

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Population-wide active case finding and prevention for tuberculosis and leprosy elimination in Kiribati – the PEARL study protocol
AUTHORS	Coleman, Mikaela; Hill, Jeremy; Timeon, Eretii; Tonganibeia, Alfred; Eromanga, Baraniko; Islam, Tauhid; Trauer, James; Chambers, Stephen; Christensen, Amanda; Fox, Gregory; Marks, Guy; Britton, Warwick; Marais, B

VERSION 1 – REVIEW

REVIEWER	Luabeya, Angelique University of Cape Town Faculty of Health Sciences, Pathology
REVIEW RETURNED	04-Aug-2021

GENERAL COMMENTS	<p>This is a well written protocol, with clear objectives, description of the study setting and population. It address an important problem of reduction of TB and Leprosy incidence in a geographical defined and isolated population. The methodology is adequate and straightforward.</p> <p>Minor comments:</p> <ol style="list-style-type: none">1. Adherence to TPT will be key to the success of this intervention. It is not clear how this aspect will be measured in the population(Line 30).2.It might be useful to include HIV testing in the screening process, even if the prevalence is low in the population (Line 46).3.There has been no mention of the impact of COVID 19 pandemic in this region. Is it relevant in this setting? if yes, will it affect screening procedures and will people be tested for SARS COV-2?4. Will COVID 19 preventing measures such as wearing a mask and maintaining physical distancing affect TB transmission in this community?
-------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

REVIEWER	Mieras, Liesbeth NLR, Medical Technical
REVIEW RETURNED	29-Aug-2021

GENERAL COMMENTS	<p>This is an interesting study that will provide new and useful insights in combined mass screening programmes.</p> <p>In the final sentences of the introduction: "The aim of the proposed study is to achieve major reductions in TB and leprosy incidence and transmission in Tarawa, providing a pathway to future elimination." - the duration of the study is probably too short to see an impact on leprosy incidence. The active case finding component of the study will first lead to an increase of the number of new leprosy patients identified. At best a decrease is expected to be seen in the third year and onwards (see final LPEP results - Lancet). The time path and</p>
-------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

	<p>duration of the study are anyway not very clearly mentioned in the manuscript, though I understand the duration to be three years on the basis of the years mentioned in the primary outcome measures paragraph. Will there be repetitive mass screenings + MDA or will it be just once? Will there be routine contact screening for new TB/leprosy patient after the mass intervention?</p> <p>The adverse events listed are not all adverse events (negative effects of drugs), some are unwanted aspects of the intervention.</p> <p>There are additional exclusion criteria for SDR-PEP - see Leprosy/Hansen disease: Contact tracing and post-exposure prophylaxis, WHO Technical guidance - that are not mentioned in the document, but should be added: Persons with a history of liver or kidney disorders; Pregnancy; SDR can be given after the delivery.</p> <p>Detailed spatial analysis is one of the secondary outcomes, but mapping is not described as part of the methodology.</p> <p>The 'selfie' component may be more clearly addressed in the 'ethics and dissemination' section.</p> <p>Regarding the sample size calculation: this is purely based on TB data. How does this sample size relate to the leprosy component of the study?</p> <p>NB: abbreviations used are not systematically written in full when they are first used in the manuscript (eg: LTBI, ARTI, M (Mycobacterium) etc.)</p>
--	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This is a well written protocol, with clear objectives, description of the study setting and population. It addresses an important problem of reduction of TB and Leprosy incidence in a geographical defined and isolated population. The methodology is adequate and straightforward.

Thank you

1. Adherence to TPT will be key to the success of this intervention. It is not clear how this aspect will be measured in the population (Line 30).

Encouraging optimal TPT adherence is a major study challenge, but this will be done with various forms of individual and community support. TPT adherence will be recorded in the 'TPT passport' and this will be the source document for assessing TPT adherence. TPT adherence (number of doses taken, as marked on TPT passport and verified by pill count) will be assessed and recorded at the final study visit. Every effort will be made to capture this outcome and it should be feasible in most participants, given the small and close-knit communities within which we will be working.

The text has been revised to clarify this on pages 10-11: "Medicines are dispensed at 4-8 week intervals, or according to patient preference and adherence. All participants who commence TPT are visited once after 3-4 weeks to support adherence and screen for adverse events, and again when they near TPT completion to assess treatment adherence and either extend treatment or assign a

treatment outcome. Additional supportive visits are scheduled as needed. Assessment of adherence is performed and recorded at each visit by interviewing the participant, reviewing the TPT passport and counting remaining pills. Treatment completion is determined according to WHO recommendations (Table 3)”

2. It might be useful to include HIV testing in the screening process, even if the prevalence is low in the population (Line 46).

Unlike sub-Saharan Africa, HIV infection rates in the Pacific are extremely low. Local guidelines are that all TB cases should be tested for HIV and no cases of TB/HIV co-infection have been detected in the past 2 years. HIV testing will be offered by the National TB Program (NTP) to all patients diagnosed with TB, in accordance with local guidance. However, we do not believe it is justified or feasible to offer this to all study participants. All patients with signs or symptoms suggestive of possible HIV infection will be referred for appropriate medical care.

3. There has been no mention of the impact of COVID 19 pandemic in this region. Is it relevant in this setting? If yes, will it affect screening procedures and will people be tested for SARS COV-2?

We have clarified the COVID-19 situation and PEARL study commitments in the revised text. Bottom of page 6: “

As of November 2021, no confirmed cases of COVID-19 have been recorded in Kiribati, and no mask-wearing or social distancing measures have been employed. However, these practices have been part of the protocols in place as preparatory and response interventions for COVID-19 should the pandemic spread to Kiribati. A COVID-19 vaccination programme commenced in May 2021, which is on track to achieve full vaccination coverage of >90% of the adult population by early 2022. Future application of public health measures to control the spread of COVID-19 will be determined by the Ministry of Health and Medical Services (MHMS) based on ongoing assessment of the risk posed to health and health systems in Kiribati and according to the National COVID-19 preparatory and response plan and the Standard Operations Procedures (SOPs) in place.” The PEARL study will comply with all public health measures.

4. Will COVID 19 preventing measures such as wearing a mask and maintaining physical distancing affect TB transmission in this community?

Please see comments above – no physical distancing or mask wearing has been implemented to date. If these recommendations are implemented in the future, this would be a potential confounder, but we believe it is unlikely and something that we will account for in the final analysis.

Of note, the epidemiology of TB is markedly different to COVID-19 such that it is difficult to gauge the overall effect of COVID-19 control measures upon TB. Emerging evidence suggests that COVID-19-related lung damage increases vulnerability to TB in addition to disrupting TB health services (McQuaid et al 2021). The StopTB partnership have reported that 12 months of COVID-19 has eliminated 12 years of progress in the global fight against TB. For these reasons, we believe that the potential short-term reduction in TB transmission due to COVID-19 physical distancing and mask-wearing measures is unlikely to have a major impact on study outcomes, if the pandemic were it to reach Kiribati.

Reviewer 2

This is an interesting study that will provide new and useful insights in combined mass screening

programmes.

Thank you

1. In the final sentences of the introduction: "The aim of the proposed study is to achieve major reductions in TB and leprosy incidence and transmission in Tarawa, providing a pathway to future elimination." - the duration of the study is probably too short to see an impact on leprosy incidence. The active case finding component of the study will first lead to an increase of the number of new leprosy patients identified. At best a decrease is expected to be seen in the third year and onwards (see final LPEP results - Lancet).

We agree that case numbers will increase with active case finding during the intervention, but we expect that there will be a rapid decline in incidence once all community members have been screened and referred for treatment or provided with prophylaxis. A large proportion of participants (20-30% of the population) will receive TB preventive treatment, which includes 3 months of rifamycin treatment. This is likely to have a stronger effect than SDR alone on leprosy prevention and the treatment of incipient or sub-clinical disease. To ensure that we capture the full effect of the intervention, we will continue to monitor programmatic notifications of leprosy incidence in the five years following the intervention. This is part of an established leprosy support programme, which is overseen by our partner, the Pacific Leprosy Foundation (PLF). PLF have worked in Kiribati for 20 years and will continue engagement until leprosy eradication is achieved.

2. The time path and duration of the study are anyway not very clearly mentioned in the manuscript, though I understand the duration to be three years on the basis of the years mentioned in the primary outcome measures paragraph. Will there be repetitive mass screenings + MDA or will it be just once?

The expected study duration is 4 years. The intervention will be completed over 2 to 3 years, depending on the rate of 'scale up' possible in light of potential future restrictions to community engagement relating to COVID-19. The whole population will be screened and MDA/TPT provided once only. However, leprosy PEP and TB preventive treatment will be made available to all eligible contacts on an ongoing basis, as part of programme strengthening efforts that will persist beyond the end of the study.

3. Will there be routine contact screening for new TB/leprosy patients after the mass intervention?

Yes, there will. As stated above, TB contact investigation will be part of local capacity building and programme strengthening efforts. Leprosy contact screening has been in place since 2012 due to strong support from study partners at the PLF.

4. The adverse events listed are not all adverse events (negative effects of drugs), some are unwanted aspects of the intervention.

We have nominated adverse events based on the definition provided by the Australian National Health and Medical Research Council: "Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment". Adverse events attributable to the study drugs will be distinguished from other adverse events. We have clarified this distinction in the text (page 11) by separating the adverse events listed into drug-related and other adverse events.

5. There are additional exclusion criteria for SDR-PEP - see Leprosy/Hansen disease: Contact tracing and post-exposure prophylaxis, WHO Technical guidance - that are not mentioned in the document, but should be added: Persons with a history of liver or kidney disorders; Pregnancy; SDR can be

given after the delivery.

Participants with a history of liver or kidney disorders, as well as pregnant women, will be excluded. We have clarified this in the text and added a table for contraindications to SDR (table 4). Pregnant women may be offered either TPT or SDR 3 months after delivery.

6. Detailed spatial analysis is one of the secondary outcomes, but mapping is not described as part of the methodology.

We will be collecting GPS coordinates for all households and also have access to GIS data from the most recent (2020) national census. The text has been adjusted to describe methods for spatial data capture and access on page 10. Additional detail describing spatial analysis outcomes have been added to the list of secondary outcomes on page 16. We hope this explains the intended methodology for mapping and analysis more clearly and at a level of detail that is consistent with the other outcomes. Author JH has training and experience in spatial analysis, and we are working with regional organisations Beyond Essentials and the Pacific Community who have considerable expertise in mapping of Pacific populations and health services, including in Kiribati.

7. The 'selfie' component may be more clearly addressed in the 'ethics and dissemination' section.

A more expansive consideration of the 'health selfie' has been included in the Ethical issues section of the manuscript on page 15. In brief, the use of secure facial recognition software for biometric identification in this study was developed in partnership with the Kiribati Ministry of Health. Kiribati colleagues indicated that this would be acceptable, as long as participant privacy is protected. The system developed by Simprints (Cambridge, UK) is specifically designed for health application in remote settings, with privacy as a primary concern. In this study, biometric identifiers are captured in a standalone mobile application and stored in a secure database maintained by the biometric identification provider which is siloed from biographical data in the study database and inaccessible to users. Records in the two databases are linked by a unique, randomly generated identifier. When study staff use biometric identification to retrieve a participant record, the linking identifier is accessed by the biometric identification application without further input by the user. Participants are free to refuse or withdraw consent to record the biometric identifier, while still participating in the study. Participants are expressly invited to withdraw consent to share biometric identification data with the Kiribati MHMS at the time of capture.

8. Regarding the sample size calculation: this is based on TB data. How does this sample size relate to the leprosy component of the study?

For the TB and leprosy case notification rate outcomes which are assessed programmatically, the sample size is the whole population of South Tarawa and so the sample size for this leprosy outcome is not calculated. However, we have added additional analysis of the estimated alpha at different effect sizes in supplementary material to demonstrate the efficacy of the sample size. Furthermore, leprosy outcomes are secondary outcomes of the study. The sample size calculation on page 14 relates specifically to the annual risk of TB infection, which is a primary outcome and an objective marker of TB community transmission.

9. NB: abbreviations used are not systematically written in full when they are first used in the manuscript (eg: LTBI, ARTI, M (Mycobacterium) etc.)

Sorry for this oversight – checked and corrected.

Thank you once again for the helpful feedback received. We have also made minor changes to enhance the clarity and readability of the manuscript and to reflect more up-to-date information. This includes updated population numbers from the latest 2020 census, changes to digital X-ray review age cut-offs in alignment with recent WHO guidelines and a revised abstract to reflect these edits. More substantial changes (all marked) involve inclusion of the transmission outcome for TB (annual risk of TB infection calculation) as a co-primary outcome and an expanded discussion around lead time bias.

Please indicate if any additional information or clarification is required.

VERSION 2 – REVIEW

REVIEWER	Mieras, Liesbeth NLR, Medical Technical
REVIEW RETURNED	17-Dec-2021
GENERAL COMMENTS	Good luck with the study - looking forward to the results.