treatment for TB or leprosy if required
- You (and your child) will get treatment for sleeping TB (TPT) or to keep leprosy away
- You will help to eliminate TB and leprosy from Tarawa
- Study results will help other Pacific Island nations to eliminate TB and leprosy in the future

What if I have a complaint or any concerns about the study?

This research has been reviewed by an independent group of people called a Human Research Ethics Committee (HREC) at the University of Sydney and the Kiribati Ministry of Health and Medical Services.

If you are concerned about the way this study is being conducted please inform the study team; we want to learn and hear how we can improve things. If you wish to make a complaint to someone independent then please contact any of the people listed below.

Terotia Tabwaka Kelese, Human Resource Officer, Republic of Kiribati

Email: ttabwaka@gmail.com

or

The Manager, Ethics Administration, University of Sydney:

Telephone: +61 2 8627 8176

Email: human.ethics@sydney.edu.au

Fax: +61 2 8627 8177 (Facsimile)

Ethical Approval

This research plan (protocol) was approved by the ethics committee of the faculty of medicine and health at the University of Sydney. This helps to ensure that we do everything possible to keep you safe and to respect your rights and privacy at all times.

We thank you for your time and cooperation.

The PEARL Research Team with the support of the Kiribati National TB and Leprosy Control Programmes. **Further information can be found at www.thepearlstudy.org**

On behalf of the Kiribati Health Secretary

……

SUPPLEMENT 4. Informed Consent Form

INFORMED CONSENT PROCESS FORM

Date of informed consent Today D-M-Y

Does the participant have capacity to consent?
- Yes
- No - young person <18 years of age
- No - disability
- No - other reason

reset

Name of Consenting Guardian

Relationship of consenting guardian
- parent
- spouse
- grandparent
- aunt/uncle
- sibling
- other relative
- non-relative guardian

reset

Does the participant assent to participate in the study?
- Yes
- No

reset

Does the participant/primary caregiver agree to participate in study?
- Yes
- No

reset

Can participant/caregiver read Kiribati?
- Yes
- No

reset

Can participant/caregiver read English?
- Yes
- No

reset

Participant information given and all participant questions answered?
- Yes
- No

reset

Participant is aware that this is a public health intervention endorsed and supported by the Kiribati Ministry of Health and Medical Services?
- Yes
- No

reset

Participant is aware that screen may involve providing sputum or blood samples?
- 1. Yes / Yes
- 0. No / No

reset

Date & Time Participant/caregiver signed documentation of consent Now D-M-Y H:M

Sign

Add signature

Other comments

Mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NA not a trial
	2b	All items from the World Health Organization Trial Registration Data Set	NA not a trial
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2; 22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	13-14; table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14; figure 1; table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13; 18-19; Supplement 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-15; 18-19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-15; 18-19; S2
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA non-random
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA population-wide
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA population-wide
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA open-label
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA open-label
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18; Supplement 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18-19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4-5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19; Table 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22-23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4-5
	31b	Authorship eligibility guidelines and any intended use of professional writers	22-23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3-4
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

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TITLE

The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

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ABSTRACT

Progress towards leprosy elimination is threatened by increasing incidence in 'hot-spot' areas where more effective control strategies are urgently required. In these areas, active case finding and leprosy prevention limited to known contacts is insufficient for control. Population-wide active case-finding together with universal prevention through mass drug administration (MDA) has been shown to be effective in 'hot-spot' areas, but is logistically challenging and expensive. Combining leprosy screening and MDA with other population-wide screening activities such as for tuberculosis may increase programme efficiency. There has been limited evaluation of the feasibility and effectiveness of combined screening and MDA interventions. The COMBINE study aims to bridge this knowledge gap.

Methods and analysis

This implementation study will assess the feasibility and effectiveness of active leprosy case-finding and treatment, combined with MDA using either single-dose rifampicin or rifamycin-containing tuberculosis preventive or curative treatment, for reducing leprosy incidence in Kiribati. The leprosy programme will run over 2022–2025 in concert with population-wide tuberculosis screening-and-treatment in South Tarawa. The primary research question is to what extent the intervention reduces the annual leprosy new case detection rate (NCDR) in adults and children compared to routine screening and post-exposure prophylaxis (PEP) among close contacts (baseline leprosy control activities). Comparisons will be made with 1) the pre-intervention NCDR separably amongst adults and children in South Tarawa (before-after study) and 2) the corresponding NCDRs in the rest of the country. Additionally, the post-intervention prevalence of leprosy obtained from a survey of a 'hot-spot' sub-population will be compared to prevalence documented during the intervention. The intervention will be implemented in collaboration with the Kiribati National Leprosy Program.

Ethics and dissemination

Approval has been obtained from the Kiribati Ministry of Health and Medical Services (MHMS), the University of Otago (H22/111) and the University of Sydney (2021/127) Human Research Ethics Committees. Findings will be shared with the MHMS, local communities and internationally through publication.

Strengths and limitations of this study

- Designed for both rapid and sustained reduction in leprosy prevalence using a combination of active case-finding with treatment and mass drug administration for population-wide chemoprophylaxis
- Geographically isolated island with high rates of leprosy, relatively small population and limited population mobility, facilitating proof-of-principle testing with low risk of dilution of intervention effect
- Dovetailing of existing leprosy and tuberculosis elimination activities has the potential to maximise efficiency and impact, especially in settings with a high-incidence of both diseases
- The absence of randomisation limits attribution of effect to the intervention; partially compensated for by employing multiple comparator assessments
- Despite the geographic isolation, the long implementation period (3 years) may allow leprosy re-infection events to occur in the community through inter-island travel

INTRODUCTION

Since the 1991 World Health Association resolution to eliminate leprosy,[1][1] tremendous progress has been made towards global leprosy elimination.[2] However, despite enhanced early detection and availability of effective treatment and prevention options, progress has reversed in some leprosy 'hot-spots' (regions of high leprosy endemicity).[3] National leprosy disease and disability rates have stagnated in most of the 23 leprosy global priority countries with an increase in grade-2 disability reported in 2020 for 7 of these countries, including Kiribati.[3] Global de-funding for leprosy control and health system prioritisation of diseases with more obvious and immediate clinical presentations than leprosy have exacerbated these challenges. Point prevalence surveys in leprosy endemic regions reveal many undetected cases, with major case detection and reporting gaps responsible for the 'missing millions'.[4-10] Although the relatively low incidence of childhood leprosy (6.8% of all newly detected cases) indicates that transmission has declined globally, this is not true in all areas with cases among children increasing in some countries.[3]

The ongoing leprosy disease burden in the Pacific Island nation of Kiribati is emblematic of the global situation in high burden countries. Kiribati has one of the highest leprosy incidence rates in the world and these rates are on the rise; the Ministry of Health and Medical Services (MHMS) reports a 17% increase in incidence from 2010 to 2020, with 15.9 new cases detected per 10,000 people in 2020.[3] Curative and preventive services are routinely provided by the National Leprosy Program (NLP) in line with World Health Organization (WHO) guidelines, in partnership with the Pacific Leprosy Foundation (PLF). The NLP screens contacts for leprosy and, if active leprosy is not identified, provides single-dose rifampicin for post-exposure prophylaxis (SDR-PEP) immediately and one year later. In addition, contacts are screened for signs and symptoms of leprosy annually for four more years after the initial screening. SDR-PEP was introduced in 2018 and has since been provided to 89% of all eligible leprosy contacts recorded since 2010, which amounts to screening and prophylaxis for ~9% of the total population of Kiribati (10,406 contacts). Despite these interventions, most new leprosy

cases in Kiribati are detected passively rather than by contact tracing with many presenting with advanced disease; almost half of all cases have multibacillary disease. These cases have long infectious periods before diagnosis and are an important source of transmission in the community.

To make an impact on the leprosy epidemic in Kiribati and to meet the ambitious Zero Leprosy target to halve global leprosy incidence by 2030,[11] bold new strategies are needed. Such strategies should be designed to break the chain of leprosy transmission and to reduce the risk of disease progression in highly endemic regions. One avenue for exploration is to expand the reach of active case-finding (ACF) and preventive interventions in high-risk populations. In previous studies, regions with smaller populations, but similar disease burdens to Kiribati, have benefitted from population wide ACF and mass drug administration (MDA) with SDR to reduce the risk of progression to leprosy disease in the community, irrespective of contact status.[12 13] Population-wide programmes can be very challenging to implement on a large scale because of the logistical demands of reaching whole populations, difficulties achieving acceptability and buy-in, poor access to microbial confirmation in resourced-limited settings, a lack of clinical expertise for diagnoses, and challenges in mobilising resources to support population-wide programmes. The result is that leprosy MDA for large populations (>5,000 people) is often considered unfeasible in the regions where it is most needed.

Twenty-one of the 23 leprosy priority countries also have endemic tuberculosis (TB).[3] The relatively greater funding for TB and the global movement towards expanded ACF for TB,[14-16] the shared susceptibility of *Mycobacterium leprae* and *Mycobacterium tuberculosis* to rifamycins for preventive therapy, and the similar social determinants of transmission and disease all present opportunities for leprosy control programs to leverage TB programmes for mutual gain. Where the burden of both diseases is sufficiently high, this can take the form of combined population wide ACF and MDA chemoprophylaxis activities. In South Tarawa, the PEARL study (Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis (as

well as leprosy) in the Pacific)[17] provides the mechanism by which a combined intervention may be delivered at a fraction of the cost of a separate programme. Modelling of a mass chemoprophylaxis strategy for leprosy suggests this is an effective strategy,[18] and combining mass screening and treatment for TB are expected to greatly increase efficiency and cost-effectiveness. South Tarawa was chosen for the PEARL study as it is the centre with the highest population density in Kiribati and has the highest estimated incidence of TB and leprosy.

The COMBINE study is designed to inform programmatic strategies towards leprosy elimination in the Pacific and elsewhere. We aim to assess the effectiveness, feasibility, efficiency and cost of a programme of leprosy screening and mass rifamycin-based chemoprophylaxis delivered in combination with a TB screening, treatment and prevention initiative in Kiribati.[17] We will provide evidence for practicable means of integrating leprosy control with other communicable disease programmes that can be used to effectively accelerate leprosy prevention and care in endemic regions. Many of the research questions addressed by the COMBINE study must be answered to achieve scalable and durable leprosy elimination in countries like Kiribati.

OBJECTIVES

The COMBINE study assesses the feasibility and effectiveness of leprosy screening and MDA chemoprophylaxis in a highly endemic population using a programmatic approach that:

- Investigates whether combined population-wide screening and treatment for leprosy and TB together with MDA chemoprophylaxis and ongoing SDR-PEP for contacts can achieve rapid and durable reductions in leprosy incidence;
- Evaluates the effectiveness of leprosy MDA chemoprophylaxis using a pragmatic combination of either SDR or rifamycin-based TB preventive treatment;
- Measures the cost of MDA delivery when integrated with infrastructure from an existing population-wide screening program (the PEARL study[17]);
- Documents operational strategies to feasibly integrate enhanced leprosy and TB control efforts, and to reduce leprosy associated stigma.

METHODS AND ANALYSIS

Study design

COMBINE is a pragmatic controlled non-randomised before-and-after implementation study designed to evaluate the impact of the intervention upon leprosy NCDR. The COMBINE study will leverage infrastructure created by the PEARL study to deliver population-wide leprosy ACF and chemoprophylaxis. We will deliver the intervention over 3 years commencing November 2022 and ending November 2025, aiming to reach the entire population of South Tarawa in that time. The timeline of planned activities for the COMBINE study is illustrated in Supplementary Figure 1.

Setting

The Republic of Kiribati is a geographically isolated nation in the Pacific region comprising 32 atolls and one raised coral island spread over a land territory of 811 km^2 amid an ocean territory of 3.5 million km^2. The intervention site is the capital atoll of South Tarawa (population

63,439) which is the densely-populated 'transmission hot-spot' and amplifier of leprosy disease throughout the country (see **Table 1** for baseline characteristics of the study population).[19] Kiribati has only one specialised leprosy clinic which is located in South Tarawa. Residents live in village communities on a chain of low-lying islets connected by a causeway. Visitors from 'outer islands' to the capital often stay for an extended period. Anecdotally, this pattern of travel in and out of South Tarawa is associated with clusters of TB and leprosy in outer island communities.

While diagnosis and contact-tracing practices have been improved and standardised since 2010, it is uncertain whether the upward trend in new case detection rate (NCDR) in Kiribati over the past decade is an accurate measure of worsening epidemic control or reflective of enhanced case detection. What is clear, is that child NCDR has exceeded 30% of all newly detected cases for the past 3-years (2019-2021), indicating that the background community-level leprosy transmission has outpaced the potential to control the disease burden with existing leprosy programme interventions. Our study reports NCDR amongst both adults and children to examine variations in leprosy distribution between the two groups.

Table 1. Baseline characteristics of the population and intervention group

	Intervention group *South Tarawa*	**No intervention group** *Rest of Kiribati*	**Whole of Kiribati**
Population, 2020 *	63,439	56,501	119,940
- **Females (%)**	32,981 (52.0%)	27,805 (49.2%)	60,786 (50.7%)
- **Median age (years)**	23.2	22.3	22.9
- **Average household size (people)**	6.6	4.9	5.0
- **Net migration rate (% of population)**	2%	0.7%	1.4%
Urbanisation	Majority urban; some rural	Majority rural; some urban	Mixed urban and rural
BCG coverage, 2021 (% of live births) **	2434/2525 (96.4%)	839/888 (94.5%)	3273/3413 (95.9%)
Leprosy new cases, 2020 (rate per 10,000) **	93 (14.44)	62 (11.15)	155 (12.92)

- **Child cases (%)**	18 (19.4%)	18 (29.0%)	36 (23.2%)
- **MB cases (%)**	50 (53.8%)	20 (32.3%)	70 (45.2%)
Eligible contacts 2010–2020 **	9527	2264	11,811
- **received SDR (%)**	8381 (88%)	2021 (89%)	10,402 (89%)

Selected baseline characteristics or populations in the intervention area (South Tarawa), no intervention area (rest of Kiribati) and for the whole of Kiribati. BCG – Bacille Calmette-Guerin; MB – multibacillary; SDR – single-dose rifampicin.

* *National Statistics Office, 2020 census data*

** *Ministry of Health and Medical Services, programme data*

Intervention group and recruitment

The intervention group comprises residents of South Tarawa (and the small communities of Buota and Abatao adjacent to South Tarawa) aged 3-years and above, and aged less than 3-years if they have documented household contact (relevant definitions are provided in **Box 1**) with someone who has had TB in the past 1 year, or leprosy at any time since they were born. Study participants will be identified via household and village-level lists of residents from the 2020 census, and then invited to attend screening locations using door-to-door visits at households and community-based institutions (businesses, churches, et cetera). Basic demographic, social and geographic data will be collected at enrolment by the PEARL study screening teams.

Box 1. Definitions

Case of leprosy – clinical definition classified as multibacillary (MB) or paucibacillary (PB) according to WHO criteria that has been diagnosed by the doctor of the NLP.

Household - all those using the same kitchen, including members of extended families, the Maneaba (communal hospitality shelters), and dormitories in individual locations.

Household contact - any person who has been in contact with a new leprosy case for at least 20 hours per week for at least three months during the past five years.*

*adapted from WHO definition for the Kiribati context

Interventions

An illustration of the combined TB and leprosy interventions is provided in **Figure 1**, comparing the intervention group and standard care in the comparison group. Interventions are described in detail below. In practice, these interventions will be delivered in the setting of a combined community-based screening, diagnosis, treatment and prevention service.

Case detection, diagnosis and treatment

Screening for leprosy will be conducted by a physical examination and questionnaire (**Supplement 1**). People with presumptive leprosy will be referred to the National Leprosy Program (NLP) for expert diagnosis. Cases will be validated by a leprologist and skin biopsies from all patients with clinically diagnosed leprosy will be tested by PCR for *M. leprae* and drug resistance mutations, according to WHO guidelines.[14] Leprosy treatment will be provided by the NLP according to Kiribati national guidelines. Further details of the leprosy screening, diagnosis and treatment eligibility criteria are available in the PEARL study protocol.[17]

Contact Tracing and Post-Exposure Prophylaxis

Contact tracing and SDR-PEP will be ongoing for all index cases identified during the intervention within the study site and throughout the rest of Kiribati, as is consistent with routine practice (**Box 1**). WHO recommends that leprosy contacts should be given SDR-PEP at ≥2 years of age.[20] This has been adopted by the Kiribati NLP since 2018 and will be supported by the COMBINE study to scale-up SDR-PEP delivery throughout the intervention period, as enhanced index case detection will increase contact tracing needs. Children who are younger than 2-years and are leprosy contacts will be followed up and offered SDR-PEP by the NLP when they reach 2 years of age.

Leprosy Mass Drug Administration Chemoprophylaxis

Rifamycin-based MDA chemoprophylaxis is provided using a composite of treatments. After integrated leprosy and TB screening, participants will be commenced on treatment for TB, treatment for leprosy, or TPT using a rifamycin-based regimen, depending on the screening outcome. For participants who are not eligible for any of those treatments, we will then offer a single dose of rifampicin according to the inclusion/exclusion criteria in **Table 2**. Considered together as in **Table 3**, all participants will be offered a rifamycin-based treatment; effectively a rifamycin-based leprosy MDA chemoprophylaxis. Detailed dosing information is provided in **Supplement 2**. SDR for PEP and MDA will be provided without baseline blood tests, consistent with the standard of care in Kiribati.

Table 2. Inclusion and exclusion criteria for single dose rifampicin

Inclusion criteria	**Exclusion criteria**
1. Enrolled in the screening intervention 2. Not eligible for any other rifamycin-based treatment 3. Aged ≥2 years 4. Informed consent. For children (<18 years) consent will be obtained from the parent or guardian, and children (≥10 years) will also provide assent.	1. History of serious liver or kidney disease. 2. Known pregnancy (SDR can be given after delivery). 3. Known allergy or severe adverse effects experienced with rifampicin use. 4. Refuses participation.

Inclusion criteria are shown for single dose rifampicin. Other treatment regimens are determined by indications and contraindications relevant to those regimens. MDA – mass drug administration; SDR – single-dose rifampicin.

Table 3. Overview of combined treatment and chemoprophylaxis

Screening outcome	**Treatment offered**	**Rifamycin component**
Leprosy	Leprosy MDT	Monthly rifampicin for 6-12 months
TB	TB treatment	Daily rifampicin for 6-12 months

RR-TB	DR-TB treatment + SDR	Single dose rifampicin
Eligible for TPT	3HP or 3RH	Weekly rifapentine or daily rifampicin for 3 months
Leprosy HHC	SDR-PEP	Rifampicin given at baseline and one year later
None of the above	SDR-MDA	Single dose of rifampicin

Screening outcomes are exhaustive but not mutually exclusive. The rifamycin component of each treatment strategy includes sufficient exposure to offer prevention for leprosy, in effect a mass drug administration of leprosy chemoprophylaxis. 3HP – 3-months of weekly rifapentine and isoniazid; 3RH – 3-months of daily rifampicin and isoniazid; DR-TB – drug-resistant tuberculosis; HHC – household contact; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; RR-TB – rifampicin-resistant tuberculosis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – tuberculosis preventive treatment.

Community Engagement and Stigma Prevention

The objective of community engagement and mass communications is to encourage participation in the screening programme and sensitise community members to appropriate, non-stigmatising messages related to leprosy and leprosy screening. This approach is supported by the best practice statement of the Global Partnership for Zero Leprosy.[11 21] The COMBINE study supports community engagement and stigma prevention through various activities developed in concert with the PLF (who have 10 years of experience in leprosy advocacy in Kiribati) and the MHMS. These activities include:

- bi-annual advocacy activity drives which may include leprosy awareness parades, plays, signage and mass communication.
- convening of a leprosy community support group for patients diagnosed with leprosy and their close contacts/families. COMBINE nurses will assist with mentoring the community group, training in coping strategies and supporting activities.

- annual training and development workshops including all staff of the national leprosy and TB programmes with anti-stigma training for health staff delivering the COMBINE screening intervention
- job-aids and resources to support health staff and people with leprosy, for example a flipbook to aid counselling sessions between health workers and people with leprosy

Post-intervention prevalence survey

A follow-up leprosy prevalence survey will be conducted in Betio islet (~18,500 people, located within the South Tarawa intervention group) 3-4 years after the intervention there has been completed.

Outcome measures and planned analyses

The primary research question of interest is the extent to which the intervention reduces leprosy annual adult & child NCDR compared with standard routine passive case-finding and post-exposure prophylaxis of close contacts. This will be assessed 1) by comparing the post-intervention NCDRs in South Tarawa (in 2025) with the pre-intervention NCDRs (in 2021) and 2) by comparing the change in adult & child NCDRs in South Tarawa (the intervention site) with the change in NCDRs observed in the outer Kiribati islands (non-intervention sites). A supplementary analysis will compare the prevalence rate of leprosy in Betio (~15,000 people) found in the initial population-wide screening intervention with the rate found from a survey in the same population performed 3-4 years later. All primary, supplementary and planned analyses will be performed using standard statistical methods, for example using Poisson regression for the NCDR outcomes and logistic regression to compare prevalence during and after the intervention.

Due to the long latency of leprosy, we expect that the full effect of the intervention will only become apparent after several years have elapsed. MHMS and PLF are committed to

continuing leprosy surveillance in Kiribati, enabling ongoing assessments of long-term trends in disease burden beyond 2025.

Other planned analyses will examine:

1. Diagnostic yield of leprosy screening using an optimised clinical examination and brief history in the setting of a community-based multi-disease screening intervention. Examinations of yield amongst discrete age bands in children (0-4, 5-9, 10-14 years) will also indicate effect of the intervention on transmission over time.
2. Description of the spectrum of leprosy disease in South Tarawa.
3. Description of leprosy clusters and transmission patterns using geospatial data and social contact mapping
4. The prevalence ratio of genotypic *M. leprae* resistance to rifampicin, dapsone and quinolones before and after the MDA programme (using PCR-based assays of skin biopsies) [22-25]
5. The costs of leprosy-only activities, TB-only activities and shared activities to inform the cost-efficiency of future combined leprosy elimination projects in the Pacific and elsewhere
6. The relative risk of leprosy diagnosis in participants with and without prior exposure to rifamycins (provided as part of routine activities of the NLP and NTP), prior BCG vaccination and prior TB infection and/or disease in a high-incidence setting
7. The feasibility of combined TB and leprosy elimination efforts in the intervention site assessed using a mixed methods approach: measurement of treatment coverage, description of health service requirements (health care worker mix and person-time), description of infrastructure requirements, and surveys and interviews conducted with healthcare workers, decision makers, community representatives and study participants.

8. Mathematical modelling of the dynamics of leprosy incidence using 'real life' data from the COMBINE study with the aim of refining previous models[18] to improve accuracy of forecasting and decision support

Sample size

Assuming mass chemoprophylaxis coverage of 80% of the population and given an overall leprosy NCDR of 1600/1,000,000 for South Tarawa (the intervention group, population ~65,000) and 872 per 1,000,000 for the rest of the country (comparison group, population ~55,000), the study would provide greater than 99% power ($\alpha \leq 0.05$) to detect a 50% reduction (before versus after difference) in NCDR in South Tarawa (the intervention group) and 82% power to detect a 50% reduction in South Tarawa compared with no change in the rest of the country. Predicted sample sizes were calculated using the mean number of cases observed between 2018 and 2020 and simulated number of cases observed in 2025, drawn from a Poisson distribution (10,000 replicates) according to the parameters above and assuming a population growth of 5,000 in each area.

Economic analysis and costing

COMBINE proposes to estimate unit costs for screening per patient, working closely with the PEARL study to perform a cost analysis of TB-only activities, leprosy-only activities and shared activities. Accurate costing data will inform future leprosy elimination projects in the Pacific region and beyond, and will have additional benefits for subsequent planning, budgeting and modelling exercises. To enhance the application of our findings, we will seek to align costing data with existing interagency costing tools.

Data collection and monitoring

All leprosy and TB screening, chemoprophylaxis and outcome data will be captured offline on encrypted tablet devices using Research Electronic Data Capture (REDCap) surveys. Data will be uploaded and stored on a high security REDCap database server managed by the

University of Sydney. Leprosy case and contact management data are already archived in a comprehensive NLP database, with maintenance supported by the PLF before, during and after the study. We will contribute case and contact data from the COMBINE study to the existing supported database through routine study procedures. Mass screening and MDA data will be available to NLP as needed and handed over to the NLP after study completion.

Post-study follow-up activities

Country-wide ACF and PEP for household contacts will continue beyond the COMBINE study as a joint-program implemented by the NLP and the PLF. We consider that the early findings of the present study will enable mobilisation of funds to deliver similar population-wide leprosy control activities in other parts of the country, as part of a 'Zero Leprosy Roadmap'. Case and contact management records are already maintained in a comprehensive database, and relevant data from the COMBINE study will be added as part of study procedures. Together with mass screening data, this will provide a rich source for future analysis of long term outcomes in the study population.

ETHICS AND DISSEMINATION

Ethical approval for the COMBINE study has been obtained from the University of Sydney (project no. 2021/127), the University of Otago (H22/111) and the Kiribati Ministry of Health and Medical Services. Government support for the study to occur in collaboration with the NLP has been provided by Kiribati National Cabinet.

Participant information and counselling is provided to all prospective participants and again before treatment is offered (**Supplement 3**). Editable versions of study patient tools and a counselling flipbook are available at www.leprosy.org.nz and www.thepearlstudy.org. Informed consent is gathered verbally before participant enrolment and a signed record of consent is collected in the study REDCap database (**Supplement 4**). Verbal consent for participants attending the NLP for confirmation of diagnosis and treatment management will

be obtained according to standard programme practice. Written informed consent for a skin biopsy will be taken as is usual in the clinic. This includes consent to send the specimen abroad for analysis.

The safety of treatments for TB are discussed in the PEARL study protocol.[17] SDR is very safe, and has been used in Kiribati[18 19] and elsewhere[12 26-28] with little or no recorded side-effectsA study hotline and walk-in clinic will be freely available for adverse event (AE) management throughout the study period. Information on the signs and symptoms of leprosy and instructions to access the permanent leprosy clinic are provided to all participants (including those who decline to participate). Serious AEs are reported in accordance with national and University of Sydney pharmacovigilance standards. Intervention monitoring and auditing procedures will be conducted annually by the MHMS in accordance with routine practice with study reports made annually to ethics and funding bodies.

All study data will be shared with the MHMS. Reports of study progress will be made to the Kiribati community by mass communication and on the Pacific Leprosy Foundation and the PEARL study websites. Study findings will be presented at international conferences and in peer reviewed publications.

Patient Involvement Statement

This study was developed with the involvement of a reference group of I-Kiribati people affected by leprosy. This group will be involved in the COMBINE study in an ongoing basis. In particular, they will give advice concerning the practical implementation of the research, including the best ways of liaising with patients, their families and the community to ensure that communication is positive and does not contribute to stigma for people identified with leprosy and their contacts.

DISCUSSION

Innovative solutions are required to achieve progress towards leprosy elimination in Kiribati and in other areas of continuing high incidence. This is essential if we are to overcome the barriers to achieving global Zero Leprosy targets,[11] and eventually, true global leprosy elimination. As leprosy continues to require long and complex treatment programs, there is also urgency to find novel control strategies before antibiotic resistance emerges and accelerates in high transmission populations.[29]

The proposed study design combines a robust public health intervention in response to the dual epidemics of leprosy and TB in Kiribati, along with rigorous evaluation of the intervention. Population-wide leprosy active case-finding and MDA with rifamycin-based chemoprophylaxis in a population of approximately 60,000 represents a bold step towards acceleration of leprosy control. Combining this intervention with a similar population-wide TB screening, treatment and prevention programme is an innovative health systems approach that could improve efficiency and feasibility of large-scale interventions for both diseases. If successful, this would present an important model that may be implemented in other settings.

There are several limitations associated with this study protocol that may affect outcomes. First, the population wide screening and mass drug administration intervention in this study is in essence a change in health policy whereby the target population is expanded to include all residents of South Tarawa, rather than just specific contacts or groups of individuals. As with any health policy change or community-facing intervention, the impact of this new approach is dependent on the new policy reaching a large proportion of the target population and being delivered with high fidelity to the proposed design. We will take every effort to achieve high uptake and retention in care by conducting extensive community mobilisation and health communication activities. Although the outcomes of this study are defined at population level (NCDR measured before and after) and not dependent on individual level enrolment and withdrawal, we will also maintain detailed individual level records to enhance follow-up. Second, the intervention is not randomised. This will limit our ability to make inferences about

causation, especially if the impact on NCDR is small. We hope that by including the rest of the country as a non-randomised 'control' group we will have some basis for comparison. Finally, the proposed combined approach to screening and prevention means that the intervention is more time consuming to deliver and will take longer to reach the entire target population. We anticipate some level of reinfection to occur in already-screened areas of South Tarawa, while we continue to deliver the intervention across the island. Although reinfections may reduce the impact on measured NCDR, we anticipate that this would still be valuable information since we are taking a 'real world' public health approach that could serve as an example to other settings.

In Kiribati (and elsewhere[12,30]), MDA chemoprophylaxis in the 1990s led to reductions in leprosy case detection but ultimately failed to produce a lasting decline in incidence in some settings. The long latency period of the disease and the absence of surrogate measures of leprosy transmission make robust short-to-medium-term outcome measures of the population-level effect of interventions particularly limited. These are challenges intrinsic to population-level leprosy research. This study is designed to address these challenges by rigorous evaluation of scaled-up interventions in combination with durable partnership for evaluation of longer-term incidence and transmission outcomes. This 'real-life' operational research design to evaluate the main intervention is accompanied by a commitment by the MHMS together with the PLF to deliver leprosy control activities over the longer term, until leprosy is eliminated in Kiribati (www.leprosy.org.nz); this includes surveillance, continuation of rigorous contact identification and management, and expansion of population-wide screening and mass drug administration to the rest of the country. In the shorter and medium term, improvements in the accuracy of modelling of the intervention impact (using data from the COMBINE study) will provide useful insights and interim measures of the effect of COMBINE interventions upon leprosy incidence. This will be valuable to inform programs facing similar challenges to Kiribati. The present study, along with short, medium and long term aims and commitments are currently being integrated using a 'Leprosy elimination roadmap', adapting the methods and

experiences of the Global Partnership for Zero Leprosy. By embedding this study within long-term strategic partnerships, with ongoing funding and a comprehensive strategy, we hope that the missteps of previous MDA interventions can be avoided and lasting impact can be achieved along with research outputs that will guide future interventions.[19]

Kiribati is in a unique position, given its geographic isolation, low migration rate and limited population size, to identify and test innovative elimination strategies as proof-of-principle for leprosy control in other locations. We plan to grasp this opportunity and deliver much-needed evidence to reinvigorate attempts to eliminate this age-old scourge of humankind.

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Contributors

All authors contributed to the conceptualisation and panning of this research. MC, JH, NMD, JT, JW, BMJ, WJB and STC wrote the study proposal. ET, ER, TB, NI, AC, NMD, TI, POC and PP made important intellectual contributions to the final protocol manuscript. MC and JH contributed equally to this paper. The funding agency played no part in any aspect of the study, nor the decision to submit this manuscript for publication.

Acknowledgements

We thank the chair of the Leprosy Reference Group in Kiribati, Ms Nanoo Maribo, for her support of the COMBINE study and the Kiribati National Leprosy Program for their outstanding contributions to this work. We thank Ms Kantaake Corbett, Kiribati Health Information Unit, Ms Aritita Tekaieti, Kiribati National Statistics Office, and Mr Luis de la Rua, Pacific Community Statistics for Development Division, for their assistance with baseline data.

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Competing interests' statement

Some project funding is provided by the Pacific Leprosy Foundation, which also supports consultancy work of co-authors AC and NI.

Figure 1. Overview of COMBINE study intervention

Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

REFERENCES

1. Resolution to eliminate leprosy as a public health problem by the year 2000 resolution WHA449. World Health Assembly: Geneva: 44th World Health Assembly, 1991.
2. WHO. World Health Organization leprosy elimination project: status report 2002: World Health Organization, 2003.
3. WHO. World Health Organization Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. *Weekly Epidemiology Record* 2021;96(36):421-44.
4. Urgesa K, Bobosha K, Seyoum B, et al. Evidence for hidden leprosy in a high leprosy-endemic setting, Eastern Ethiopia: The application of active case-finding and contact screening. *PLoS neglected tropical diseases* 2021;15(9):e0009640.
5. Bernardes F, Paula NAd, Leite MN, et al. Evidence of hidden leprosy in a supposedly low endemic area of Brazil. *Memórias do Instituto Oswaldo Cruz* 2017;112:822-28.
6. Smith WC, van Brakel W, Gillis T, et al. The missing millions: a threat to the elimination of leprosy. *PLoS neglected tropical diseases* 2015;9(4):e0003658.
7. de Oliveira GL, Oliveira JF, Pescarini JM, et al. Estimating underreporting of leprosy in Brazil using a Bayesian approach. *PLoS Neglected Tropical Diseases* 2021;15(8):e0009700.
8. Frade MAC, de Paula NA, Gomes CM, et al. Unexpectedly high leprosy seroprevalence detected using a random surveillance strategy in midwestern Brazil: A comparison of ELISA and a rapid diagnostic test. *PLoS Neglected Tropical Diseases* 2017;11(2):e0005375.
9. Mangeard-Lourme J, Singh A, Singh RK, et al. Enhanced active case-finding, identifying leprosy cases missed by recent detection campaigns in Munger District, Bihar, India. *Leprosy Review* 2017;88(4):452-62.
10. Salgado CG, Barreto JG, da Silva MB, et al. Are leprosy case numbers reliable? *The Lancet Infectious Diseases* 2018;18(2):135-37.

11. WHO. World Health Organization Towards zero leprosy. Global leprosy (Hansen's Disease) strategy 2021–2030. 2021

12. Tiwari A, Dandel S, Djupuri R, et al. Population-wide administration of single dose rifampicin for leprosy prevention in isolated communities: a three year follow-up feasibility study in Indonesia. *BMC Infectious Diseases* 2018;18(1):324. doi: 10.1186/s12879-018-3233-3 [published Online First: 2018/07/13]

13. Bakker MI, Hatta M, Kwenang A, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *The American Journal of Tropical Medicine and Hygiene* 2005;72(4):443-48.

14. WHO. World Health Oorganization consolidated guidelines on tuberculosis Module 2: Screening – Systematic screening for tuberculosis diseas. *Global Tuberculosis Programme* 2021

15. WHO. Rapid communication on systematic screening for tuberculosis. 2020

16. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New England Journal of Medicine* 2019;381(14):1347-57. doi: 10.1056/NEJMoa1902129 [published Online First: 2019/10/03]

17. Coleman M, Hill J, Timeon E, et al. Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati: the PEARL study protocol. *BMJ Open* 2022;12(4):e055295. doi: 10.1136/bmjopen-2021-055295

18. Gilkison C, Chambers S, Blok DJ, et al. Predicting the impact of household contact and mass chemoprophylaxis on future new leprosy cases in South Tarawa, Kiribati: A modelling study. *PLoS Neglected Tropical Diseases* 2019;13(9):e0007646. doi: 10.1371/journal.pntd.0007646 [published Online First: 2019/09/21]

19. Chambers ST, Ioteba N, Timeon E, et al. Surveillance of Leprosy in Kiribati, 1935–2017. *Emerging Infectious Diseases* 2020;26(5):833.

20. WHO. Leprosy/Hansen disease: Contact tracing and post-exposure prophylaxis. 2020

21. van Brakel WH, da Silva Pereira ZB, Barbosa JC, et al. Global Partnership for Zero Leprosy Research Agenda Working Group Subgroup on Stigma, 2019.

22. Coppola M, van den Eeden SJ, Robbins N, et al. Vaccines for leprosy and tuberculosis: opportunities for shared research, development, and application. *Frontiers in Immunology* 2018;9:308.

23. Lahiri R, Adams LB. Cultivation and viability determination of Mycobacterium leprae. *International Textbook of Leprosy* 2016

24. Davis GL, Ray NA, Lahiri R, et al. Molecular assays for determining Mycobacterium leprae viability in tissues of experimentally infected mice. *PLoS Neglected Tropical Diseases* 2013;7(8):e2404.

25. Williams DL, Torrero M, Wheeler PR, et al. Biological implications of Mycobacterium leprae gene expression during infection. *Microbial Physiology* 2004;8(1):58-72.

26. Richardus JH, Tiwari A, Barth-Jaeggi T, et al. Leprosy post-exposure prophylaxis with single-dose rifampicin (LPEP): an international feasibility programme. *Lancet Global Health* 2021;9(1):e81-e90. doi: 10.1016/s2214-109x(20)30396-x [published Online First: 2020/11/02]

27. Schoenmakers A, Mieras L, Budiawan T, et al. The State of Affairs in Post-Exposure Leprosy Prevention: A Descriptive Meta-Analysis on Immuno- and Chemo-Prophylaxis. *Research and Reports in Tropical Medicine* 2020;11:97-117. doi: 10.2147/rrtm.S190300 [published Online First: 2020/10/30]

28. Feenstra SG, Pahan D, Moet FJ, et al. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. *Leprosy Review* 2012;83(3):292-304. [published Online First: 2013/01/30]

29. Cambau E, Saunderson P, Matsuoka M, et al. Antimicrobial resistance in leprosy: results of the first prospective open survey conducted by a WHO surveillance network for the period 2009–15. *Clinical Microbiology and Infection* 2018;24(12):1305-10.

30. Nguyen LN, Cartel JL, Grosset JH. Chemoprophylaxis of leprosy in the southern Marquesas with a single 25 mg/kg dose of rifampicin. Results after 10 years. *Leprosy*

Review 2000;71 Suppl:S33-5; discussion S35-6. doi: 10.5935/0305-7518.20000064

[published Online First: 2001/02/24]

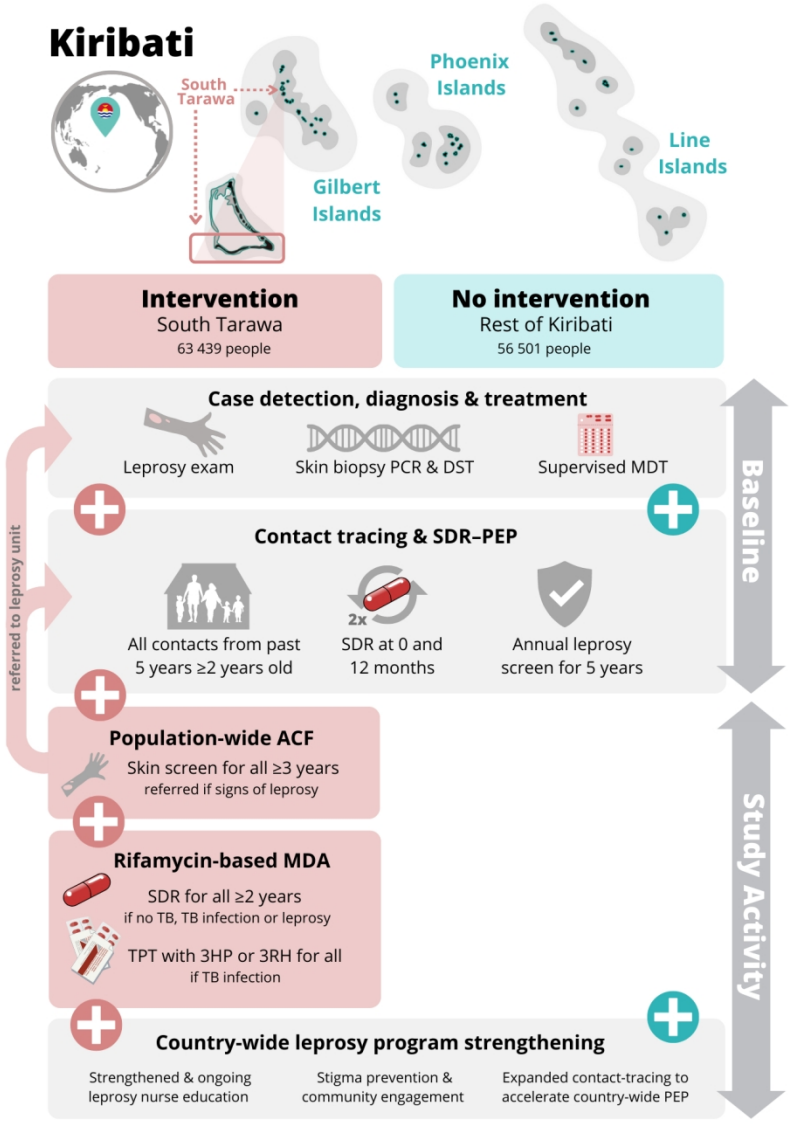


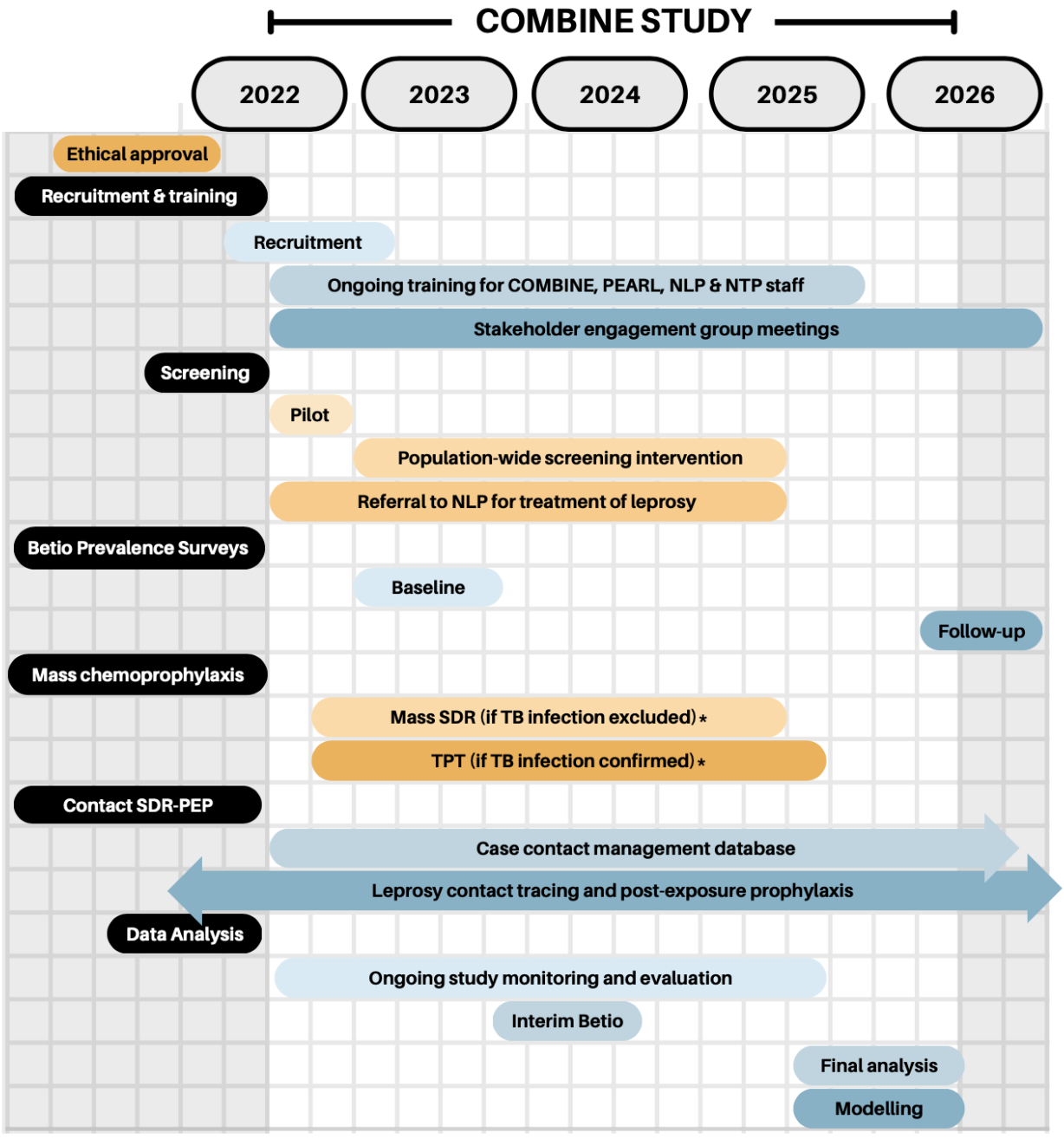
Figure 1. Overview of COMBINE study intervention. Overview of COMBINE study activities, comparing interventions delivered in South Tarawa (pink, intervention group) and in the rest of Kiribati (green, no intervention group). Activities are further divided according to those available at baseline across the country and continued during the study period, and those activities that will be delivered during the study period (vertical arrows at right). Geographical context is illustrated at top (not to scale). 3HP – three months of weekly isoniazid and rifapentine; 3RH – three months of daily isoniazid and rifampicin; ACF – active case finding; DST – drug susceptibility testing; MDA – mass drug administration; MDT – multi-drug treatment; NLP – national leprosy program; PCR – polymerase chain reaction; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TB – tuberculosis; TPT – TB preventive treatment.

536x758mm (67 x 67 DPI)

Supplementary Materials

The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SUPPLEMENTARY FIGURE 1:



Supplementary Figure 1. Timeline of COMBINE study activities

Formal COMBINE activities commenced in July 2022 and should conclude in June 2026, with data analysis and dissemination of outcomes included in this period. Left-facing arrow indicates activity which began prior to the COMBINE study. Right-facing arrows indicate activities which will continue beyond the end of the COMBINE study through NLP and PLF activities, provided adequate funding is procured. NLP – National leprosy program; NTP – National tuberculosis program; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TPT – tuberculosis preventive treatment. ***TB and leprosy disease also excluded*

SUPPLEMENT 1. Leprosy screening Standard Operating Procedure

Population leprosy screening – general steps

1. Ask about leprosy (this may be done at a history taking station)
2. Conduct a physical check for leprosy
3. Record findings in CRF
    a. Take a photo of any examination findings
4. Refer for further evaluation if there are any findings (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)

Population leprosy screening – details

Ask (this may be done at a history taking station)

- Have you had or do you have leprosy? Have you ever been treated for leprosy?
- Are you a household contact* of someone who has had leprosy?
- Are you worried you might have leprosy? If so, why?
- Do you have any skin lesions or other abnormalities that you think could be leprosy?

Exposure

- Remove footwear and any outer layers of clothing

Areas of body to inspect

- Face including eyelashes, eyebrows, nose and mouth
- Ears
- Neck
- Arms and hands
- Legs and feet
- Lift the shirt and lower the waistband for back and upper buttocks

Looking for

- Skin lesions (pale, red, thick, raised, shiny)
    - Check if itchy, if so, don't refer to NLP (consider alternative referral if concerning)
- Skin nodules
- Altered shape of nose or ears
- Loss of eyelashes or eyebrows
- Altered shape of hand or foot
    - Check if present from birth, if so, don't refer
- Ulcers on hand or foot

Who to refer?

- People with physical examination findings consistent with leprosy
- People who are worried they might have leprosy (any reason)

How to record

- Fill the CRF
- Take a photo (good lighting, ruler or TST syringe for scale)
- Refer for further evaluation (this may be within the screening clinic, or to the leprosy clinic, depending on staffing)
- Give referral letter if needed

* Household contact is defined according to WHO. *"Household contacts: contacts living in the same dwelling or sharing the same kitchen as the index case. These include family members but also domestic staff or aids or co-workers or others sharing the same accommodation. A family member living elsewhere should not be considered as a contact."*

SUPPLEMENT 2.

Table S1. Single dose rifampicin (SDR) chemoprophylaxis dosing.

Age/body weight	Rifampicin single dose
15 years and above	600 mg
10-14 years	450 mg
Children 6-9 years (weight ≥ 20 kg)	300 mg
Children 6-9 years (weight < 20 kg)	150 mg
Children <5 years	10-15 mg/kg

Table S2. Tuberculosis preventive treatment dosing.

S2A. 12 doses of weekly isoniazid (H) and rifapentine (P) for adults and children ≥25 kg

Weight band	HP (300mg/300mg) tablets
25-30kg (or <15ys)	2
≥30kg and ≥15ys	3

S2B. 3 months of daily dosing of child-friendly water-dispersible rifampicin (R) and isoniazid (H) tablets for children <25kg

Weight band	RH (75mg/50mg) tablets
4-7kg	1
8-11kg	2
12-15kg	3
16-25kg	4

SUPPLEMENT 3. Participant Information

PARTICIPANT INFORMATION

Finding and preventing TB and leprosy cases in Tarawa

Dear participant,

We would like to invite you (and your child if relevant) to be treated for latent or sleeping TB. This document provides information about the study, but we will also explain the study to you in person. You will have the opportunity to ask questions if there is anything that you do not understand or if you want more information. You may refuse participation and this will not be held against you or affect any future access to healthcare.

What is this study about?

TB is a disease caused by germs that are coughed into the air by someone who is ill with TB. Most people who are infected with the TB germ do not become ill and do not even know that they are infected, this is referred to as latent or 'sleeping' TB. **Sometimes sleeping TB can wake up and make you ill, which may spread the germ to others**. This research aims to treat all people with TB, those who are ill and those with sleeping TB, so that we can try to eliminate TB from Tarawa. At the same time we are also trying to eliminate leprosy from Tarawa.

This Participant Information Form tells you about the study so that you can know what it involves. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Who is conducting the study?

The study is carried out by researchers at the University of Sydney, Australia, in close collaboration with the Kiribati National TB and Leprosy Programme (NTP). The study is funded by the Australian Medical Research Future Fund and fully supported by the Kiribati Ministry of Health.

What will happen?

This study involves screening for TB (both 'sleeping TB' and illness caused by TB) and leprosy. People who are ill with TB or leprosy will be referred to the TB and Leprosy Programme for appropriate treatment. People with 'sleeping TB' will be offered TB preventive treatment (TPT) and those without any illness or TB infection will be offered leprosy preventive prophylaxis.

To check if someone is able to be given medication for sleeping TB, a study nurse will ask some personal questions. This may include questions about previous and current illnesses, medications used, drinking of alcohol or kava, and questions about pregnancy if you are a woman. Every person older than 20 years will be given a rapid test to see if they have hepatitis B infection, which is important for us to know before considering treatment for 'sleeping TB'. This test involves a finger prick to get a small drop of blood. People with risk factors will need to have a small amount of blood drawn to make sure their liver function stays healthy during the time that they are treated for sleeping TB.

How much of my time will the study take?

We will try to waste as little of you time as possible. To complete the TB and leprosy screening will require you (and your whole household) to be seen on two separate days. This is to complete all the necessary documentation and tests. It is expected that this will take about 2-3 hours of your time on each of these days. These diagnosed with sleeping TB will need to take tablets once a week for 12 weeks. Tablets will be given out at the mobile health clinic on a monthly basis and can be collected between 9am and 4pm on weekdays**.**

Who can take part in the study?

Every person older than 3 years of age living in Tarawa and Betio islet is invited to take part.

Do I have to be in the study? Can I withdraw from the study once I've started?

Taking part in this study is strongly recommended by the Kiribati Ministry of Health and Medical Services (MHMS) to get rid of TB and leprosy across Tarawa. However, participation is completely voluntary and you do not have to take part. Your decision will not affect your current or future relationship with the researchers, the Kiribati National TB and leprosy Program or the Ministry of Health.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by visiting the study clinic and speaking with a study nurse who will give you exit information and advice on how to stay healthy from TB in the future.

If you decide to withdraw from the study, we will not collect any further information from you. Information that we have already collected will be kept in our study records and may be included in the study results.

Are there any costs or risks associated with being in the study?

There are no costs associated with study participation. Mobile study clinics will be conveniently situated to be easily accessible and all study tests or treatment will be funded by the study.

If treatment for 'sleeping TB' is provided it is normal to feel a bit tired and to have bright orange urine while you are taking the tablets. Rarely people may develop some of the symptoms below, in which case it is important to inform us immediately. Rare symptoms to look out for include:

- ongoing nausea, vomiting or loss of appetite
- new rash or itchy skin
- yellowing skin or eyes
- tingling or numbness in fingers or toes
- any other symptoms of concern to you

Study nurses and doctors are available Monday to Friday, 9am to 4pm to see anyone who is feeling sick and thinks this may be due to their treatment. You may also call the 24-hour treatment hotline using the number on the back of your treatment card (TPT passport).

Are there any benefits associated with being in the study?

Yes, there are major benefits to yourself and the wider community of Tarawa, including Betio islet

- You (and your child) will get treatment for TB or leprosy if required
- You (and your child) will get treatment for sleeping TB (TPT) or to keep leprosy away
- You will help to eliminate TB and leprosy from Tarawa
- Study results will help other Pacific Island nations to eliminate TB and leprosy in the future

What if I have a complaint or any concerns about the study?

This research has been reviewed by an independent group of people called a Human Research Ethics Committee (HREC) at the University of Sydney and the Kiribati Ministry of Health and Medical Services.

If you are concerned about the way this study is being conducted please inform the study team; we want to learn and hear how we can improve things. If you wish to make a complaint to someone independent then please contact any of the people listed below.

Terotia Tabwaka Kelese, Human Resource Officer, Republic of Kiribati

Email: ttabwaka@gmail.com

or

The Manager, Ethics Administration, University of Sydney:

Telephone: +61 2 8627 8176

Email: human.ethics@sydney.edu.au

Fax: +61 2 8627 8177 (Facsimile)

Ethical Approval

This research plan (protocol) was approved by the ethics committee of the faculty of medicine and health at the University of Sydney. This helps to ensure that we do everything possible to keep you safe and to respect your rights and privacy at all times.

We thank you for your time and cooperation.

The PEARL Research Team with the support of the Kiribati National TB and Leprosy Control Programmes. **Further information can be found at www.thepearlstudy.org**

On behalf of the Kiribati Health Secretary

……

SUPPLEMENT 4. Informed Consent Form

INFORMED CONSENT PROCESS FORM

Date of informed consent Today D-M-Y

Does the participant have capacity to consent?
- Yes
- No - young person <18 years of age
- No - disability
- No - other reason

reset

Name of Consenting Guardian

Relationship of consenting guardian
- parent
- spouse
- grandparent
- aunt/uncle
- sibling
- other relative
- non-relative guardian

reset

Does the participant assent to participate in the study?
- Yes
- No

reset

Does the participant/primary caregiver agree to participate in study?
- Yes
- No

reset

Can participant/caregiver read Kiribati?
- Yes
- No

reset

Can participant/caregiver read English?
- Yes
- No

reset

Participant information given and all participant questions answered?
- Yes
- No

reset

Participant is aware that this is a public health intervention endorsed and supported by the Kiribati Ministry of Health and Medical Services?
- Yes
- No

reset

Participant is aware that screen may involve providing sputum or blood samples?
- 1. Yes / Yes
- 0. No / No

reset

Date & Time Participant/caregiver signed documentation of consent Now D-M-Y H:M

Sign

Add signature

Other comments

Mass drug administration for leprosy control in Kiribati: The COMBINE protocol

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	NA not a trial
	2b	All items from the World Health Organization Trial Registration Data Set	NA not a trial
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2; 22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	13-14; table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14; figure 1; table 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13; 18-19; Supplement 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-15; 18-19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-15; 18-19; S2
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA non-random
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA population-wide
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA population-wide
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA open-label
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA open-label
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16-18; Supplement 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18-19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4-5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18-19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19; Table 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22-23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4-5
	31b	Authorship eligibility guidelines and any intended use of professional writers	22-23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 3-4
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.