PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effectiveness of population-wide screening and mass drug administration for leprosy control in Kiribati: The COMBINE protocol
AUTHORS	Coleman, Mikaela; Hill, Jeremy; Timeon, Eretii; Rimon, Erei; Bauro, Temea; Ioteba, Nabura; Cunanan, Arturo; Douglas, Nicholas M; Islam, Tauhid; Tomlinson, Jill; Campbell, Patrick O; Williman, Jonathan; Priest, Patricia; Marais, B; Britton, Warwick; Chambers, Stephen

VERSION 1 – REVIEW

REVIEWER	liu, dianchang Shandong Provincial Hospital for Skin Diseases & Shandong Provincial Institute of Dermatology and Venereology, Shandong First Medical University & Shandong Academy of Medical Sciences
REVIEW RETURNED	11-Sep-2022

GENERAL COMMENTS	1. Before MDA, is it better to give testing of liver and kidney function of participants? 2. How to deal with the side effects of MDA? are people with side effects treated freely or can get any compensation? 3. In limitition part, it is better to mention that the outcome or conclusion of this study can be used in areas with high prevalence of leprosy.

REVIEWER	Saunderson, Paul American Leprosy Missions
REVIEW RETURNED	26-Sep-2022

GENERAL COMMENTS	This is a clear and concise protocol. The authors note in the Discussion (p22 of 44) that previous attempts at MDA in similar island settings in the 1990s ultimately failed, at least in part due to the absence of serious follow-up activities, as far as I understand it. I would like to suggest more specific planning for long-term surveillance and follow-up in Kiribati, after the defined study period. It is stated on p 18 of 44 that PLF is committed to doing this, but few details are given. I suggest two areas that could be planned more specifically - and there may be others. Firstly, while some aspects of data management may not be needed after the study period, it would be very valuable if the research team left in place a well-planned data management program for MHMS and PLF to take over. This is very likely intended, but it would be worth making it a specific objective. I have seen many examples of data management collapsing after the end of a well-funded research study. One issue, for example, is the statement that data will be stored at the University of Sydney, so where will data be stored

	subsequently? The second area that could be more specifically planned for is funding - it could be an objective that funding would be sought for a further 5 years of surveillance, run by MHMS and PLF, after the end of this project. This could perhaps enable engagement by some of the current team in planning future follow-up activities. A minor comment about the statement on p20 of 44 that "Ethics for the COMBINE study has been obtained....." 'Ethical approval....' sounds better.

REVIEWER	Barreto, Ikaro Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada
REVIEW RETURNED	05-Oct-2022

GENERAL COMMENTS	I'd like to commend you on your efforts in conducting a methodological paper. However, I would like the authors to better describe the hypothesis tests, models, assumptions, effect sizes, software, significance level, and all the details of the statistical analysis because, despite the fact that the authors indicated that it was described on pages 16-18, I was unable to identify any of these details that are important to determining whether the results will be robust and reliable, as they are related to SPIRIT topics 20a and 20b.

REVIEWER	Vamsi , DKK Sri Sathya Sai Institute of Higher Learning, DMACS
REVIEW RETURNED	06-Oct-2022

GENERAL COMMENTS	In my opinion, the COMBINE protocol designed for leprosy control in Kiribati is an innovative study design. This protocol, when implemented effectively, can give important insights about the spread of the disease and its effective control strategies. This protocol is designed more for a practical use as it is a combination of screening and MDA intervention. Also the strengths and limitations of this protocol are clearly discussed in this paper. I have two comments regarding this work. 1. Any protocol paper must contain details of planned and ongoing studies along with dates. In my understanding of this paper, all the study designs are ongoing and none of them are planned. I request authors to include a table containing a summary of ongoing studies along with the dates (of a 3 years timeline, as mentioned in the paper). 2. This protocol allows participants to withdraw in the middle of the study. Since the objective of the current protocol is only to calculate and compare the annual NCDR, these withdrawals might not make a significant difference in the results. As other planned analyses will also include mathematical modeling with “real data", these withdrawals will lead to many null values in the data. Request authors to comment on these withdrawals.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. Before MDA, is it better to give testing of liver and kidney function of participants? How to deal with the side effects of MDA? Are people with side effects treated freely or can get any compensation?

Thank you for this important question. In Table 2 we include the criteria for single-dose rifampicin eligibility, which includes exclusion if there is a history of serious liver or kidney disease. Individuals who are at risk of liver abnormality during TB preventive treatment (TPT) are evaluated for liver function prior to treatment commencement, but not for single dose rifampicin (SDR; for further TPT details, please see the PEARL study protocol, Coleman, Hill et al 2022, BMJ Open). The reasons for this are highlighted in the ETHICS AND DISSEMINATION section of the text as follows:

“SDR is very safe and has been used in Kiribati and elsewhere with little or no recorded side-effects. A study hotline and walk-in clinic will be freely available for adverse event (AE) management throughout the study period…. SDR for PEP and MDA will be provided without baseline blood tests, consistent with the standard of care in Kiribati.”

2. In limitation part, it is better to mention that the outcome or conclusion of this study can be used in areas with high prevalence of leprosy.

Thank you for this guidance. As suggested, we have amended bullet 3 to read:

• “Dovetailing leprosy and tuberculosis elimination activities has the potential to maximise efficiency and impact, especially in settings with a high-incidence of both diseases”

Reviewer 2

1. This is a clear and concise protocol.

Thank you for these positive comments.

2. The authors note in the Discussion (p22 of 44) that previous attempts at MDA in similar island settings in the 1990s ultimately failed, at least in part due to the absence of serious follow-up activities, as far as I understand it. I would like to suggest more specific planning for long-term surveillance and follow-up in Kiribati, after the defined study period. It is stated on p 18 of 44 that PLF is committed to doing this, but few details are given. I suggest two areas that could be planned more specifically - and there may be others.

Firstly, while some aspects of data management may not be needed after the study period, it would be very valuable if the research team left in place a well-planned data management program for MHMS and PLF to take over. This is very likely intended, but it would be worth making it a specific objective. I have seen many examples of data management collapsing after the end of a well-funded research study. One issue, for example, is the statement that data will be stored at the University of Sydney, so where will data be stored subsequently?

Thank you for this insightful feedback. We have amended the ‘Data collection and monitoring’ section of the manuscript to include greater detail about how the data are managed in the study. In particular, we emphasize that:

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

over to the NLP after study completion."

3. The second area that could be more specifically planned for is funding - it could be an objective that funding would be sought for a further 5 years of surveillance, run by MHMS and PLF, after the end of this project. This could perhaps enable engagement by some of the current team in planning future follow-up activities.

This is an excellent recommendation which we have incorporated under a new section in the manuscript entitled 'Post-study follow-up activities'. This section reads:

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

4. A minor comment about the statement on p20 of 44 that "Ethics for the COMBINE study has been obtained....." 'Ethical approval....' sounds better.

Thank you – we agree with this comment and have made the changes suggested.

Reviewer 3

1. I'd like to commend you on your efforts in conducting a methodological paper.

Thank you for your commendation.

2. However, I would like the authors to better describe the hypothesis tests, models, assumptions, effect sizes, software, significance level, and all the details of the statistical analysis because, despite the fact that the authors indicated that it was described on pages 16-18, I was unable to identify any of these details that are important to determining whether the results will be robust and reliable, as they are related to SPIRIT topics 20a and 20b.

Thank you for pointing out the areas in which our manuscript may differ from the SPIRIT checklist. We have included a SPIRIT checklist with the manuscript because this was the closest checklist available for a population-wide intervention. However, the COMBINE study is a pragmatic implementation study, not a clinical trial for which the SPIRIT checklist is designed. Thus, not all elements of the checklist are applicable to the COMBINE study design, but we have endeavoured to provide as much information requested by the SPIRIT checklist as is possible, with some unavoidable differences in available/relevant information.

Requested details that we have included under the 'Sample Size' section of the manuscript include information on assumptions and significance information. The epidemiological measures of effect are bulleted under the 'Outcome Measures and Planned Analyses' section.

Reviewer 4

1. In my opinion, the COMBINE protocol designed for leprosy control in Kiribati is an innovative study

design. This protocol, when implemented effectively, can give important insights about the spread of the disease and its effective control strategies. This protocol is designed more for a practical use as it is a combination of screening and MDA intervention. Also the strengths and limitations of this protocol are clearly discussed in this paper. I have two comments regarding this work.

We thank the reviewer for this detailed positive feedback and for the support for the pragmatic design of this study.

2. Any protocol paper must contain details of planned and ongoing studies along with dates. In my understanding of this paper, all the study designs are ongoing and none of them are planned. I request authors to include a table containing a summary of ongoing studies along with the dates (of a 3 years timeline, as mentioned in the paper).

Thank you for this requested clarification which identifies a gap in the manuscript. We have included a timeline overview in the supplementary data to address this need, as below.

Supplementary Figure 1. Timeline of COMBINE study activities
Formal COMBINE activities commenced in July 2022 and should conclude in June 2026, with data analysis and dissemination of outcomes included in this period. Left-facing arrow indicates activity which began prior to the COMBINE study. Right-facing arrows indicate activities which will continue beyond the end of the COMBINE study through NLP and PLF activities. NLP – National leprosy program; NTP – National tuberculosis program; PEP – post-exposure prophylaxis; SDR – single-dose rifampicin; TPT – tuberculosis preventive treatment. *TB and leprosy disease also excluded

3. This protocol allows participants to withdraw in the middle of the study. Since the objective of the current protocol is only to calculate and compare the annual NCDR, these withdrawals might not make a significant difference in the results. As other planned analyses will also include mathematical modelling with “real data", these withdrawals will lead to many null values in the data. Request authors to comment on these withdrawals.

Thank you for highlighting this critical issue. Before enrolment in the COMBINE study, potentially eligible participants will be invited to attend screening locations and will provide consent prior to confirmation of diagnosis. People with leprosy who do not consent to participate in screening, or who withdraw prior to seeing the NLP, may not have their diagnosis confirmed and will not be counted as a new case. This would potentially lower the NCDR. However, leprosy is a notifiable disease in Kiribati and as such, once a case is diagnosed he/she will be included in the NCDR, even if he/she withdraws or has previously withdrawn consent to having their data collected as part of the study. As such the annual NCDR results should be minimally affected by study withdrawals.
We also propose to perform mathematical modelling which will use simulated data of fictitious individuals within a closed population, where the model parameters and assumptions will be informed by the ‘real life’ data collected as part of this project. The withdrawal of participants from receiving treatment, or from having their outcome data collected, may slightly reduce the precision by which these parameters are estimated, but will not otherwise negatively impact on the mathematical modelling.

VERSION 2 – REVIEW

REVIEWER	Saunderson, Paul American Leprosy Missions
REVIEW RETURNED	01-Mar-2023

GENERAL COMMENTS	The paper is now an excellent article. I have only one further comment, which is about child cases of leprosy. You present the child case rate as the percentage of children amongst all cases, which is a traditional indicator, but no longer fit for purpose. It is reasonable when the number of cases is large, but when the denominator (the total number of cases) becomes small, the child rate starts to become unstable and fluctuates markedly. Most programs (and even WHO) now report the new case detection rate amongst children (the number of new cases in children, per million children), which is then totally independent of the number of adult cases. An additional refinement which may prove useful in future is to document child cases in narrower age bands, such as 0-4, 5-9, 10-14, etc. This is now easy to do as your database can probably cope with documenting the actual age of each child. We expect to see a decline in cases in the youngest group first as transmission is reduced.

REVIEWER	Barreto, Ikaro Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada
REVIEW RETURNED	27-Feb-2023

GENERAL COMMENTS	No more corrections for me.

REVIEWER	Vamsi , DKK Sri Sathya Sai Institute of Higher Learning, DMACS
REVIEW RETURNED	07-Mar-2023

GENERAL COMMENTS	No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 5 – April 2023

1. You present the child case rate as the percentage of children amongst all cases, which is a traditional indicator, but no longer fit for purpose. It is reasonable when the number of cases is large, but when the denominator (the total number of cases) becomes small, the child rate starts to become unstable and fluctuates markedly. Most programs (and even WHO) now report the new case detection rate amongst children (the number of new cases in children, per million children), which is then totally independent of the number of adult cases.

Thank you for this insightful recommendation. We agree that reporting new case detection rate amongst children will add significant value to our study and have updated the manuscript and our procedures to incorporate this reporting. Our amended primary outcomes now read:

“The primary research question of interest is the extent to which the intervention reduces leprosy annual adult & child NCDR compared with standard routine passive case-finding and post-exposure prophylaxis of close contacts. This will be assessed 1) by comparing the post-intervention NCDRs in South Tarawa (in 2025) with the pre-intervention NCDRs (in 2021) and 2) by comparing the change in adult & child NCDRs in South Tarawa (the intervention site) with the change in NCDRs observed in the outer Kiribati islands (non-intervention sites).”

2. An additional refinement which may prove useful in future is to document child cases in narrower age bands, such as 0-4, 5-9, 10-14, etc. This is now easy to do as your database can probably cope with documenting the actual age of each child. We expect to see a decline in cases in the youngest group first as transmission is reduced.

We are very grateful for this advice, and see that this will significantly improve our capacity to measure effect/impact of the intervention. We have included a note in the 'other planned analysis' section specifying this change:

"Diagnostic yield of leprosy screening using an optimised clinical examination and brief history in the setting of a community-based multi-disease screening intervention. Examinations of yield amongst discrete age bands in children (0-4, 5-9,10-14 years) will also indicate effect of the intervention on transmission over time."