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Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati – the PEARL study protocol

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TITLE

Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati
– the PEARL study protocol

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ABSTRACT

Introduction

Population-wide interventions offer a pathway to tuberculosis (TB) and leprosy elimination, but 'real-world' implementation in a high-burden setting using a combined approach has not been demonstrated. This implementation study aims to demonstrate the feasibility and evaluate the effect of population-wide screening, treatment and prevention on TB and leprosy incidence rates, as well as TB transmission.

Methods and analysis

A non-randomised 'screen-and-treat' intervention conducted in the Pacific atoll of Tarawa, Kiribati. Households are enumerated and all residents ≥ 3 years, as well as children < 3 years with recent household exposure to TB or leprosy, invited for screening. Participants are screened using tuberculin skin testing, signs and symptoms of TB or leprosy, digital chest X-ray with computer aided diagnosis (Delft CAD4TB®) and sputum evaluation (Xpert MTB/RIF Ultra®). Those diagnosed with disease are referred to the National TB and Leprosy Program for management. Participants with TB infection are offered TB preventive treatment (TPT) and those without TB disease or infection, or leprosy, offered universal leprosy prophylaxis. The primary study outcome is the difference in the annual TB case notification rate before and after the intervention. The effect on TB transmission will be measured by comparing the estimated annual risk of TB infection in primary school children (aged 7-15 years) before and after the intervention. The effect on leprosy is measured by comparing the leprosy case notification rate in Tarawa before and after the intervention, as well as comparing Tarawa (the intervention group) to the rest of Kiribati (the control group).

Ethics

Approval has been obtained from the University of Sydney Human Research Ethics Committee (project no. 2021/127) and from the Kiribati Ministry of Health and Medical Services (MHMS).

Dissemination

Findings will be shared with the Kiribati MHMS and local communities. It will also be published in peer-reviewed journals and presented at international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The 'real-world' implementation approach will inform the feasibility and effectiveness of population-wide active TB and leprosy case finding and prevention strategies.
- Concurrent active TB case finding and infection detection with treatment, should durably reduce the TB disease burden by preventing future TB re-activation and reinfection.
- Combining TB and leprosy elimination efforts increases efficiency and could serve as a template for other countries with a dual disease burden, although this increases the complexity of the intervention.
- TB preventive treatment will be self-administered, which may result in lower adherence than with directly observed treatment (DOT), but is more feasible in the context of population-wide scale-up.
- Implementing this intervention in a Pacific island setting will demonstrate an important 'proof-of-principle' for population-wide interventions. Its findings should be generalizable to other Pacific and geographically circumscribed settings, with relevance for 'disease hot spots' globally.

INTRODUCTION

Tuberculosis (TB, caused by *Mycobacterium tuberculosis*) is a leading infectious disease killer globally and in the Pacific,¹ while leprosy (caused by *M. leprae*) elimination remains a major challenge as well.² It is estimated that TB killed ~1.5 million people in 2019, despite being a preventable and curable disease.¹ At the 2018 United Nations High-Level Meeting on TB,³ world leaders committed to step up TB elimination efforts, with improved TB case finding and expanded use of TB preventive treatment (TPT) identified as key interventions in the global “End TB strategy”.⁴

Historical population-wide TB elimination programmes demonstrated considerable success and are enjoying renewed attention, with specific emphasis on active case finding and prevention strategies^{5,6}. A randomized controlled trial (RCT) in Vietnam recently demonstrated that population-wide active TB case finding can achieve substantial reductions in TB incidence and transmission.⁷ Historic studies and modelling projections suggest that this effect, and its durability, can be enhanced by concurrent treatment of TB infection^{8,9}, but data on ‘real-life’ implementation remain scarce. Given World Health Organization (WHO) endorsement of integrated active TB case finding and preventive treatment approaches,¹⁰⁻¹⁵ there is urgency to develop implementation models that demonstrate feasibility and population impact.

Around 55% of the Kiribati population (53,748 from 2015 population census) lives on the capital atoll of Tarawa.¹⁶ Of all TB cases detected in Kiribati in 2019, 76% (319 of 419) were from Tarawa - equating to a TB incidence of >500/100,000 population, the threshold incidence level above which the WHO recommends population-wide screening interventions.¹⁷ *M. tuberculosis* strain typing data¹⁸ and the dominance of young adults among TB cases indicate high levels of community transmission,¹⁹ which emphasises the need for case finding and prevention strategies to be combined in order to prevent rapid re-infection.

Leprosy rates in Kiribati, and Tarawa in particular, are also among the highest in the world (>200 cases/100,000 population, compared to the WHO elimination threshold of 10/100,000 population) and have been rising rapidly after a nadir in the late 1990s when elimination efforts were discontinued.² Modelling studies done in Kiribati indicate that a single population-wide active case finding intervention,

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3 combined with 'universal leprosy prophylaxis' using single-dose rifampicin, could dramatically decrease
4 leprosy prevalence with a sustained effect.²⁰
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9 Although both TB and leprosy pose daunting public health challenges in this resource-limited setting,
10 their co-occurrence within a geographically defined and isolated population presents a unique
11 opportunity to evaluate combined elimination efforts. The aim of the proposed study is to achieve major
12 reductions in TB and leprosy incidence and transmission in Tarawa, providing a pathway to future
13 elimination. If successful, the proposed study will provide a template for TB and leprosy elimination
14 efforts throughout the Pacific and in other remote settings.
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20 21 22 **METHODS AND ANALYSIS**

23 24 **Study Design**

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26 The PEARL study is a before and after evaluation of a population-wide systematic screening
27 intervention, combined with a comprehensive treatment and prevention program for both tuberculosis
28 and leprosy.
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32 33 34 **Setting**

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36 Kiribati is a lower-middle income country of ~120,000 people residing on low-lying atolls and islands in
37 the western Pacific Ocean, with the lowest gross domestic product (GDP) per-capita of any country of
38 Oceania²¹. The country has among the highest TB incidence rates in the world²², and is one of 23 WHO
39 priority-countries for leprosy control²³. Small numbers of people have been diagnosed with drug-
40 resistant (DR) TB (3 out of 419 cases in 2019) with limited evidence of community transmission of drug-
41 resistant TB. The prevalence of HIV infection is low, and no cases of TB/HIV coinfection were reported
42 in 2019. However, there is a high burden of non-communicable disease, with the adult diabetes
43 prevalence exceeding 20%,²⁴ high rates of childhood malnutrition and substantial levels of smoke
44 exposure from cooking fires and cigarette smoking.²⁵
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55 The Tarawa atoll serves as the capital of Kiribati. Residents of South Tarawa, Betio Islet and the small
56 communities of Buota and Abatao at the southernmost end of North Tarawa are included in the
57 intervention and referred to as 'Tarawa'. Tarawa accommodates ~55% of the Kiribati population and
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3 has the highest rates of TB and leprosy disease. Betio Islet in particular is the most densely populated
4 area in the Pacific with an estimated population density of >15,000 people/km².
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9 TB diagnostics available in Tarawa include smear microscopy, Xpert MTB/RIF (Cepheid, Sunnyvale,
10 California) and chest radiography, but culture facilities are unavailable. Sputum samples can be sent to
11 the regional reference laboratory in Adelaide, Australia, for culture and susceptibility testing. However,
12 this is problematic due to logistical issues and high rates of bacterial overgrowth. Most people with TB
13 are hospitalised during the first few weeks of treatment at the local government hospital (Betio and
14 Tungaru hospitals). Household contact investigation is advised, but not universally implemented
15 because of resource constraints. National guidelines recommend preventive treatment for household
16 contacts for whom TB disease has been excluded, but implementation and uptake are again
17 inconsistent. Leprosy is diagnosed using clinical assessment and microscopy, with genotypic diagnosis
18 available by sending punch biopsy samples to the regional reference laboratory in Christchurch, New
19 Zealand. Curative treatment, occupational therapy and chronic disease management is provided by the
20 National Leprosy Program. Post-exposure prophylaxis of household contacts using single-dose
21 rifampicin (SDR) has been scaled up in recent years with the help of the Pacific Leprosy Foundation.
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36 **Study population**

37 The study population comprises all residents of Tarawa aged three and above, with children <3 years
38 additionally included if they have documented household contact with someone who had TB (in the
39 past 1 year), or leprosy (at any time since they were born). Household contact is defined by regular
40 meals being prepared in the same kitchen. See Table 1 for overview of inclusion and exclusion criteria.
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42 Study recruitment is guided by identification of all 'places of residence' using high resolution satellite
43 images. All identified residences are visited by study workers to enumerate household members, collect
44 baseline data, ascertain the eligibility of children aged <3 years of age and invite everyone to an
45 assigned screening day.
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55 **Study intervention**

56 The study intervention comprises population-wide systematic screening and treatment of TB disease,
57 TB infection and leprosy, together with the provision of leprosy prophylaxis to those not requiring
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3 treatment. In practice this equates to universal leprosy prophylaxis, given that TB and leprosy treatment,
4 as well as TPT with rifamycin-based regimens, provides adequate leprosy prophylaxis. The enrolment
5 and screening process are summarised in Figure 1; more detailed algorithms are included in the
6 supplement (Figures S1 and S2).
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10 11 12 **Systematic screening procedures**

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14 All households are enumerated and eligible participants invited for screening. During the first clinic visit,
15 study personnel obtain written informed consent from adult participants (≥ 18 years of age), or
16 parents/legal guardians in those aged < 18 years, with verbal assent from children aged 10-18 years.
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18 Participants provide a 'selfie' to aid future re-identification, using biometric (facial coordinate) analyses
19 (SimPrints Technology Limited, Cambridge, UK). Study nurses complete a short TB symptom
20 questionnaire and a brief physical examination for signs and symptoms suggestive of TB disease
21 (especially extrapulmonary signs such as a visible cervical lymph node mass or gibbus) or leprosy
22 (insensate or hypopigmented skin patches, or suggestive deformities).
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31 A TST is placed using the Mantoux method and sputum collection attempted in all participants aged
32 ≥ 10 years; age appropriate diagnostic specimens may be collected in children < 10 years who have
33 symptoms suggestive of TB, but it is not part of the screening procedure. Sputum specimens are tested
34 using Xpert MTB/RIF Ultra®, recently endorsed by WHO as a sensitive front-line diagnostic test²⁶. A
35 digital chest radiograph (CXR) is performed on everyone aged ≥ 10 years, and children aged < 10 years
36 with symptoms suggestive of TB. Delft CAD4TB is used to assist CXR interpretation for participants
37 aged ≥ 10 years, especially those without any TB concern. The use of CAD software for TB screening,
38 including the Delft CAD4TB® system used in this study, is supported by recent WHO guidelines²⁷.
39 Studies using Delft CAD4TB® software have demonstrated very high negative predictive values with a
40 CAD score of less than 50²⁸. CXRs for younger participants will be interpreted by study medical staff.
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53 At a second clinic visit two days later, the TST is read and considered positive if induration is ≥ 10 mm,
54 or ≥ 5 mm if the participant has had household contact with a person with infectious TB in the past 12
55 months. The CXRs of all participants with a CAD score of ≥ 50 (and a random selection of those with
56 scores < 50), a positive Xpert Ultra® or symptoms suggestive of TB (especially children < 10 years) will
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3 be manually reviewed by a study doctor. Patients with confirmed or clinically diagnosed TB disease or
4 leprosy will be referred to the Kiribati NTP or NLP for treatment; with close coordination between study
5 and program clinicians.
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10 ***TPT eligibility***

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12 Participants with a positive TST or children <5 years with recent household contact are considered for
13 TPT if they do not have TB disease and have not completed a course of TB treatment or TPT within
14 the last 12 months. Potential TPT contraindications (eg. allergies to TB medicines, risk factors for
15 hepatotoxicity) are assessed using a brief questionnaire. There is a high prevalence of hepatitis B (HBV)
16 infection among older people in Kiribati;²⁹ routine HBV vaccination introduced in the 1990s reduced
17 infection rates among younger people³⁰. A point-of-care HBV rapid test (Determine™ HBsAg 2) is
18 performed in all participants aged ≥40 years who agree to TPT and are otherwise at low risk, since they
19 are at increased risk of HBV infection and possible liver disease. Participants diagnosed with HBV
20 infection are referred to the HBV treatment programme for management.
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32 ***Hepatotoxicity risk assessment***

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34 Baseline serum alanine aminotransferase (ALT) testing is conducted in all participants aged ≥60 years,
35 or with identified risk factors for hepatotoxicity, and results stratified according to hepatotoxicity risk
36 (Table 2). Participants with ALT ≥3x upper limit of normal (ULN) are not offered TPT, those with ALT 2-
37 3x ULN are offered TPT (if the bilirubin in <2x ULN) with repeat ALT testing after 3-4 weeks, and
38 participants with ALT <2x ULN (or no need for a baseline test) are offered TPT without further ALT
39 monitoring. All participants receive information on the signs and symptoms of hepatotoxicity, guidance
40 to limit alcohol and kava intake and access to a 'hotline' linked to a rapid evaluation service.
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49 ***TPT regimens and treatment initiation***

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51 Participants who are eligible, have no contraindications and accept TPT are offered a choice of short-
52 course rifamycin-based regimens according to clinical characteristics, patient preference and
53 availability. Currently used regimens are: 12 weekly doses of isoniazid and rifapentine (3HP), four
54 months of daily rifampicin (4R), or 3 months of daily isoniazid and rifampicin (3RH, preferred for young
55 children due to availability of child-friendly water-dispersible formulations). Dosing is chosen according
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3 to recommendations from the WHO and the Kiribati NTP. In participants with a documented history of
4 household contact with someone diagnosed with drug-resistant TB, TPT using six months of daily
5 levofloxacin is considered under expert supervision^{31 32}. New evidence and normative guidance
6
7 supporting the use of shorter TPT regimens may be released during the study. Consistent with the
8
9 implementation approach, additional regimens may be offered to participants in collaboration with the
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11 Kiribati NTP and with updated ethical approval. All medicines used in the study will be obtained from
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13 WHO prequalified manufacturers, procured from the Global Drug Facility (GDF).
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18 ***Community-based adherence support and treatment monitoring for TPT***

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20 At each stage of treatment initiation, adherence support, treatment monitoring, management of adverse
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22 events and assignment of treatment outcome, participants are provided with appropriate counselling on
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24 risks, benefits and options available. A detailed patient information sheet is provided together with group
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26 and/or individual counselling with the aid of an illustrated flip chart and a 'TPT passport' (Figure S3) to
27
28 assist adherence and adverse event monitoring. After taking the first dose under direct supervision,
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30 TPT will be self-administered with use of pragmatic adherence support strategies tailored to the
31
32 particular study community. Medicines are dispensed every four weeks, or according to patient
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34 preference. All participants who commence TPT are contacted once after 3-4 weeks to support
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36 adherence and screen for adverse events, and again when they near TPT completion to assess
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38 treatment adherence and either extend treatment or assign a treatment outcome. Treatment completion
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40 is determined according to WHO recommendations (Table 3).
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44 ***Detection and management of adverse events***

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46 This is an implementation study that uses medicines recommended by the NTP in Kiribati and which
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48 have been shown to be safe and effective^{10 33-38}. Adverse events associated with the study intervention
49
50 are similar to those encountered in routine programme delivery. Misidentification and misclassification
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52 during screening steps may be detected at follow-up visits. These will be minimised through adequate
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54 planning and testing of all procedures, using ongoing quality assurance measures built into a secure
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56 Research Electronic Data Capture (REDCap) database³⁹ and close oversight from local study
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58 coordinators. Actions on referrals to government treatment programs (TB, leprosy, hepatitis) will be
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60 tracked.

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5 Participants receiving TPT will have access to a 'TPT hotline' as well as a walk-in service for adverse
6 event assessment. Study staff are trained to identify the most common and most severe adverse events
7 associated with TPT, with a particular focus on hepatotoxicity. Drug-related adverse events are triaged
8 and referred for further medical evaluation as appropriate, including liver function testing. If needed,
9 referral and linkage to urgent care services is available.
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16 The following adverse events will be recorded and reported as part of the study:

- 17 • Misclassification or misinterpretation of screening results resulting in mistreatment
- 18 • Post-positive screen treatment delay for TB disease (>7 days) and leprosy (>14 days)
- 19 • Drug-induced liver injury (DILI - defined as suggestive symptoms plus ALT >3 times upper limit
20 of normal or ALT >5 times upper limit of normal without symptoms) while on TPT
- 21 • Drug-related adverse events resulting in TPT interruption or cessation⁴⁰
- 22 • All serious adverse events among people taking TPT (SAEs, as defined by the Australian
23 National Health and Medical Research Council)⁴¹.
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32 Anyone with DILI during treatment or with an abnormal ALT ($\geq 2x$ ULN) at baseline will receive an HBV
33 rapid test (if not previously performed). In addition, blood drawn from participants with DILI and matched
34 controls will be stored (with additional consent) for expanded risk factor determination, using an efficient
35 nested case-control study design.
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41 ***Leprosy prophylaxis***

42 Single dose rifampicin for leprosy prophylaxis is offered to participants who do not commence any other
43 form of treatment. Those who commence treatment for TB or leprosy, or TPT, already receive multiple
44 doses of a rifamycin as part of those regimens, which constitutes effective leprosy prophylaxis. SDR is
45 dosed according to WHO age and weight bands (with dispersible tablets for children <25kg)⁴² and is
46 given as directly observed treatment (DOT). Single dose rifampicin is well tolerated and widely used for
47 post-exposure prophylaxis in household contacts of people with leprosy^{43 44} and recognised as an
48 effective measure to reduce leprosy prevalence if applied at a population scale in high incidence
49 settings^{20 44 45}. Among published studies evaluating leprosy prophylaxis, SDR was reported to be safe
50 with no observed SAEs⁴³, and we are not aware of any SAEs reported during programmatic
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3 implementation. Offering either single dose rifampicin, TPT, TB treatment and/or leprosy treatment to
4 every participant equates to universal leprosy prophylaxis.
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8 **Outcome measures**

9 **Primary outcome**

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11 The primary outcome measure of this study is the difference between TB case notification rates in
12 Tarawa, recorded from NTP data, during the 12 months before the intervention (2020) and the 12
13 months after it concludes (2024/5). The denominator is the population of Tarawa, as reported by the
14 National Statistics Office. This outcome measure has been chosen to reflect the programmatic intent of
15 the intervention, and the aim of the study to effect a step-change in TB prevalence as a pathway to
16 elimination. Annual TB notification rates will be monitored throughout the study period and are expected
17 to first increase as a result of active case finding, before declining towards the end of the intervention
18 and after its completion.
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30 **Secondary outcomes**

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32 1. Estimated relative annual risk of TB infection (ARTI) among primary school children (aged 8-
33 10 years) in Tarawa, measured by TST at the start of the intervention and in a comparable
34 stratum of children at least 6 months after the intervention.
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37 2. Population prevalence of TST positivity in different age bands.
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- 39
40 3. Description of the observed disease spectrum among people with TB and/or leprosy.
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- 42
43 4. Comparison of TB case notification rates in Tarawa (the intervention site) and the rest of Kiribati
44 (control) before, during and after the intervention.
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47 5. Percentage of participants retained at each step along the 'cascade of care'⁴⁶ (invited to
48 screening, TST placed, TST read, completed screening, offered TPT, commenced TPT,
49 completed TPT).
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- 51
52 6. Diagnostic yield of mobile digital CXRs with computer-aided detection (CAD), compared to
53 sputum testing using Gene Xpert Ultra®, in patients who had both tests performed
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56 7. Incidence rate of DILI among people taking TPT, and the population attributable fraction of HBV
57 infection and other documented risk factors
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- 3 8. Difference in leprosy case notification rates in Tarawa, recorded from NLP data, during the 12
- 4 months before the intervention (2020) and the 12 months after its conclusion (2024/5).
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- 7 9. Comparison of leprosy case notification rates in Tarawa (the intervention site) and the rest of
- 8 Kiribati (control) before, during and after the intervention.
- 9
- 10
- 11 10. Detailed spatial analysis of TB and leprosy cases detected during the intervention, including
- 12 relevant demographic, socioeconomic, environmental and geographic risk factors
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- 15 11. Documenting the cost of the combined intervention, as well as TB and leprosy components
- 16 separately, to estimate the incremental cost-effectiveness ratio in comparison to modelled
- 17 outcomes without the intervention
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23 **Sample Size**

24 For systematic screening and treatment, the sample size for the intervention is the whole population of
25 Tarawa aged ≥ 3 years (53,748 people from 2015 population census, and currently estimated to be
26 $\sim 55,000$ people). The secondary ARTI outcome is calculated from estimated TB infection prevalence
27 using the formula $ARTI = 1 - (1 - TB\ infection\ prev)^{1/a}$, where $a =$ mean age, estimated as 1.8% / year
28 in primary school-aged children (mean age 9 years, LTBI prevalence 15%)⁴⁷. The ability to detect a
29 50% reduction in ARTI with a power of 0.8 (alpha of 0.05), comparing two samples of children at
30 baseline and after the intervention, requires a sample size of 2,580 children at each measurement
31 (G*Power 3.1)⁴⁸. Primary school-aged children will be representatively sampled from the same age
32 categories and schools at both measurements.
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44 **Governance**

45 The Study Management Committee (responsible for day-to-day running and monitoring of the study) is
46 composed of the Kiribati-based medical lead, an i-Kiribati doctor nominated by the Kiribati MHSM, the
47 Kiribati-based nursing lead, the study coordinator, the overall study lead and the education coordinator.
48 All SAEs are reported within 1 week of its recognition to the University of Sydney Human Research
49 Ethics Committee and the Kiribati MHMS by the study coordinator. An independent Data Safety and
50 Monitoring Board (DSMB) will assess study progress and the adverse events recorded and reported as
51 described above. Figure 2 provides an overview of government arrangements.
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ETHICS AND DISSEMINATION

Ethical issues

Adults aged ≥ 18 years will provide written informed consent. Children aged < 18 years will require written parental or caregiver consent, with those aged 10-18 years asked to give verbal assent that is recorded. Participants may voluntarily withdraw from the study at any time. All records are strictly confidential, and all study data will be collected on password-protected electronic devices. A complete database will be stored on a high security data repository administered by the University of Sydney in Sydney, Australia. Relevant data will be extracted for the Kiribati MHMS and NTP as required for clinical or public health purposes, and made available at study completion for future patient care and population benefit.

Dissemination

Study findings will be presented at international conferences and submitted for publication in peer-reviewed journals. Future authorship will include all substantial contributors to the work and there will be a statement of the role of the funder and any potential conflicts of interest. There will be due recognition and acknowledgement of study participants, local study staff and contributions made by i-Kiribati colleagues. There is an overarching commitment to involve i-Kiribati colleagues in all aspects of the study design and execution and to invest in local capacity building. Interim and final reports will be shared with the Kiribati MHMS, with regular updates provided to the Kiribati public and study participants.

Patient and Public Involvement

There was no patient involvement in the design of the study. The study is strongly aligned with national priorities in Kiribati, which recognises TB and leprosy as major infectious disease challenges. The study was informed by the need for an urgent TB and leprosy control solution in Kiribati, as articulated by the Kiribati MHMS. A community Stakeholder Engagement Group (SEG) comprised of i-Kiribati TB and leprosy survivors, local lay leadership and health practitioners will provide community feedback and guidance throughout the intervention period. Patient advisors will be thanked in the acknowledgements of future study publications. Testing bold TB elimination strategies in the Pacific is also aligned with the 'Regional Framework for Action on Implementation of the End TB Strategy in the Western Pacific'⁴⁹.

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3 The framework calls for a paradigm shift in TB control and articulates a need to “integrate diagnosis
4 and management of LTBI into systematic screening for TB disease among high-risk populations”^{49 50}.
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9 **Training, monitoring and evaluation**

10 Building skills, knowledge and workforce capacity is seen as an essential component of the study.
11 Regular staff development training will be conducted by the Australian Respiratory Council. Senior
12 research staff and the Kiribati MHMS will conduct ongoing internal monitoring. Data quality control and
13 critical review of processes will be performed on a weekly basis throughout the study by the study
14 coordinator. Protocol compliance, recruitment, screening and treatment practice, and laboratory
15 processes will be externally reviewed on a quarterly basis, with physical inspection whenever possible.
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24 **Data management and analysis**

25 Data will be collected offline in a standardised fashion and captured on electronic tablets, with daily
26 upload into a secure web-based REDcap database.³⁹ Participants will be assigned a unique study
27 identifier, which will be matched with a facial coordinate scan (SimPrints, Cambridge, UK) at enrolment
28 and will add security to subsequent retrieval of patient records. The study coordinator will review data
29 uploads on a daily basis. At the end of the intervention and while awaiting conduct of the final TST
30 survey among school children, we will complete data cleaning and start analysis. At this time, we will
31 also consolidate the transfer of knowledge and skills and focus on assisting the Kiribati MHMS with
32 longer term planning. A detailed data analysis plan will be drafted focusing on the primary and
33 secondary outcome measures articulated above. In order to assess the durability of the effect we will
34 track annual TB and leprosy case notification numbers beyond the end of the project, which should also
35 inform future interventions and complementary studies.
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49 **DISCUSSION**

50 Ambitious action is needed to change the course of the global TB epidemic, and to make up ground
51 lost to the COVID-19 pandemic. Scaling up access to systematic screening and TPT for high-burden
52 communities has been identified as a key intervention to achieve this,⁵¹ and is reflected in multilateral
53 targets and commitments. For example, at the UN High Level Meeting on TB held in 2018, countries
54 committed to providing 20 million courses of TPT to HIV-negative adult household contacts. Less than
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3 1% of this target has been met, despite abundant evidence that these individuals are at high risk of
4 developing TB and perpetuating the cycle of transmission at the community level.
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9 Recently published WHO guidelines on systematic screening for TB recommend that population level
10 systematic screening can be adopted where the estimated incidence is above 500/100,000 – this
11 threshold is met in Tarawa. Current WHO TPT guidelines state that population-based LTBI testing and
12 treatment is not considered feasible in the absence of locally available tests for LTBI and reliable tests
13 to rule out TB disease, and while it is recognised that it may assist TB elimination efforts, the public
14 health benefit remains unproven³². A population-wide intervention to diagnose and treat TB disease
15 and infection was recently implemented in the Marshall Islands; the ‘TB and Leprosy Free Majuro’⁵²
16 project demonstrated the safety and feasibility of this approach in a Pacific context. For leprosy, WHO
17 acknowledges that universal leprosy prophylaxis, in addition to active case finding, can be valuable to
18 assist elimination efforts,⁴³ which presents a major opportunity for combined TB and leprosy elimination
19 efforts.
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32 Implementing a comprehensive TB elimination strategy in Tarawa has important benefits for TB control.
33 First, population-wide active case finding will facilitate early TB disease detection and treatment,
34 reducing associated morbidity and mortality and limiting ongoing TB transmission within the community.
35 Second, detection and treatment of LTBI will reduce future disease re-activation and greatly increase
36 the durability of the positive impact achieved by the intervention. The feasibility of such an ambitious
37 project is highly dependent on support from the people of Tarawa, strong political commitment from the
38 Kiribati government and cooperation with relevant partners and stakeholders. Third, this study will
39 provide detailed information on the prevalence of TB infection, active TB and leprosy, and document
40 the impact of population-wide screening approaches to inform modelling of TB and leprosy control
41 strategies in the Pacific^{9 20}.
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53 Beyond the domain of TB control, this study will also strengthen the health system of Kiribati. Updated
54 household- and individual-level information collected during the study will facilitate public health
55 interventions in other disease areas as well. Leprosy screening is included in the main intervention, and
56 a proportion of participants will be screened for HBV; these activities will be accompanied by system
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3 changes that align the efforts of the three disease control programmes and could serve as an example
4 in other areas. Strengthened laboratory and radiology capacity will have benefits for the health system
5 overall: for example, expansion of access to GeneXpert and CAD systems would both be of direct
6 benefit in the event of a COVID-19 outbreak. Ultimately, this study is aligned with national and regional
7 priorities for health system strengthening and universal health care.
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14 Study limitations include the reliance on case notification rates as our primary outcome measure, which
15 reflect the operational nature of the intervention. However, we will also compare ARTI, which provides
16 an objective marker of community transmission, and track active case finding, treatment and prevention
17 rates throughout the intervention. Early diagnosis and treatment of cases through active case finding
18 using sensitive tests may increase the measured effect due to lead time bias, but the effect is expected
19 to be small given that all participants with TB infection will receive either TB treatment or TPT. We will
20 also continue monitoring of the intervention effect beyond the life of the project.
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30 The PEARL study benefits from extensive collaboration with the Kiribati MHMS and NTP, as well as
31 established partnerships with the WHO Western Pacific Regional Office (Manila, Philippines), the office
32 of the WHO Representative in the South Pacific (Suva, Fiji), the United Nations Development Program
33 (UNDP) and the Australian Department of Foreign Affairs and Trade (DFAT) amongst others. In
34 addition, extensive community engagement, communication and mobilisation forms the cornerstone of
35 study implementation. Pacific Island Nations like Kiribati are in a unique position, given their geographic
36 isolation and limited population size, to 'lead the way' by implementing ambitious elimination strategies
37 that serve as proof-of-principle for others to learn from and replicate.
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47 **CONCLUSION**

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49 The PEARL study addresses the need for rigorous implementation science to assess the feasibility and
50 impact of population-wide active case finding and treatment, combined LTBI detection and treatment,
51 to durably reduce the TB burden in high incidence settings. The study also explores complementarity
52 between TB and leprosy elimination efforts, with the promise of developing scalable strategies suitable
53 for remote settings with high disease burdens.
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Contact for public and scientific queries

The contact for scientific and public queries is the Principal Investigator, Professor Ben Marais (ben.marais@sydney.edu.au).

Study status

Advanced preparation

Contributors

BJM wrote the initial study proposal. MC and JH contributed equally to this paper. MC, JH, GJF, ET, AT, BE, TI, JMT, AC, GBM, WJB and BJM made important intellectual contributions to the final study protocol. GBM and GJF performed sample size calculations. MC prepared the first draft of the manuscript. The funding agency played no part in any aspect of the study, nor the decision to submit this manuscript for publication.

Competing interests

None declared.

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Table 1. Study inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none">• Everyone aged ≥ 3 years• Children aged < 3 yrs who have had household contact with someone with TB in the past 12 months, or with someone with leprosy since birth	<ul style="list-style-type: none">• Refuse participation

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Table 2. TB preventive treatment (TPT) eligibility and hepatotoxicity risk classification

Assessment	Hepatotoxicity risk category			
	Low	Moderate	Moderate high	High
Definition				
Risk factors <ul style="list-style-type: none"> • Known viral hepatitis • Known HIV infection • Chronic liver disease • Alcohol/kava use* • Age ≥60 years • Test HBV positive** 	No risk factors present	Any risk factor	Any risk factor	Any risk factor
ALT baseline test result (if any risk factors)	Not done	ALT <2x ULN	ALT 2-3x ULN and bilirubin <2xULN	ALT ≥3x ULN (or ALT 2-3x ULN and bilirubin ≥2x ULN)
Management				
Monitoring while on TPT##	No repeat ALT	No repeat ALT	Repeat ALT after 3-4 weeks	Not applicable
Eligibility for TPT	YES	YES	YES	NO
Other reasons for TPT ineligibility	<ul style="list-style-type: none"> • Diagnosed with TB disease • TPT refused • Pregnancy • Allergies to TPT medicines 			

ALT - alanine aminotransferase; HBV - hepatitis B virus; HIV - human immunodeficiency virus; TB – tuberculosis; TPT - TB preventive treatment; ULN - upper limit of normal

*'Excessive use' defined as ≥3 days/week and/or (for alcohol) getting drunk every week

**Everyone ≥40 years with a positive TST who agrees to TPT and is otherwise at low risk is tested with an HBV rapid antigen test

Everyone on TPT receives adherence and adverse event counselling, a TPT passport (Figure S3), as well as access to community-based treatment monitoring and adherence support

Table 3: Criteria for TPT completion

<u>Regimen</u>	Expected duration	Expected total doses	Minimum doses for completion	Maximum time for completion	TPT incomplete
3HP (weekly)	12 weeks	12	11	16 weeks	<8 doses after 12 weeks
3RH (daily)	3 months	84	68	4 months	<40 doses after 3 months
4R (daily)	4 months	120	96	5 months	<68 doses after 4 months

H - isoniazid; P - rifapentine; R - rifampicin; TB - tuberculosis; TPT - TB preventive treatment

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3 **Figure 1. Overview of study enrolment and population-wide TB and leprosy screening**
4 **approach**
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10 HH - household; LTBI - latent TB infection; LPT - leprosy preventive therapy; NTP - Kiribati National TB
11 Control Programme; TB - tuberculosis; TST - tuberculin skin test; TPT - TB preventive treatment; yrs -
12 years; 3HP - 12 once-weekly doses of isoniazid and rifapentine; 3RH - 3 months of daily isoniazid and
13 rifampicin.

14 *Chest X-ray to be performed in everyone ≥ 10 yrs of age and all children < 10 yrs with current symptoms
(cough, fever, weight loss/failure to thrive or visible neck nodes).

15 **The TST can be read up to 96 hours (4 days) after placement if the 2-day follow-up is missed.
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For peer review only

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3 **Figure 2. Overview of study governance**
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8 PEARL - Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis in the Pacific; NTP
9 - National TB program; NLP - Leprosy program in the NTP; MHMS - Ministry of Health and Medical
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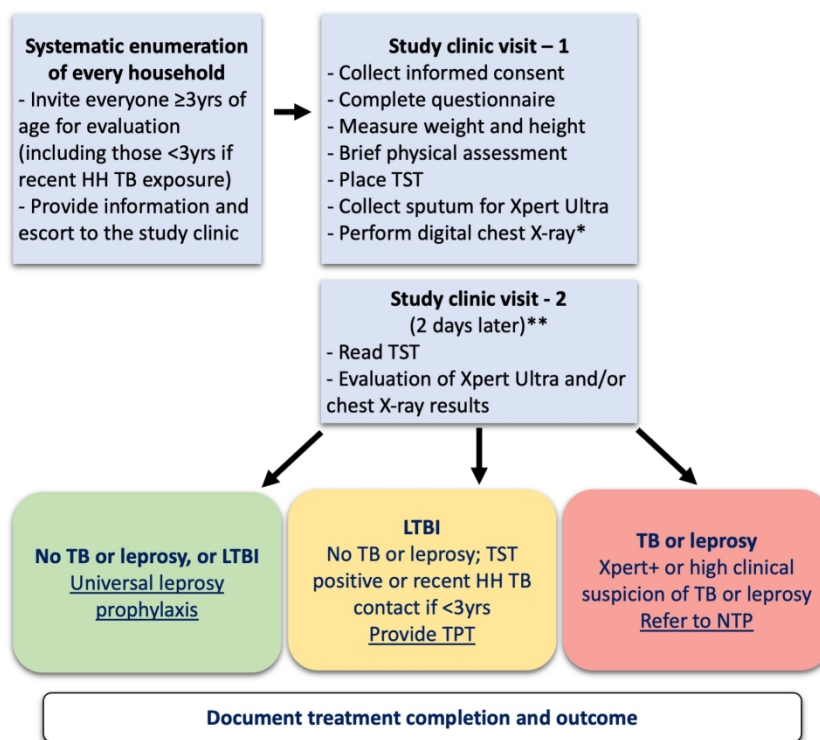


Figure 1. Overview of study enrolment and population-wide TB and leprosy screening approach

HH - household; LTBI - latent TB infection; LPT - leprosy preventive therapy; NTP - Kiribati National TB Control Programme; TB - tuberculosis; TST - tuberculin skin test; TPT - TB preventive treatment; yrs - years; 3HP - 12 once-weekly doses of isoniazid and rifampentine; 3RH - 3 months of daily isoniazid and rifampicin.

*Chest X-ray to be performed in everyone ≥ 10 yrs of age and all children < 10 yrs with current symptoms (cough, fever, weight loss/failure to thrive or visible neck nodes).

**The TST can be read up to 96 hours (4 days) after placement if the 2-day follow-up is missed.

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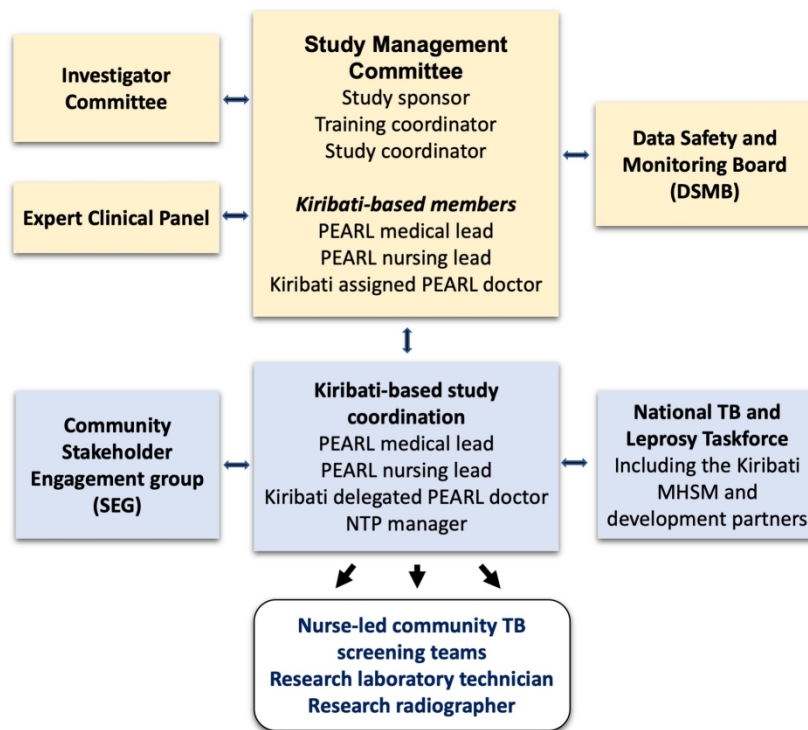


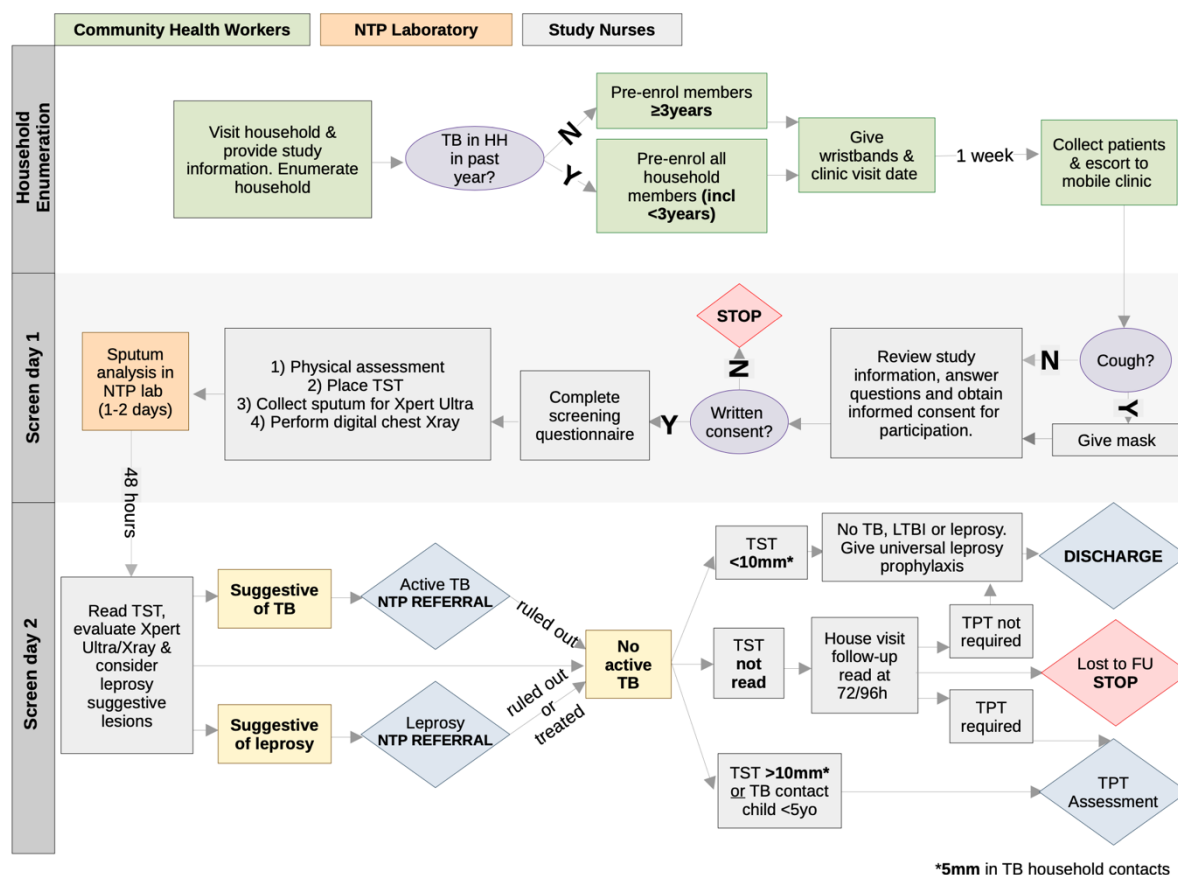
Figure 2. Overview of study governance

PEARL - Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis in the Pacific; NTP - National TB program; NLP - Leprosy program in the NTP; MHMS - Ministry of Health and Medical Services

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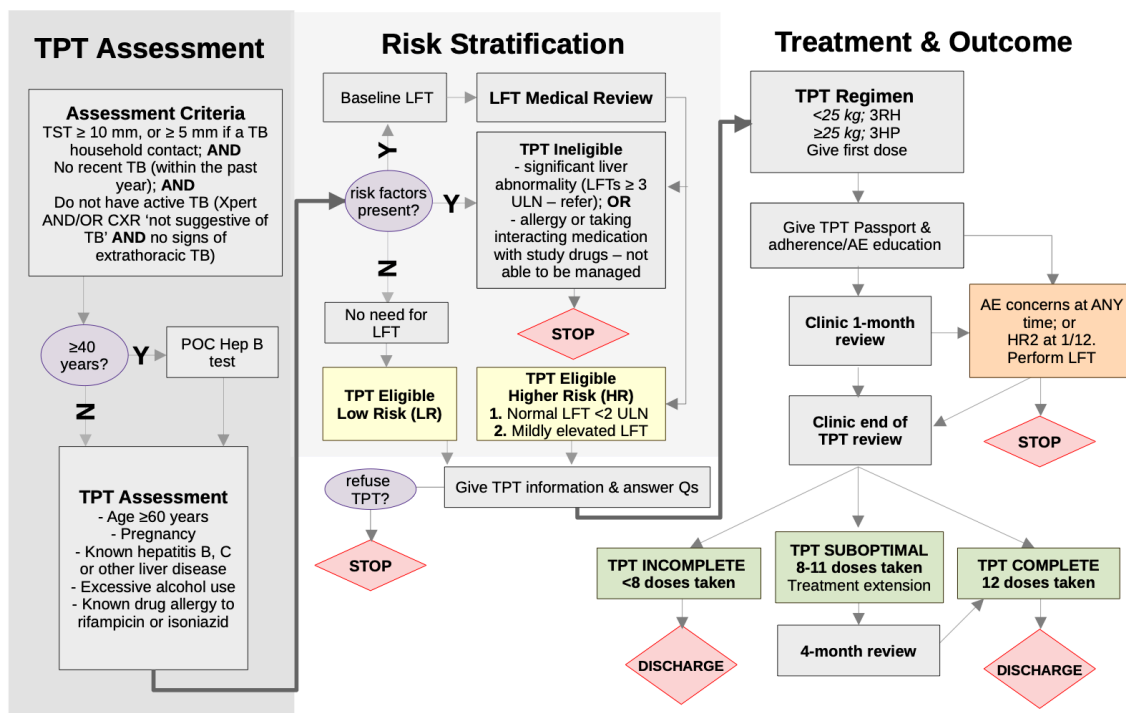
Supplementary Material

Figure S1. PEARL TB and leprosy screening algorithm



FU – follow-up; HH - household; LTBI - latent TB infection; N - no; NTP - National TB Program; TB - tuberculosis; TPT - TB Preventive Treatment; TST - Tuberculin Skin Test; Y - yes

Figure S2. TB preventive Therapy (TPT) algorithm



3HP - 3-months weekly rifapentine and isoniazid; 3RH - 3-months daily rifampicin and isoniazid; AE - adverse event; CXR - chest X-ray; FU - follow-up; HR2 - higher risk group 2; LFT - liver function test; LTBI - latent TB infection; NTP - National TB Program; POC - point-of-care; TB - Tuberculosis; TPT - TB Preventive Treatment; TST - Tuberculin Skin Test; ULN - upper limit of normal

Figure S3. TPT patient passport

3HP

National TB Program &

TPT Passport



We are working together to fight the spread of TB and leprosy in Kiribati

Treatment Diary

QR code

Name: _____ SID: _____

Week 1							Week 9						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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1-month check-in ↓ 3-month check-in

Treatment Completion

Taking my medicine

What is sleeping TB?

Many people infected with the germ that causes TB do not become ill and do not know that they are infected. This is called Latent or Sleeping TB.

Why do I need treatment?

Sometimes sleeping TB can 'wake up' and slowly become infectious TB. People need to take medication to treat sleeping TB and prevent TB from spreading.

Missed dose?

1-2 days missed: take when you remember, then continue the next week on your regular day
3+ days missed: skip a week and start again on your regular day
Not sure? contact your treatment nurse

Reminders

- 1** Take your tablets **once a week** for 12 weeks **Don't miss any!**
- 2** Take your tablets on the **same day** every week
- 3** Record **every time** you take your tablets in your **Treatment Passport**
- 4** **Don't drink alcohol** when you take your tablets
- 5** **Store your tablets at room temperature** and out of reach from children



Things to look out for

Treatment for sleeping TB is safe to take!

It is **normal** to have bright orange urine after taking the medications. **Do not stop taking your tablets!**

Tell a Nurse or Doctor if you have:

- ongoing fatigue/tiredness/sleepiness
- ongoing nausea/vomiting/loss of appetite or abdominal pain
- new rash or itchy skin
- yellowing skin or eyes
- tingling or numbness in fingers/toes


Call or visit the treatment clinic on the day the symptoms occur

Call +6467777777

Treatment Clinic open 9-4pm weekdays




Figure S4. Study Participant Information Form



PEARL 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. Screening will include providing a sputum sample, having a chest X-ray taken and you may be asked to remove your shirt in a private area to have a skin assessment by a nurse or doctor. 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 40 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 your 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

1



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. People younger than 3 years of age who live in a house that shares a kitchen with someone who has had TB or leprosy in the past 12 months are also 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 will happen to information about me that is collected during the study?

My information will be kept in my private medical records with the National TB Program. My data collected during the screen will be separated from my name so that the screening results cannot



be identified as my data. This information will be used to guide the Ministry of Health and Medical Services and the PEARL team about TB and leprosy transmission and occurrence in Tarawa. This information may be reported in international publications, but my name and personal information will never be shared.

What if I would like further information about the study?

Further information about the study can be found on our website www.pearlpacific.com*

Will I be told the results of the study?

The results of the study will be reported to the residents of Tarawa by radio announcement and will also be accessible on the website www.pearlpacific.com.*

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

On behalf of the Kiribati Health Secretary

.....

*in development

Figure S5. Study Participant Informed Consent Form

INFORMED CONSENT PROCESS FORM

Name of Guardian/ Name of Guardian
* must provide value

Date of informed consent
/Date of informed consent
* must provide value D-M-Y

If not done, please specify the reason If not done, please specify the reason

Can participant read Kiribati? Can participant read Kiribati?
* must provide value
 Yes/ Yes
 No/ No reset

Can participant read English? Can participant read English?
* must provide value
 1. Yes/ Yes
 0. No/ No reset

Participant information given and all participant questions answered? 8. Does study staff discuss with participant about content of the participant information statement and answer all questions from participant?
* must provide value
 1. Yes/ Yes
 0. No/ No reset

Participant is aware that screen may involve providing sputum or blood samples? Participant is aware that screen may involve providing sputum or blood samples?
* must provide value
 1. Yes/ Yes
 0. No/ No reset

Does the participant/guardian agree to participate in study? 9. Does the participant agree to participate in study?
* must provide value
 1. Yes/ Yes
 0. No/ No reset

Does the young person assent to participate in the study? 9. Does the young person assent to participate in the study?
* must provide value
 Yes/ Yes
 No/ No reset

Date & Time Participant/relative/witness signed Written Consent Form 10. Date & Time Participant/relative/witness signed Written Consent Form
* must provide value D-M-Y H:M

Sign
[Add signature](#)

Witness Sign
[Add signature](#)

Other comments Other comments



Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati – the PEARL study 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	___19___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1-2; 19___
	5b	Name and contact information for the trial sponsor	___19___
	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	___19___
	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)	___13-15___

1 **Introduction**

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3 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 5-6

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6 6b Explanation for choice of comparators 5-6

7

8 Objectives 7 Specific objectives or hypotheses 5-6

9

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) 6

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12

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14 **Methods: Participants, interventions, and outcomes**

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16 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 6-7

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19 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) 7; table 1

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 7-12

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25 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) 10-11; table 2

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 10

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 10-11

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34 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 12-13

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40 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) table 3; fig 1

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 13
 2 clinical and statistical assumptions supporting any sample size calculations

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 8; 13

6 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any NA non-random
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, NA population-
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned wide
 18 mechanism

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to NA population-
 21 interventions wide

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome NA open-label
 25 assessors, data analysts), and how

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's NA open-label
 28 allocated intervention during the trial

31 **Methods: Data collection, management, and analysis**

33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 12-15
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 10; 12
 40 collected for participants who discontinue or deviate from intervention protocols

1	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	10 ; 15
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5	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	12-13
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
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10		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)	12-13
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14	Methods: Monitoring			
15				
16	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	13 ; fig 2
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22		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	13 ; 15
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25	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	10-11 ; 13
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13-15 ; fig 2
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3 ; 14
35				
36				
37	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)	3 ; 14
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>14</u>
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>11; 14</u>
5				
6				
7	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	<u>14-15</u>
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>19</u>
11				
12				
13	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	<u>14</u>
14				
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16				
17	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 – Public Health intervention endorsed by the Ministry of Health
18				
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22	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	<u>14</u>
23				
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27		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>19</u>
28				
29		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA – shared with the Kiribati Ministry of Health
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34	Appendices			
35				
36	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>fig S3; S4; S5</u>
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1 Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular
2 analysis in the current trial and for future use in ancillary studies, if applicable
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NA – subject to
separate
ethics/studies will
be reported
separately

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8 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
9 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati – the PEARL study protocol

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TITLE

Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati
– the PEARL study protocol

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ABSTRACT

Introduction

Population-wide interventions offer a pathway to tuberculosis (TB) and leprosy elimination, but 'real-world' implementation in a high-burden setting using a combined approach has not been demonstrated. This implementation study aims to demonstrate the feasibility and evaluate the effect of population-wide screening, treatment and prevention on TB and leprosy incidence rates, as well as TB transmission.

Methods and analysis

A non-randomised 'screen-and-treat' intervention conducted in the Pacific atoll of South Tarawa, Kiribati. Households are enumerated and all residents ≥ 3 years, as well as children < 3 years with recent household exposure to TB or leprosy, invited for screening. Participants are screened using tuberculin skin testing, signs and symptoms of TB or leprosy, digital chest X-ray with computer-aided detection and sputum testing (Xpert[®] MTB/RIF Ultra). Those diagnosed with disease are referred to the National TB and Leprosy Program for management. Participants with TB infection are offered TB preventive treatment and those without TB disease or infection, or leprosy, are offered leprosy prophylaxis. The primary study outcome is the difference in the annual TB case notification rate before and after the intervention; a similar outcome is included for leprosy. The effect on TB transmission will be measured by comparing the estimated annual risk of TB infection in primary school children before and after the intervention, as a co-primary outcome used for power calculations. Comparison of TB and leprosy case notification rates in South Tarawa (the intervention group) and the rest of Kiribati (the control group) before, during and after the intervention is a secondary outcome.

Ethics and dissemination

Approval was obtained from the University of Sydney Human Research Ethics Committee (project no. 2021/127) and the Kiribati Ministry of Health and Medical Services (MHMS). Findings will be shared with the MHMS and local communities, published in peer-reviewed journals and presented at international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Real-world population-wide active case finding and prevention approach for TB and leprosy control
- Concurrent screening and treatment of TB disease and infection for durable public health impact
- Combined TB and leprosy elimination efforts increases efficiency, but also complexity
- Findings generalizable to other remote settings, but uncertain about 'disease hot spots' globally
- Non-randomised study design limits confidence in attribution of effects to the intervention

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INTRODUCTION

Tuberculosis (TB, caused by *Mycobacterium tuberculosis*) is a leading infectious disease killer globally and in the Pacific,¹ while leprosy (caused by *Mycobacterium leprae*) elimination remains a major challenge as well.² It is estimated that TB killed ~1.5 million people in 2020, despite being a preventable and curable disease.¹ At the 2018 United Nations High-Level Meeting on TB,³ world leaders committed to step up TB elimination efforts, with improved TB case finding and expanded use of TB preventive treatment (TPT) identified as key interventions in the global “End TB strategy”.⁴

Historical population-wide TB elimination programmes demonstrated considerable success and are enjoying renewed attention, with specific emphasis on active case finding and prevention strategies.^{5,6} A randomized controlled trial in Vietnam recently demonstrated that population-wide active TB case finding can achieve substantial reductions in TB incidence and transmission.⁷ Historic studies and modelling projections suggest that this effect, and its durability, can be enhanced by concurrent treatment of TB infection,^{8,9} but data on ‘real-life’ implementation remain scarce. Given World Health Organization (WHO) endorsement of integrated active TB case finding and preventive treatment approaches,¹⁰⁻¹⁵ there is urgency to develop implementation models that demonstrate feasibility and population impact.

At the 2020 census, around 59% of the i-Kiribati population lived on the capital atoll of Tarawa.¹⁶ Of all TB cases detected in Kiribati in 2020, 69% (267 of 385) were from Tarawa - equating to an estimated TB incidence of >500/100,000 population, the threshold incidence level above which the WHO recommends population-wide screening interventions.¹⁷ *M. tuberculosis* strain typing data¹⁸ and the dominance of young adults among TB cases indicate high levels of community transmission,¹⁹ which emphasises the need for case finding and prevention strategies to be combined in order to prevent rapid re-infection.

Leprosy rates in Kiribati, and South Tarawa in particular, are also among the highest in the world (>200 cases/100,000 population, compared to the WHO elimination threshold of 10/100,000 population) and have been rising rapidly after a nadir in the late 1990s when elimination efforts were discontinued.² Modelling studies done in Kiribati indicate that a single population-wide active case finding intervention,

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3 combined with 'universal leprosy prophylaxis' using single-dose rifampicin, could dramatically decrease
4 leprosy prevalence with a sustained effect.²⁰
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9 Although both TB and leprosy pose daunting public health challenges in this resource-limited setting,
10 their co-occurrence within a geographically defined and isolated population presents a unique
11 opportunity to evaluate combined elimination efforts. The aim of the proposed study is to achieve major
12 reductions in TB and leprosy incidence and transmission in South Tarawa over the medium term,
13 providing a pathway to future elimination. If successful, the proposed study will provide a template for
14 TB and leprosy elimination efforts throughout the Pacific and in other remote settings.
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22 **METHODS AND ANALYSIS**

23 **Study Design**

24 The PEARL study is a before and after evaluation of a population-wide systematic screening
25 intervention, combined with a comprehensive treatment and prevention program for both TB and
26 leprosy. It is executed in close collaboration with the Kiribati Ministry of Health and Medical Services
27 (MHMS).
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36 **Setting**

37 Kiribati is a lower-middle income country of ~120,000 people residing on low-lying atolls and islands in
38 the western Pacific Ocean, with the lowest gross domestic product (GDP) per-capita of any country in
39 Oceania.²¹ The country has among the highest TB incidence rates in the world,²² and is one of 23 WHO
40 priority-countries for leprosy control.²³ Small numbers of people have been diagnosed with drug-
41 resistant (DR-) TB (7 out of 385 cases in 2020) with limited evidence of community transmission of DR-
42 TB. The prevalence of human immunodeficiency virus (HIV) infection is low, and no cases of TB/HIV
43 coinfection were reported in 2019. However, there is a high burden of non-communicable disease, with
44 the adult diabetes prevalence exceeding 20%,²⁴ high rates of childhood malnutrition and substantial
45 levels of smoke exposure from cooking fires and cigarette smoking.²⁵
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56 As of November 2021, no confirmed cases of coronavirus disease 2019 (COVID-19) have been
57 recorded in Kiribati, and no mask-wearing or social distancing measures have been employed.
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3 However, these practices and protocols are in place if required, should the COVID-19 pandemic spread
4 to Kiribati. A COVID-19 vaccination programme commenced in May 2021, which is on track to achieve
5 full vaccination coverage of >90% of the adult population by early 2022. Future public health measures
6 to control the spread of COVID-19 will be determined by the Kiribati MHMS based on ongoing
7 assessment of the risk posed and according to the National COVID-19 preparatory and response plan,
8 and the standard operating procedures (SOPs) in place (Kiribati MHMS, unpublished).
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16 Tarawa atoll serves as the capital of Kiribati. Residents of villages in South Tarawa and the small
17 communities of Buota and Abatao at the southernmost end of North Tarawa are included in the
18 intervention and hereunder referred to as 'South Tarawa'. South Tarawa accommodates ~59% of the
19 i-Kiribati population and has the highest rates of TB and leprosy disease. Betio Islet in particular is the
20 most densely populated area in the Pacific with an estimated population density of >15,000 people/km².
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28 TB case management is provided by the National TB Program (NTP). TB diagnostics available in South
29 Tarawa include smear microscopy, rapid genotypic testing and chest X-ray, but culture facilities are
30 unavailable. Sputum samples can be sent to the regional reference laboratory in Adelaide, Australia,
31 for culture and susceptibility testing. However, this is problematic due to logistical issues and high rates
32 of bacterial overgrowth. Most people with TB are hospitalised during the first few weeks of treatment at
33 the local government hospital (Betio and Tungaru hospitals). Household contact investigation is
34 advised, but not universally implemented because of resource constraints. National guidelines
35 recommend TPT for household contacts for whom TB disease has been excluded, but implementation
36 and uptake are again inconsistent. Leprosy is diagnosed using clinical assessment and microscopy,
37 with genotypic diagnosis available by sending punch biopsy samples to the regional reference
38 laboratory in Christchurch, New Zealand. Curative treatment, occupational therapy and chronic disease
39 management is provided by the National Leprosy Program (NLP). Post-exposure prophylaxis (PEP) of
40 household contacts using single-dose rifampicin (SDR) has been scaled up in recent years with the
41 help of the Pacific Leprosy Foundation (PLF).²
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56 **Study population**

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3 The study population comprises all residents of South Tarawa. All adults, adolescents and children
4 aged three and above are included (Table 1). Children aged less than three years are included if they
5 have documented household contact with someone who had TB (in the past 1 year), or leprosy (at any
6 time since they were born). Household contact is defined as being between two people who have
7 regular meals prepared in the same kitchen. Members of the study population are only excluded if they
8 prefer not to participate.
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16 **Study intervention**

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18 The study intervention comprises population-wide systematic screening and treatment of TB disease,
19 TB infection and leprosy, together with the provision of leprosy prophylaxis to those not requiring
20 treatment. In practice this equates to universal leprosy prophylaxis, given that TB and leprosy treatment,
21 as well as TPT with rifamycin-based regimens, provides adequate leprosy prophylaxis. The enrolment
22 and screening process are summarised in Figure 1; more detailed algorithms are included in the
23 supplement (supplements S1 and S2). The study intervention is delivered over a period of 3 years.
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32 **Systematic screening procedures**

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34 All households are enumerated based on location and demographic data collected during the 2020
35 census (Kiribati National Statistics Office 2021, unpublished). Study staff visit each residence, collect
36 GPS coordinates, ascertain eligibility in a brief household survey conducted with the household head,
37 and invite eligible participants for screening. During the first clinic visit, study personnel obtain written
38 informed consent from adult participants (≥ 18 years of age), or parents/legal guardians in those aged
39 < 18 years, with verbal assent from children aged 10-18 years. Identifying information is collected at
40 registration, including a photograph and a biometric identifier to aid future re-identification (facial
41 coordinate scan 'health selfie', Simprints Technology Limited, Cambridge, UK). Study nurses complete
42 a short TB symptom questionnaire and a brief physical examination for signs and symptoms suggestive
43 of TB disease (visible lymph node mass or gibbus) or leprosy (suggestive skin lesions or altered shape
44 of face, nose, ears, hands or feet).
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56 A tuberculin skin test (TST) is placed using the Mantoux method and sputum collection is attempted in
57 all participants aged ≥ 10 years; age-appropriate diagnostic specimens may be collected in children < 10
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3 years who have symptoms suggestive of TB, but it is not part of the screening procedure. Sputum
4 specimens are tested using Xpert® MTB/RIF Ultra, recently endorsed by WHO as a sensitive front-line
5 diagnostic test²⁶. A digital chest X-ray (CXR) is performed on everyone aged ≥ 10 years, and children
6 aged < 10 years with symptoms suggestive of TB. CXR interpretation is conducted with computer-aided
7 detection (CAD) software certified for use in TB screening (CAD4TB v6, Diagnostic Image Analysis
8 Group, Radboud University Medical Center, Nijmegen, The Netherlands). The use of CAD software for
9 TB screening is recommended by recent WHO guidelines, and good experiences with implementation
10 have been reported in a variety of settings^{27 28}. Screening CXRs for participants aged < 15 years will
11 also be interpreted by study medical staff, with the age threshold for CAD interpretation to be re-
12 evaluated as evidence and experience accumulates during the intervention period.

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24 At a second clinic visit two days later, the TST is read and considered positive if induration is ≥ 10 mm,
25 or ≥ 5 mm if the participant has had household contact with a person with infectious TB in the past 12
26 months. The CXRs of all participants with a CAD score of ≥ 50 (and a random selection of those with
27 scores < 50), *M. tuberculosis* detected on Xpert® MTB/RIF Ultra or symptoms suggestive of TB will be
28 reviewed by a study doctor. The CAD threshold score will be adjusted if necessary to optimise screening
29 performance in the study population. Patients with bacteriologically confirmed or clinically diagnosed
30 TB disease or leprosy will be referred to the Kiribati NTP or NLP for treatment, with close coordination
31 between study and program clinicians.

32 33 34 35 36 37 38 39 40 41 ***TB preventive treatment eligibility***

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43 Participants with a positive TST or children < 5 years with recent household contact are considered for
44 TPT if they do not have TB disease and have not completed a course of TB treatment or TPT within
45 the last 12 months. Potential TPT contraindications (eg. allergies to TB medicines, risk factors for
46 hepatotoxicity) are assessed using a brief questionnaire. There is a high prevalence of hepatitis B virus
47 (HBV) infection among older people in Kiribati;²⁹ routine HBV vaccination introduced in the 1990s
48 reduced infection rates among younger people³⁰. A point-of-care HBV rapid test (Determine™ HBsAg
49 2) is performed in all participants aged 40-59 years who agree to TPT and are otherwise at low risk
50 (liver function testing is done in everyone ≥ 60 years), since they are at increased risk of HBV infection
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3 and possible liver disease. Participants diagnosed with HBV infection receive a liver function test prior
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5 to TPT initiation and are referred to the HBV treatment programme for management.
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8 9 ***Hepatotoxicity risk assessment***

10 Baseline serum alanine aminotransferase (ALT) testing is conducted in all participants aged ≥ 60 years,
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12 or with identified risk factors for hepatotoxicity, and results stratified according to hepatotoxicity risk
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14 (Table 2). Participants with ALT ≥ 3 x upper limit of normal (ULN) are not offered TPT, those with ALT 2-
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16 3x ULN are offered TPT (if the bilirubin in < 2 x ULN) with repeat ALT testing after 3-4 weeks, and
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18 participants with ALT < 2 x ULN (or no need for a baseline test) are offered TPT without further ALT
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20 monitoring. All participants receive information on the signs and symptoms of hepatotoxicity, guidance
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22 to limit alcohol and kava intake and access to a 'hotline' linked to a rapid evaluation service.
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26 27 ***TB preventive treatment regimens and treatment initiation***

28 Participants who are eligible, have no contraindications and accept TPT, are offered a choice of short-
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30 course rifamycin-based regimens according to clinical characteristics, patient preference and
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32 availability. Currently used regimens are: 12 weekly doses of isoniazid and rifapentine (3HP), four
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34 months of daily rifampicin (4R), or 3 months of daily isoniazid and rifampicin (3RH, preferred for young
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36 children due to availability of child-friendly water-dispersible formulations). Dosing is chosen according
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38 to recommendations from the WHO and the Kiribati NTP. In participants with a documented history of
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40 household contact with someone diagnosed with DR-TB, TPT using six months of daily levofloxacin is
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42 considered under expert guidance^{31 32}. New evidence and normative guidance supporting the use of
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44 shorter TPT regimens may be released during the study. Consistent with the implementation approach,
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46 additional regimens may be offered to participants in collaboration with the Kiribati NTP and with
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48 updated ethical approval. All medicines used in the study will be obtained from WHO prequalified
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50 manufacturers, procured from the Global Drug Facility.
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53 54 ***Community-based TB preventive treatment adherence support and monitoring***

55 At each stage of treatment initiation, adherence support, treatment monitoring, management of adverse
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57 events and assignment of treatment outcome, participants are provided with appropriate counselling on
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59 risks, benefits and options available. A detailed patient information sheet is provided (supplement S3)
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3 together with group and/or individual counselling with the aid of an illustrated flip chart and a 'TPT
4 passport' (supplements S4 and S5) to assist adherence and adverse event monitoring. After taking the
5 first dose under direct supervision, TPT will be self-administered with use of pragmatic adherence
6 support strategies tailored to the particular study community. Medicines are dispensed in 4-8 week
7 intervals, or according to patient preference and adherence. All participants who commence TPT are
8 visited once after 3-4 weeks to support adherence and screen for adverse events, and again when they
9 near TPT completion to assess treatment adherence and either extend treatment or assign a treatment
10 outcome. Additional supportive visits are scheduled as needed. Assessment of adherence is performed
11 and recorded at each visit by interviewing the participant, reviewing the TPT passport and counting
12 remaining pills. Treatment completion is determined according to WHO recommendations (Table 3).
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24 ***Detection and management of adverse events***

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26 This is an implementation study that uses medicines recommended by the Kiribati NTP and which have
27 been shown to be safe and effective.^{10 33-38} Adverse events associated with the study intervention
28 (defined as any untoward medical occurrence in a study participant) are similar to those encountered
29 in routine programme delivery. Misidentification and misclassification will be minimised through
30 adequate planning and testing of all procedures, using ongoing quality assurance measures built into
31 a secure Research Electronic Data Capture (REDCap) database³⁹ and close oversight from local study
32 coordinators. Linkage to care for referrals to government treatment programs (TB, leprosy, hepatitis)
33 will be monitored.
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43 Participants receiving TPT will have access to a team of community health workers, a 'TPT hotline',
44 and a walk-in service for adverse event assessment and management. Study staff are trained to identify
45 the most common and most severe adverse events associated with TPT, with a particular focus on
46 hepatotoxicity. Drug-related adverse events are triaged and referred for further medical evaluation as
47 appropriate, including liver function testing. If needed, referral and linkage to urgent care services is
48 available.
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56 The following drug-related adverse events will be recorded and reported as part of the study:
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- Drug-induced liver injury (DILI - defined as suggestive symptoms plus ALT >3 times upper limit of normal or ALT >5 times upper limit of normal without symptoms) while on TPT
- Drug-related adverse events resulting in TPT interruption or cessation⁴⁰
- All serious adverse events among people taking TPT (SAEs, as defined by the Australian National Health and Medical Research Council)⁴¹

Anyone with DILI during treatment or with an abnormal ALT ($\geq 2x$ ULN) at baseline will receive an HBV rapid test (if not previously performed). In addition, blood drawn from participants with DILI and matched controls will be stored (with additional consent) for expanded risk factor determination, using an efficient nested case-control study design.

Other adverse events that will be recorded include:

- Misclassification or misinterpretation of screening results resulting in mistreatment
- Post-positive screen treatment delay for TB disease (>7 days) and leprosy (>14 days)

Leprosy prophylaxis

All participants who do not commence any other form of treatment are eligible for leprosy prophylaxis using SDR. Those who commence treatment for TB or leprosy, or TPT using 3HP or 3HR, already receive multiple doses of a rifamycin as part of those regimens, which constitutes effective leprosy prophylaxis. Contraindications (Table 4) are assessed and if none are found SDR is given as directly observed treatment (DOT), dosed according to WHO age and weight bands (with dispersible tablets for children <25kg).⁴²

SDR is well tolerated and widely used for post-exposure prophylaxis in household contacts of people with leprosy^{43 44} and recognised as an effective measure to reduce leprosy prevalence if applied at a population scale in high incidence settings.^{20 44 45} Among published studies evaluating leprosy prophylaxis, SDR was reported to be safe with no observed SAEs,⁴³ and we are not aware of any SAEs reported during programmatic implementation. Offering either SDR, 3HP, 3HR, TB treatment and/or leprosy treatment to every participant equates to a single mass drug administration intervention.

Ongoing screening of close contacts of leprosy cases, with PEP provision, will continue beyond the study intervention, supported by the PLF. The PLF have conducted leprosy contact tracing and PEP using SDR in Kiribati since 2010 and are committed to continue this work.

Outcome measures

Primary outcomes

The first primary outcome measure of this study is the difference between TB case notification rates in South Tarawa, recorded from NTP data, during the 12 months before the intervention (2020) and the 12 months after it concludes (2024/5). The denominator is the population of South Tarawa, as reported by the National Statistics Office. This outcome measure has been chosen to reflect the programmatic intent of the intervention, and the aim of the study to effect a step-change in TB prevalence as a pathway to elimination. Annual TB notification rates will be monitored throughout the study period and are expected to first increase as a result of active case finding, before declining towards the end of the intervention and after its completion.

The second primary outcome measure is estimated annual risk of TB infection (ARTI) among primary school children in South Tarawa, measured by TST before and 6 months after the intervention. This outcome measure has been chosen to assess the impact of the intervention on community transmission of TB. Together, the primary outcomes allow us to assess the public health and epidemiological impact of the TB intervention.

Secondary outcomes

1. Population prevalence of TST positivity in different age bands.
2. Description of the disease spectrum and risk factors observed among people with TB and/or leprosy.
3. Comparison of TB case notification rates in South Tarawa (the intervention site) and the rest of Kiribati (control) before, during and after the intervention.
4. Percentage of participants retained at each step along the 'cascade of care'⁴⁶ (invited to screening, TST placed, TST read, completed screening, offered TPT, commenced TPT, completed TPT).

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- 3 5. Diagnostic yield of mobile digital CXRs with CAD, compared to sputum testing using Gene
- 4 Xpert® MTB/RIF Ultra, in patients who had both tests performed
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- 7 6. Incidence rate of DILI among people taking TPT, and the population attributable fraction of HBV
- 8 infection and other documented risk factors
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- 11 7. Difference in leprosy case notification rates in South Tarawa, recorded from NLP data, during
- 12 the 12 months before the intervention (2020) and the 12 months after its conclusion (2024/5).
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- 14 8. Comparison of leprosy case notification rates in South Tarawa (the intervention site) and the
- 15 rest of Kiribati (control) before, during and after the intervention.
- 16
- 17 9. Spatial analysis of TB and leprosy cases detected during the intervention, including data
- 18 visualisation (mapping and interpolation), identification of spatial clusters, and spatial statistical
- 19 modelling.
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- 21 10. Documenting the cost of the combined intervention, as well as TB and leprosy components
- 22 separately, to estimate the incremental cost-effectiveness ratio in comparison to modelled
- 23 outcomes without the intervention
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33 **Sample Size**

34 For the TB and leprosy case notification rate outcomes, the sample size is the whole population of
35 South Tarawa (total population 65,566 at the 2020 census, Kiribati National Statistics Office 2021).
36 Additional analysis of the sensitivity of our study design to detect an effect on TB and leprosy case
37 notification rates is included as supplementary material (supplements S6 and S7). The ARTI outcome
38 is calculated from estimated TB infection prevalence using the formula $ARTI = 1 - (1 - TB \text{ infection}$
39 $prevalence)^{1/a}$, where $a = \text{mean age}$, estimated as 1.8% / year in primary school-aged children (mean
40 age 9 years, TB infection prevalence 15%).⁴⁷ The ability to detect a 50% reduction in ARTI with a power
41 of 0.8 (alpha of 0.05), comparing two samples of children at baseline and after the intervention, requires
42 a sample size of 2,580 children at each measurement (G*Power 3.1).⁴⁸ Primary school children will be
43 representatively sampled from the same age categories and schools at both measurements.
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55 **Governance**

56 The Study Management Committee (responsible for day-to-day running and monitoring of the study) is
57 composed of the Kiribati-based medical lead, an i-Kiribati doctor nominated by the Kiribati MHSM, the
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3 Kiribati-based nursing lead, the study coordinator, the overall study lead and the education coordinator.
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5 All SAEs are reported within 1 week of its recognition to the University of Sydney Human Research
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7 Ethics Committee and the Kiribati MHMS by the study coordinator. An independent Data Safety and
8
9 Monitoring Board will assess study progress and the adverse events recorded and reported as
10
11 described above. Figure 2 provides an overview of governance arrangements.
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14 **ETHICS AND DISSEMINATION**

15 **Ethical issues**

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18 Adults aged ≥ 18 years provide written informed consent (supplement S8). Written parental or caregiver
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20 consent is provided for children and adolescents aged < 18 years, with those aged 10-18 years asked
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22 to provide verbal assent that is recorded. Participants may voluntarily withdraw from the study at any
23
24 time. All records are strictly confidential, and all study data will be collected on password-protected
25
26 electronic devices. A complete database will be stored on a high security data repository administered
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28 by the University of Sydney in Sydney, Australia. Relevant data will be extracted for the Kiribati MHMS
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30 and NTP as required for clinical or public health purposes, and made available at study completion for
31
32 future patient care and population benefit.
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36 Particular attention is given to handling of biometric data, which has been included in the study
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38 procedures after close consultation with the Kiribati MHMS and extensive collaboration with the
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40 biometric identification provider. Biometric identifiers are captured in a standalone mobile application
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42 and stored in a secure database maintained by the biometric identification provider, which is separate
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44 from the study database and inaccessible to users. Records in the two databases are linked by a
45
46 unique, randomly generated identifier. When study staff use biometric identification to retrieve a
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48 participant record, the linking identifier is accessed by the biometric identification application without
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50 further input by the user. Participants are free to refuse or withdraw consent to record biometric identifier
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52 data, while still participating in the study. Participants are specifically asked for consent to share
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54 biometric identification data with the Kiribati MHMS, and are free to refuse or withdraw.
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56 **Dissemination**

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3 Study findings will be presented at international conferences and submitted for publication in peer-
4 reviewed journals. Findings will also be disseminated through the websites of collaborating
5 organisations and in writing to donors. Editable resources developed for the study will be posted on the
6 study website for free-to-use access: www.thepearlstudy.org. Future authorship will include all
7 substantial contributors to the work and there will be a statement of the role of the funder and any
8 potential conflicts of interest. There will be due recognition and acknowledgement of study participants,
9 local study staff and contributions made by i-Kiribati colleagues. There is an overarching commitment
10 to involve i-Kiribati colleagues in all aspects of the study design and execution and to invest in local
11 capacity building. Interim and final reports will be shared with the Kiribati MHMS, with regular updates
12 provided to the i-Kiribati public and study participants.
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24 **Patient and Public Involvement**

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26 There was no patient involvement in the design of the study. The study is strongly aligned with national
27 priorities in Kiribati, which recognises TB and leprosy as major infectious disease challenges.⁴⁹ The
28 study was informed by the need for an urgent TB and leprosy control solution in Kiribati, as articulated
29 by the Kiribati MHMS. A community Stakeholder Engagement Group comprised of i-Kiribati TB and
30 leprosy survivors, local lay leadership and health practitioners will provide community feedback and
31 guidance throughout the intervention period. Patient advisors will be thanked in the acknowledgements
32 of future study publications. Testing TB elimination strategies in the Pacific is also aligned with the
33 'Regional Framework for Action on Implementation of the End TB Strategy in the Western Pacific'.⁵⁰
34 The framework calls for a paradigm shift in TB control and articulates a need to "integrate diagnosis
35 and management of LTBI into systematic screening for TB disease among high-risk populations".^{50 51}
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47 **Training, monitoring and evaluation**

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49 Building skills, knowledge and workforce capacity is seen as an essential component of the study.
50 Regular staff development training will be conducted by the Australian Respiratory Council. Senior
51 research staff and the Kiribati MHMS will conduct ongoing internal monitoring. Data quality control and
52 critical review of processes will be performed on a weekly basis throughout the study by the data
53 manager. Protocol compliance, recruitment, screening and treatment practice, and laboratory
54 processes will be externally reviewed on a quarterly basis, with physical inspection whenever possible.
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Data management and analysis

Data will be collected offline in a standardised fashion and captured on electronic tablets, with daily upload into a secure web-based REDcap database.³⁹ Participants will be assigned a unique study identifier at enrolment, which will be matched with identifying data including a photograph and a biometric identifier (Simprints, Cambridge, UK). This will add accuracy to retrieval of patient records and reduce misidentification. The data manager will review data uploads on a daily basis. At the end of the intervention and while awaiting conduct of the final TST survey among school children, we will complete data cleaning and start analysis. At this time, we will also consolidate the transfer of knowledge and skills and focus on assisting the Kiribati MHMS with longer term planning. A detailed data analysis plan will be drafted focusing on the primary and secondary outcome measures articulated above. In order to assess the durability of the effect we will track annual TB and leprosy case notification numbers beyond the end of the project, which should also inform future interventions and complementary studies.

DISCUSSION

Ambitious action is needed to change the course of the global TB epidemic, and to make up ground lost to the COVID-19 pandemic. Scaling up access to systematic screening and TPT for high-burden communities has been identified as a key intervention to achieve this,⁵² and is reflected in multilateral targets and commitments. For example, at the UN High Level Meeting on TB held in 2018, countries committed to providing 20 million courses of TPT to HIV-negative adult household contacts. Less than 1% of this target has been met, despite abundant evidence that these individuals are at high risk of developing TB and perpetuating the cycle of transmission at the community level.

Recently published WHO guidelines on systematic screening for TB recommend that population level systematic screening can be adopted where the estimated incidence is above 500/100,000 – this threshold is met in South Tarawa. Current WHO TPT guidelines state that population-based TB infection testing and treatment is not considered feasible in the absence of locally available tests for TB infection and reliable tests to rule out TB disease, and while it is recognised that it may assist TB elimination efforts, the public health benefit remains unproven.³² A population-wide intervention to

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3 diagnose and treat TB disease and infection was recently implemented in the Marshall Islands; the 'TB
4 and Leprosy Free Majuro'⁵³ project demonstrated the safety and feasibility of this approach in a Pacific
5 context. For leprosy, WHO acknowledges that universal leprosy prophylaxis, in addition to active case
6 finding, can be valuable to assist elimination efforts,⁴³ which presents a major opportunity for combined
7 TB and leprosy elimination efforts.
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14 Implementing a comprehensive TB elimination strategy in South Tarawa has important benefits for TB
15 control. First, population-wide active case finding will facilitate early TB disease detection and
16 treatment, reducing associated morbidity and mortality and limiting ongoing TB transmission within the
17 community. Second, detection and treatment of TB infection will reduce future disease re-activation
18 and greatly increase the durability of the positive impact achieved by the intervention. The feasibility of
19 such an ambitious project is highly dependent on support from the people of South Tarawa, strong
20 political commitment from the Kiribati government and cooperation with relevant partners and
21 stakeholders. Third, this study will provide detailed information on the prevalence of TB infection, active
22 TB and leprosy, and document the impact of population-wide screening approaches to inform modelling
23 of TB and leprosy control strategies in the Pacific.^{9 20}
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36 Beyond the domain of TB control, this study will also strengthen the health system of Kiribati. Updated
37 household- and individual-level information collected during the study will facilitate public health
38 interventions in other disease areas as well. Leprosy screening is included in the main intervention, and
39 a proportion of participants will be screened for HBV; these activities will be accompanied by system
40 changes that align the efforts of the three disease control programmes and could serve as an example
41 in other areas. Strengthened laboratory and radiology capacity will have benefits for the health system
42 overall: for example, expansion of access to genotypic diagnosis and digital X-ray systems with CAD
43 software would both be of direct benefit in the event of a COVID-19 outbreak. Ultimately, this study is
44 aligned with national and regional priorities for health system strengthening and universal health care.
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54 Study limitations include the reliance on case notification rates as a primary outcome measure, which
55 reflects the operational nature of the intervention. Early diagnosis and treatment of cases through active
56 case finding using sensitive tests may increase the measured effect, due to lead time bias. The
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3 provision of TPT to all participants with TB infection will reduce the number of incipient disease cases;
4 also adding to potential lead time bias. However, the impact measured will reflect 'real world' reductions
5 achieved and monitoring TB incidence rates before, throughout, and for an extended period after the
6 intervention will allow us to reflect on the potential impact of lead time bias and to assess the durability
7 of the reductions achieved. Comparing ARTI before and after the intervention provides an objective
8 marker of community transmission, which is not affected by lead time bias. This could also be
9 supplemented by a third ARTI assessment 3-5 years after study completion to assess the durability of
10 the effect, if resources are available.
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20 The PEARL study benefits from extensive collaboration with the Kiribati MHMS, NTP, NLP and other
21 agencies, as well as established partnerships with the PLF, the WHO Western Pacific Regional Office
22 (Manila, Philippines), the office of the WHO Representative in the South Pacific (Suva, Fiji), the United
23 Nations Development Program (UNDP) and the Australian Department of Foreign Affairs and Trade
24 (DFAT) amongst others. In addition, extensive community engagement, communication and
25 mobilisation forms the cornerstone of study implementation. Pacific island countries and territories like
26 Kiribati are in a unique position, given their geographic isolation and limited population size, to 'lead the
27 way' by implementing ambitious elimination strategies that serve as proof-of-principle for others to learn
28 from and replicate.
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40 **CONCLUSION**

41 The PEARL study addresses the need for rigorous implementation science to assess the feasibility and
42 impact of population-wide active case finding and treatment, combined with testing and treatment for
43 TB infection, to durably reduce the TB burden in high incidence settings. The study also explores
44 complementarity between TB and leprosy elimination efforts, with the promise of developing scalable
45 strategies suitable for remote settings with high disease burdens.
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Contact for public and scientific queries

The contact for scientific and public queries is the Principal Investigator, Professor Ben Marais (ben.marais@sydney.edu.au).

Study status

Advanced preparation

Contributors

BJM wrote the initial study proposal. MC and JH contributed equally to this paper. MC, JH, GJF, ET, AT, BE, TI, JMT, STC, AC, GBM, WJB and BJM made important intellectual contributions to the final study protocol. GBM and GJF performed sample size calculations. MC prepared the first draft of the manuscript. The funding agency played no part in any aspect of the study, nor the decision to submit this manuscript for publication.

Competing interests

None declared.

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Table 1. Study inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none">• Everyone aged ≥ 3 years• Children aged < 3 yrs who have had household contact with someone with TB in the past 12 months, or with someone with leprosy since birth	<ul style="list-style-type: none">• Refuse participation

For peer review only

Table 2. TB preventive treatment eligibility and hepatotoxicity risk classification

Assessment	Hepatotoxicity risk category			
	Low	Moderate	Moderate high	High
Definition				
Risk factors <ul style="list-style-type: none"> • Known viral hepatitis • Known HIV infection • Chronic liver disease • Alcohol/kava use* • Age ≥60 years • Test HBV positive** 	No risk factors present	Any risk factor	Any risk factor	Any risk factor
ALT baseline test result (if any risk factors)	Not done	ALT <2x ULN	ALT 2-3x ULN and bilirubin <2xULN	ALT ≥3x ULN (or ALT 2-3x ULN and bilirubin ≥2x ULN)
Management				
Monitoring while on TPT##	No repeat ALT	No repeat ALT	Repeat ALT after 3-4 weeks	Not applicable
Eligibility for TPT	YES	YES	YES	NO
Other reasons for TPT ineligibility	<ul style="list-style-type: none"> • Diagnosed with TB disease • TPT refused • Pregnancy • Allergies to TPT medicines 			

ALT - alanine aminotransferase; HBV - hepatitis B virus; HIV - human immunodeficiency virus; TB – tuberculosis; TPT - TB preventive treatment; ULN - upper limit of normal

*'Excessive use' defined as ≥3 days/week and/or (for alcohol) getting drunk every week

**Everyone ≥40 years with a positive TST who agrees to TPT and is otherwise at low risk is tested with an HBV rapid antigen test

Everyone on TPT receives adherence and adverse event counselling, a TPT passport (supplements S4 and S5), as well as access to community-based treatment monitoring and adherence support

Table 3: Criteria for TB preventive treatment completion

<u>Regimen</u>	Expected duration	Expected total doses	Minimum doses for completion	Maximum time for completion	TPT incomplete
3HP (weekly)	12 weeks	12	11	16 weeks	<8 doses after 12 weeks
3RH (daily)	3 months	84	68	4 months	<40 doses after 3 months
4R (daily)	4 months	120	96	5 months	<68 doses after 4 months

H - isoniazid; P - rifapentine; R - rifampicin; TB - tuberculosis; TPT - TB preventive treatment

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3 **Table 4. Contraindications to single dose rifampicin (SDR)**
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- | |
|---|
| <ul style="list-style-type: none">5 • History of liver or kidney disease6 • Known pregnancy7 • Known allergy to rifampicin8 • Signs and/or symptoms of leprosy9 • Signs and/or symptoms of TB |
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3 **Figure 1. Overview of study enrolment and population-wide TB and leprosy screening**
4 **approach**
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10 HH - household; LTBI - latent TB infection; LPT - leprosy preventive therapy; NTP - Kiribati National TB
11 Control Programme; TB - tuberculosis; TST - tuberculin skin test; TPT - TB preventive treatment; yrs -
12 years; 3HP - 12 once-weekly doses of isoniazid and rifapentine; 3RH - 3 months of daily isoniazid and
13 rifampicin.

14 *Chest X-ray to be performed in everyone ≥ 10 yrs of age and all children < 10 yrs with current symptoms
15 (cough, fever, weight loss/failure to thrive or visible neck nodes).

16 **The TST can be read up to 96 hours (4 days) after placement if the 2-day follow-up is missed.
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3 **Figure 2. Overview of study governance**
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8 PEARL - Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis in the Pacific; NTP
9 - National TB program; NLP - Leprosy program in the NTP; MHMS - Ministry of Health and Medical
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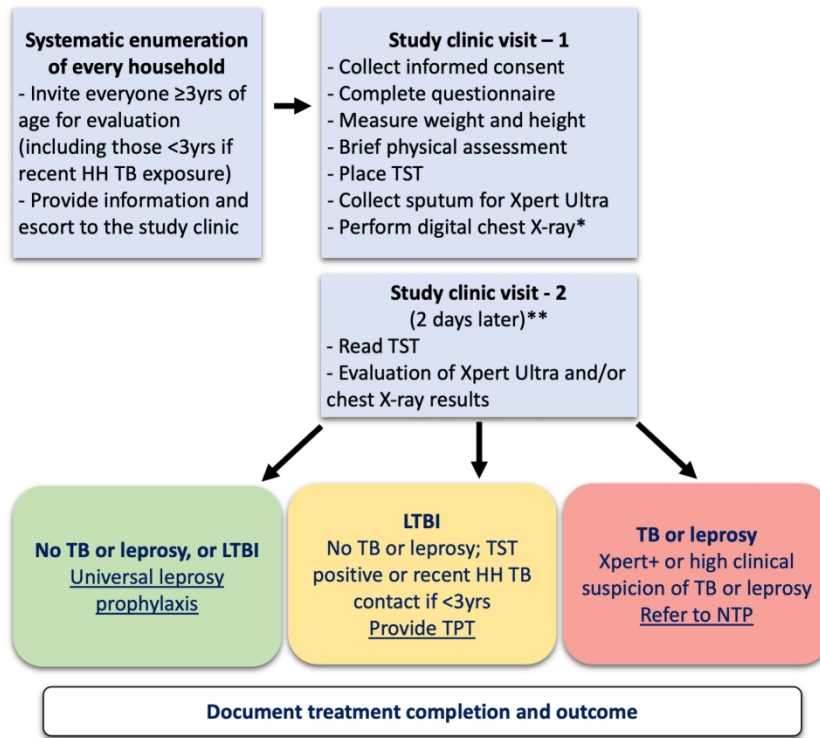


Figure 1. Overview of study enrolment and population-wide TB and leprosy screening approach

HH - household; LTBI - latent TB infection; LPT - leprosy preventive therapy; NTP - Kiribati National TB Control Programme; TB - tuberculosis; TST - tuberculin skin test; TPT - TB preventive treatment; yrs - years; 3HP - 12 once-weekly doses of isoniazid and rifampentine; 3RH - 3 months of daily isoniazid and rifampicin.

*Chest X-ray to be performed in everyone ≥ 10 yrs of age and all children < 10 yrs with current symptoms (cough, fever, weight loss/failure to thrive or visible neck nodes).

**The TST can be read up to 96 hours (4 days) after placement if the 2-day follow-up is missed.

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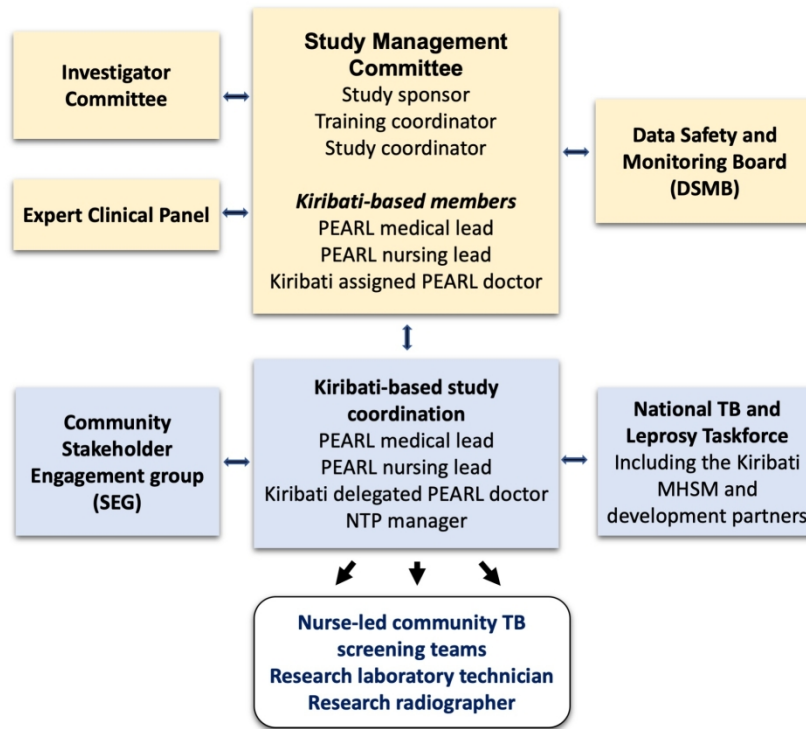


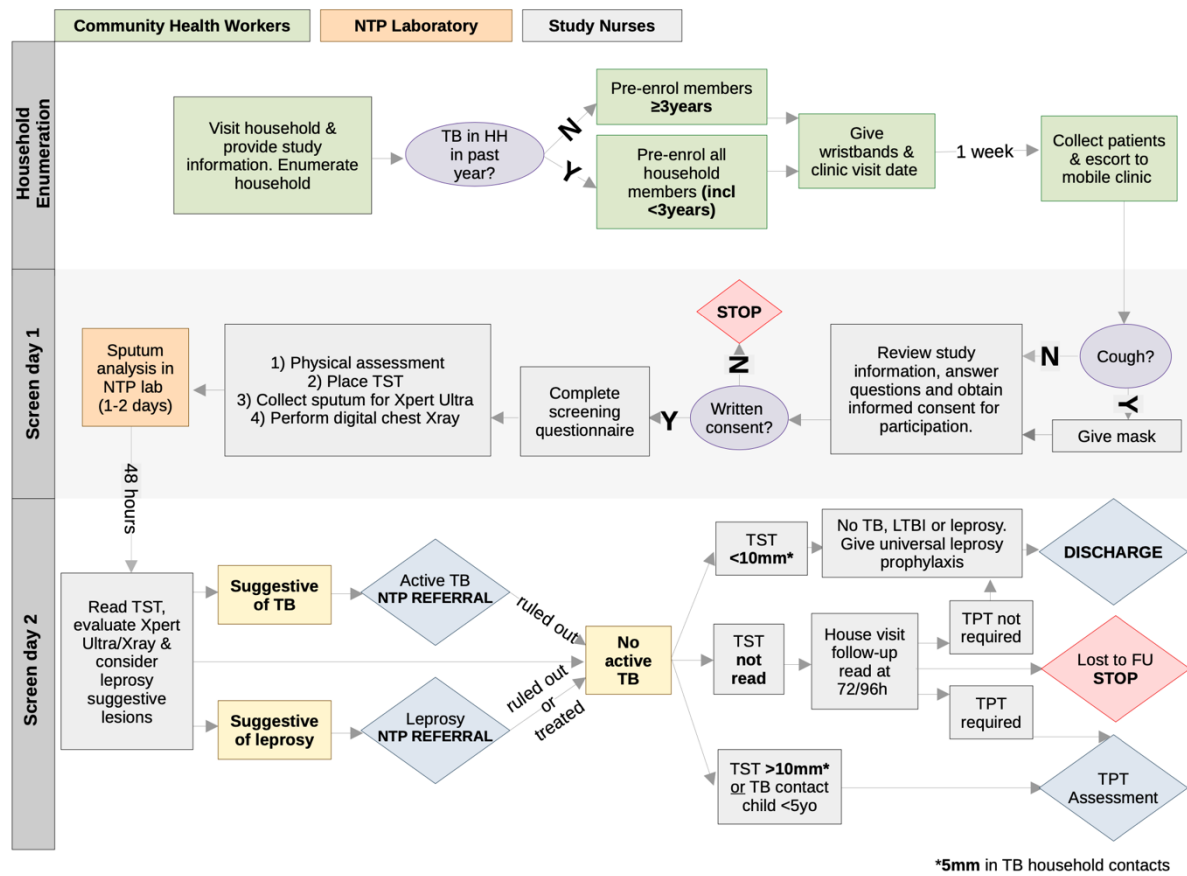
Figure 2. Overview of study governance

PEARL - Pathway to the Elimination of Antibiotic Resistant and Latent tuberculosis in the Pacific; NTP - National TB program; NLP - Leprosy program in the NTP; MHMS - Ministry of Health and Medical Services

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Supplementary Material

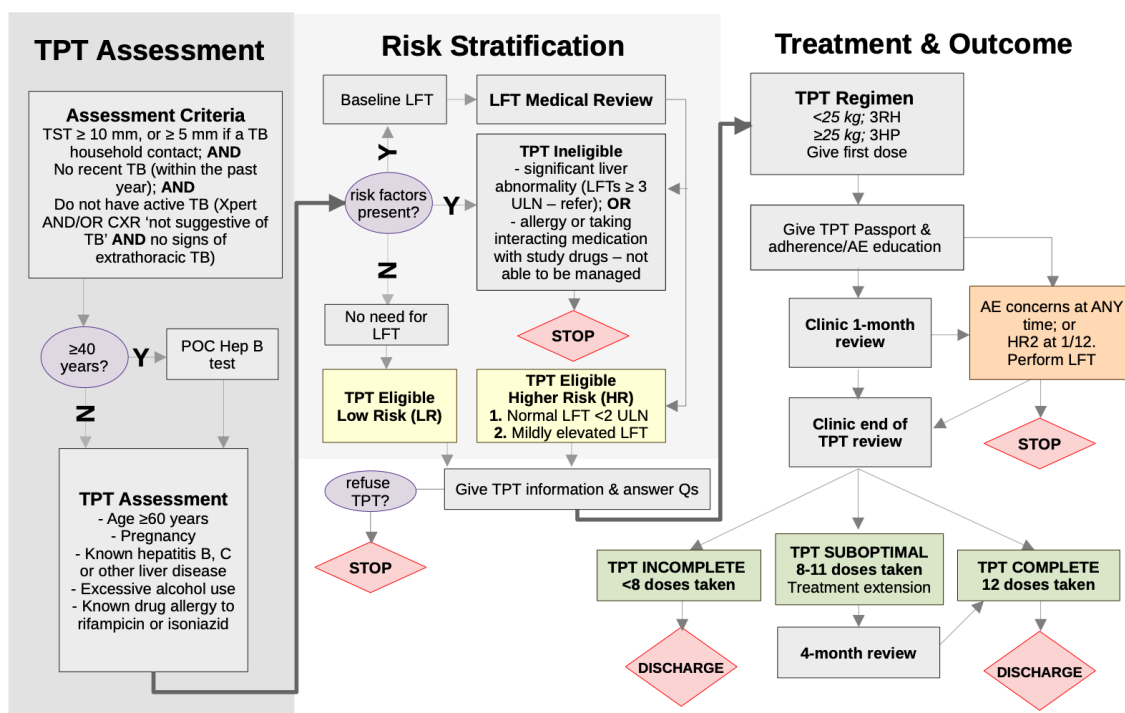
Figure S1. PEARL TB and leprosy screening algorithm



*5mm in TB household contacts

FU – follow-up; HH - household; LTBI - latent TB infection; N - no; NTP - National TB Program; TB - tuberculosis; TPT - TB Preventive Treatment; TST - Tuberculin Skin Test; Y - yes

Figure S2. TB preventive Therapy (TPT) algorithm



3HP - 3-months weekly rifapentine and isoniazid; 3RH - 3-months daily rifampicin and isoniazid; AE - adverse event; CXR - chest X-ray; FU - follow-up; HR2 - higher risk group 2; LFT - liver function test; LTBI - latent TB infection; NTP - National TB Program; POC - point-of-care; TB - Tuberculosis; TPT - TB Preventive Treatment; TST - Tuberculin Skin Test; ULN - upper limit of normal



S3. Participant Information Form

PEARL PARTICIPANT INFORMATION

Finding and preventing TB and leprosy in Tarawa

Dear participant,

We would like to invite you (and your child if relevant) to be evaluated for TB and leprosy, with treatment to be provided as appropriate. This document provides information about the intervention, but we will also explain things in person.

Please read this Participant Information sheet carefully and ask questions about anything that you don't understand or want to know more about. You may refuse participation and this will not be held against you or affect any future access to healthcare.

What is this intervention 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 also spread the germ to others.** This intervention aims to eliminate TB from Tarawa by identifying and treating all people with TB and those with sleeping TB who may become ill in future. At the same time we are also trying to eliminate leprosy, by treating people with leprosy and preventing leprosy in others.

Who is doing this?

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

What will happen?

This study involves screening for TB (both 'sleeping TB' and TB disease) and leprosy. Screening will include looking at your skin, doing a TB skin test, having a chest X-ray and providing a sputum sample. 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 prophylaxis.

People diagnosed with sleeping TB (this is common and is expected in 20-30% of people) will be offered treatment for sleeping TB. Treatment is for three months and is usually safe, but we will have to perform a few checks. A study nurse will ask some personal questions, including questions about previous and current illnesses, medications used, drinking of alcohol or kava, and questions about pregnancy if you are a woman. People between 40-59 years of age will be given a finger prick to test for hepatitis B infection. Those with hepatitis B infection or any other risk factors for TB treatment 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 it take?

We will try to waste as little of your 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. Those diagnosed with sleeping TB will need to take tablets once a week for 12 weeks (or daily for 3 months in children). Tablets will be given out at the mobile health clinic and are free of charge.



Who can take part?

Every person older than 3 years of age living in Tarawa and Betio islet is invited to take part. People younger than 3 years of age who live in a house that shares a kitchen with someone who has had TB or leprosy in the past 12 months are also 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 to help us 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, or the Kiribati Ministry of Health and Medical Services (MHMS).

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 or doctor who will ask you some questions and give you 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?

All tests and treatment are provided free of charge and study clinics will be conveniently situated to be easily accessible.

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 more serious symptoms that mainly affects the liver, which is why we do the additional testing described above. We will explain all of this to you in detail before providing you with any treatment.

What are the benefits?

There are major benefits to yourself and the wider community

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

Is my data safe?

Medical information will be kept in private MHMS medical records or with the PEARL team. Data collected during the intervention will only be shared with the Kiribati MHMS as relevant and will otherwise be kept confidential. The information may be included in reports and publications, but your name and personal information will never be shared.

Where can I get further information about the intervention?

Further information about the study can be found on our website www.thepearlstudy.org or by speaking to any of the study personnel.

Will I be informed about the results?



The results of the study will be reported to the MHMS and shared with the residents of Tarawa by radio announcement and other means, it will also be accessible on the website www.thepearlstudy.org.

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

This research has been reviewed and approved 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)

WE THANK YOU FOR YOUR TIME AND COOPERATION.

The PEARL Research Team with the support of the Kiribati National TB and Leprosy Control Programmes

On behalf of the Kiribati Ministry of Health and Medical Services

.....
Eretii Timeon
Director of Public Health

S4. 3HP TB Preventive Treatment (TPT) Passport

3HP

TPT Passport

Name: _____

Start date: ____/____/____

Dose: 3 tablets 2 tablets

Schedule: *Take once per week on the same day*

Record ID

12 doses to treat sleeping TB

Take your tablets **with water** - never with alcohol

Take your tablets on the **same day** every week

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
week 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4-week visit: ____/____/____							
week 5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8-week visit: ____/____/____							

Treatment Completion Date: _____

Missed a day? Take your tablets as soon as you remember

Store your tablets **out of the sun** and out of reach from children

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
week 9	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 11	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 12	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12-week visit: ____/____/____							
week 13	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 14	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 15	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 16	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16-week visit: ____/____/____							

PEARL staff sign: _____

Stamp

Things to look out for

NORMAL AND HARMLESS

Bright orange urine, sweat or tears

GET HELP IF THIS DOES NOT GO AWAY

headache or sore throat dizzy or light-headed

STOP MEDICINE AND GET HELP

yellowing eyes or skin nausea, vomiting, stomach pain unusual tiredness loss of appetite

How to get help

Contact a CHOW in your community
Call the PEARL helpline - XXX XXX XXX
Visit a screening clinic to see a nurse
If very unwell - go to the hospital

S5. 3RH TB Preventive Treatment (TPT) Passport

3RH

TPT Passport

Name: _____

Start date: ____/____/____

Dose: 3 tablets 2 tablets

Take once per day every day

3 months to treat sleeping TB

Mix tablets **with water** - check they drink every drop!

Give tablets **every day** for 3 months

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
week 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4-week visit: ____/____/____							
week 5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8-week visit: ____/____/____							

Missed a day? Keep giving tablets **every day** until finished

Store tablets **out of the sun** and out of reach from children

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
week 9	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 11	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 12	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12-week visit: ____/____/____							
week 13	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 14	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 15	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
week 16	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16-week visit: ____/____/____							

Things to look out for in kids

NORMAL AND HARMLESS

Bright orange urine, sweat, tears or nappies

GET HELP IF THIS DOES NOT GO AWAY

nausea, vomiting, stomach pain unusual tiredness loss of appetite

STOP MEDICINE AND GET HELP

yellowing eyes or skin face or body rash

How to get help

Contact a CHOW in your community
 Call the PEARL helpline - XXX XXX XXX
 Visit a screening clinic to see a nurse
 If very unwell - go to the hospital

Estimated alpha for effect on TB and leprosy case notifications

For study outcomes measures relating to the case notification rate (CNR) before and after the intervention, the sample size is the entire population of South Tarawa and the outcome is measured programmatically through routine service delivery. The population of South Tarawa is estimated to be 65,566 in 2021 and 71,091 in 2025 (Kiribati NSO, SPC SDD). TB CNR was 0.42% for South Tarawa in 2020 (Kiribati NTP, unpublished, November 2021) and 0.16% for leprosy (Pacific Leprosy Foundation, unpublished, November 2021). Population wide active case finding and prevention interventions for TB have achieved a reduction in case notification rate of approximately 50% in Vietnam and the Republic of the Marshall Islands (Marks et al, NEJM, 2019; RMI MoHHS and USCDC, unpublished, 2021). In Indonesia, impact on case notifications was also approximately 50% among participants in a population wide screening and prevention project (Tiwari et al, BMC ID, 2018). Using a two-tailed z-test to approximate Poisson regression in a large sample and with power of 0.8, the estimated alpha for an anticipated reduction in CNR by 50% is <0.001 for TB and leprosy. The estimated alpha is plotted for a range of effect sizes in Figures S1 and S2, which demonstrates adequacy of the sample/population size. Although the study is sufficiently powered to demonstrate a major short-term reduction in CNR, we will interpret the results with due consideration for the overall goals of achieving a durable public health impact and with careful consideration of the limitations in attribution inherent in a quasi-experimental analysis.

Figure S6. Estimated alpha as a function of post-intervention TB case notification rates (expressed as a proportion of the population), with pre-intervention population of 65,566 and post-intervention population of 71,091; baseline case notification rate of 0.42% (420/100,000 population) and power of 0.8.

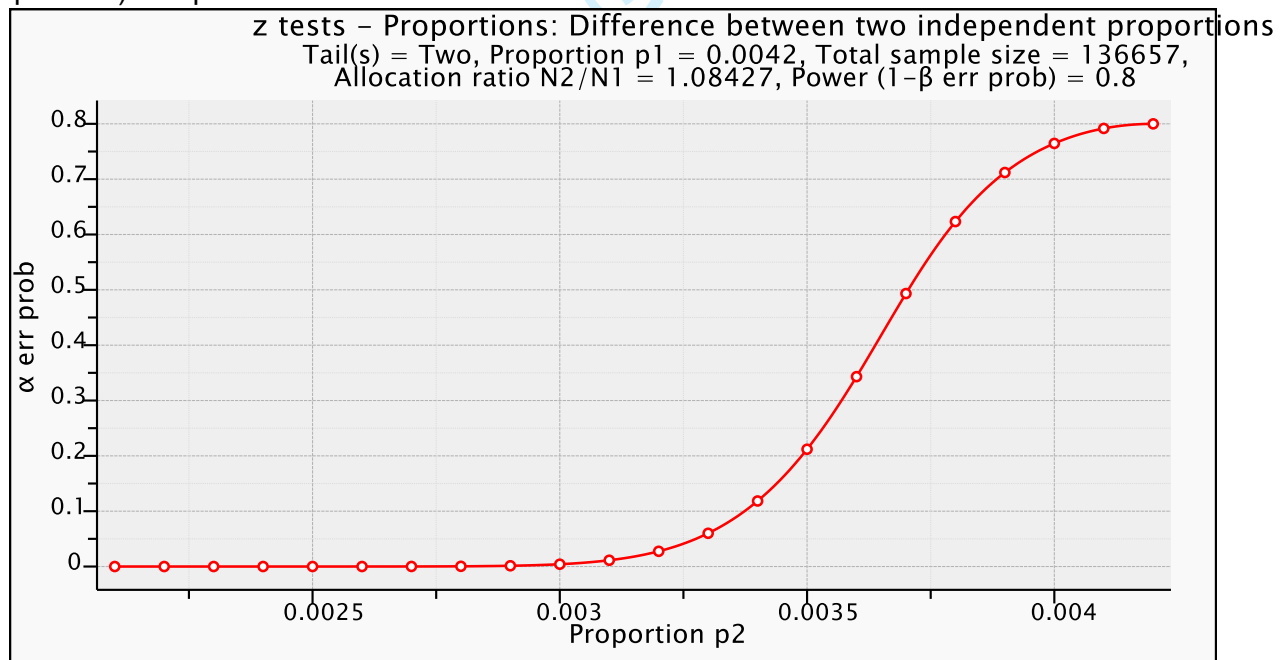
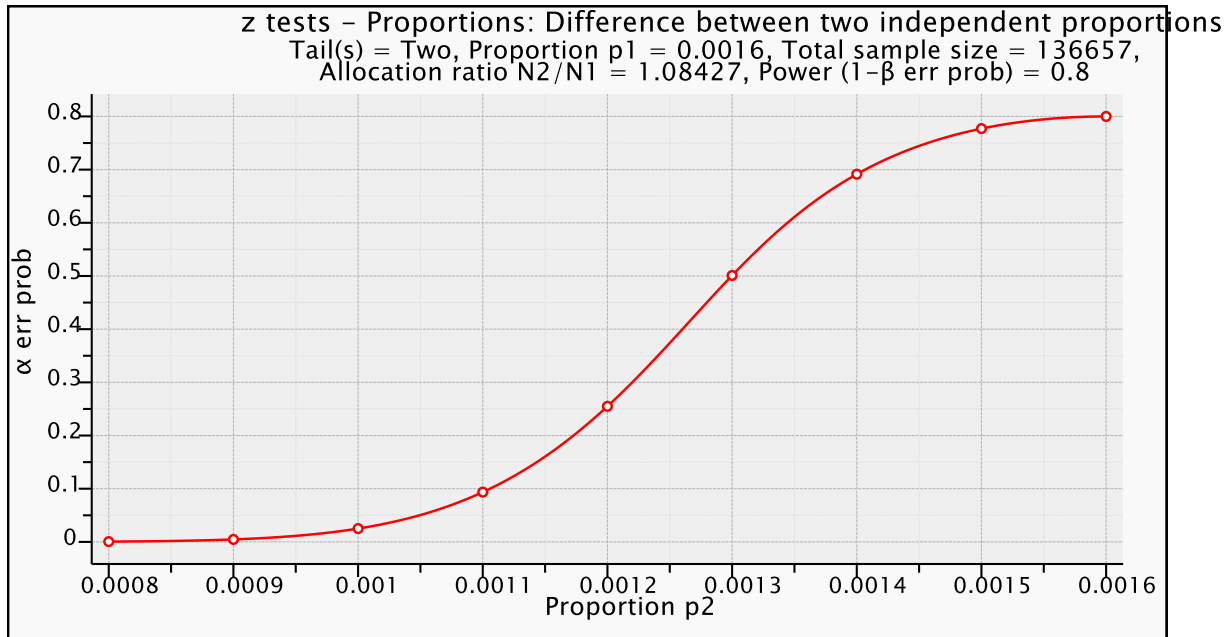



Figure S7. Estimated alpha as a function of post-intervention TB case notification rates (expressed as a proportion of the population), with pre-intervention population of 65,566 and post-intervention population of 71,091; baseline case notification rate of 0.16% (160/100,000 population) and power of 0.8.



S8. Informed Consent Form

INFORMED CONSENT PROCESS FORM

Date of informed consent
/Date of informed consent  Today D-M-Y
** must provide value*

Does the participant have capacity to consent?
** must provide value*

Yes
 No - young person < 18 years of age
 No - disability
 No - other reason

[reset](#)

Name of Consenting Guardian
** must provide value*

Relationship of consenting guardian
** must provide value*

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

[reset](#)

Does the participant assent to participate in the study?
** must provide value*

Yes
 No

[reset](#)

Does the participant/primary caregiver agree to participate in study?
** must provide value*

Yes
 No

[reset](#)

Can participant/caregiver read Kiribati?
** must provide value*

Yes
 No

[reset](#)

Can participant/caregiver read English?
** must provide value*

Yes
 No

[reset](#)

Participant information given and all participant questions answered?
** must provide value*

Yes
 No

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Participant is aware that this is a public health intervention endorsed and supported by the Kiribati Ministry of Health and Medical Services?

*** must provide value**

Yes
 No

[reset](#)

Participant is aware that screen may involve providing sputum or blood samples?


*** must provide value**

1. Yes/ Yes
 0. No/ No

[reset](#)

Date & Time Participant/caregiver signed Written Consent Form

*** must provide value**

 D-M-Y H:M

Sign

*** must provide value**

[Add signature](#)

Other comments

review only



Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati – the PEARL study 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	___20___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1-2; 20___
	5b	Name and contact information for the trial sponsor	___20___
	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	___20___
	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)	___14-17___

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	<u>5-6</u>
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	<u>5-6</u>
7				
8	Objectives	7	Specific objectives or hypotheses	<u>5-6</u>
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<u>6</u>
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	<u>6-7</u>
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	<u>8; table 1</u>
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	<u>8-13</u>
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	<u>11-12; table 2,4</u>
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	<u>10-11</u>
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>11-12</u>
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	<u>13-14</u>
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	<u>table 3; fig 1</u>
39			participants. A schematic diagram is highly recommended (see Figure)	
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1	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	__14, S3-4__
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8; 14__
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

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9				
10	Sequence	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
11	generation			
12				
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15				
16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA population-wide
21				
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23				
24	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
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA open-label
28				
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31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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	__13-17__
34	methods			
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39		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	__10-11__
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1	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	11; 16-17
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5	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	13-14; S3-4
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
9				
10		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)	13-14
11				
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14	Methods: Monitoring			
15				
16	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	16-17; fig 2
17				
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22		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	11-15
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25	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	11-15
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14-17; fig 2
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3; 15
35				
36				
37	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)	3; 15-16
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8; 15
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12; 15
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7	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	15-17
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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13	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	15
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17	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 – Public Health intervention endorsed by the Ministry of Health
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22	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	3; 16
23				
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27		31b	Authorship eligibility guidelines and any intended use of professional writers	20
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29		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA – shared with the Kiribati Ministry of Health
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34	Appendices			
35				
36	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	figs S5-8
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1 2 3 4 5 6	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	NA – subject to separate ethics/studies will be reported separately
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8 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
9 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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For peer review only