Title: Reducing contamination risk in cluster-randomised infectious disease intervention trials

Submitted to: International Journal of Epidemiology

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Abstract

Background: Infectious disease interventions are increasingly tested using cluster-randomised trials. These trial settings tend to involve a set of sampling units, such as villages, whose geographic arrangement may present a contamination risk in treatment exposure. The most widely used approach for reducing contamination in these settings is the so-called fried-egg design, which excludes the outer portion of all available clusters from the primary trial analysis. However, the fried-egg design ignores potential intracluster spatial heterogeneity and makes the outcome measure inherently less precise. While the fried-egg design may be appropriate in specific settings, alternative methods to optimise the design of cluster-randomised trials in other settings are lacking.

Methods: We present a novel approach for cluster-randomised trial design that either fully includes or fully excludes available clusters in a defined study region. The approach includes an algorithm that allows investigators to maximise the number of clusters to be included and maintain randomness in both the selection of included clusters and the allocation of clusters to either the treatment group or control group. The approach was applied to the design of a cluster-randomised trial testing the effectiveness of malaria vector control interventions in southern Malawi.

Conclusions: By identifying potential randomisation design options that meet pre-defined contamination risk criteria, this approach recognises the potential for intracluster spatial heterogeneity while maximising the number of clusters that can be included. By maintaining randomness in the allocation of clusters to either the treatment group or control group the approach also permits a randomisation-valid test of the primary trial hypothesis.

Keywords

Cluster-randomised trial; contamination; study design; randomisation; statistical precision; spatial heterogeneity

Key Messages

- The potential for treatment effect contamination in cluster-randomised trials is widely recognised, and we present a new approach for reducing risk of contamination among clusters via trial design.
- Our approach fully includes or fully excludes available clusters in a defined study region, thereby allowing both the treatment and measurement of the intervention across the entirety of included clusters.
- We present an algorithm, based on the mathematical field of graphs, that allows investigators to maximise the number of clusters to be included.
- The approach is applicable to cluster-randomised trials investigating a wide range of infectious disease interventions, including vaccines, drugs, vector control, and behaviour change communication.

Glossary

Buffer zone: in the fried-egg design, an area of the CRT cluster, the width of the contamination distance, where the households are excluded from the analysis of primary CRT outcome

Cluster: sampling unit in a CRT

Cluster-group: either a single cluster with no connections to another cluster in the CRT, or a group of two or more clusters in the CRT with connections to each other

Connection: any two clusters that are within the contamination distance of each other

Contamination distance: minimum distance that should separate clusters allocated to different trial treatment arms

Randomisation design options: alternative sets of clusters to be included in the CRT

Background

Cluster-randomised trials are increasingly used as defining phase III trials for infectious disease interventions for a number of reasons, but especially when a population-level effect is the primary endpoint of interest.[1] Population-level effects occur when an intervention alters the transmission dynamics of the target disease, and many infectious disease interventions benefit from this mechanism to show a clear effect.[2,3] Contamination is a concern for both the study design and statistical analysis.

Contamination refers to a violation of the basic assumption that one group is exposed to the effects of the intervention (i.e. the treatment group), while another is not (i.e. the control group).[4] In a CRT, the risk of contamination of treatment effects between units of randomisation depends on the spatial arrangement of the disease system components (e.g. hosts, pathogen, reservoir, vector). If a susceptible host does not overlap in space with the pathogen, the host cannot become infected. This necessary contact between the pathogen and host is often facilitated by the movement of one or more components of the disease system (e.g. human movement, vector dispersal, or pathogen movement in water). The

extent of this movement then defines a space within which a susceptible host is more likely to become infected, and a threshold distance beyond which infection of a susceptible host can be considered unlikely. This space, or focus, would probably be more accurately described as a gradient, as opposed to a discrete unit. Similarly, multiple, overlapping foci of disease transmission are probably the rule rather than the exception.

In practice, investigators must define the unit of randomisation based on considerations of pathogen transmission, social restrictions or implications, and logistics. To reduce the risk of contamination between clusters, the investigators may also define a minimum distance that should separate clusters allocated to different trial treatment arms, hereafter referred to as the contamination distance. The geographic arrangements of human settlements do not always allow for neatly separated clusters. In many cases, potential clusters may instead be either directly bordering each other or separated by less than the contamination distance. In these cases, it is critical for the investigators to consider methods of reducing contamination risk during the design phase of the trial.

Currently, there are few options available for reducing contamination in CRTs. Many CRTs for infectious disease interventions, especially in the 1990s, did not specify a contamination distance, although in some cases it was possible to calculate the effect of contamination *post hoc*.[5] As the advantages of reducing contamination risk in CRTs were increasingly recognized, the one solution that has been used widely is the fried-egg design,[6] whereby a treatment is implemented across the entire area of each respective cluster while households on the outer edge of the cluster (i.e. in a buffer zone) are excluded from the analysis of the primary CRT outcome (Figure 1). In this way, households included in the primary analysis are always located at least the contamination distance away from the implementation of other trial treatment arms.

One potential disadvantage of the fried-egg design is that it ignores the possibility of systematic spatial heterogeneity of disease burden within clusters. Yet spatial heterogeneity

is commonly found for disease vectors,[7,8] pathogens,[9-11] and disease burden.[12] Limiting analyses to data from the centre of a cluster precludes the ability to account for such well-documented variation. For example, if disease burden is consistently higher near the edge of clusters compared to the centre, excluding these households from the analysis of CRT outcomes would obscure the true effect of the intervention being tested. On the other hand, if the households are included in secondary analyses, there would still be a risk of contamination bias. Additionally, reducing the number of households within a cluster makes the outcome measure inherently less precise, leading to loss of power.

The widespread availability and continuous technological development of GPS, GIS and remotely-sensed satellite images provide expanded possibilities for investigators designing large-scale intervention trials. In this paper, we present a novel approach for trial design that attempts to reduce the risk of contamination while simultaneously accounting for systematic spatial heterogeneity. The method presented here also allows investigators to (1) maximise the inclusion of clusters in the proposed study region for increased statistical power in the analysis of trial outcomes, (2) maintain randomness in the allocation of clusters to eliminate potential selection bias, and (3) allow for consideration of social expectations of fairness in the exclusion of clusters.

Methods

The central idea of this approach is that clusters in the study region are either fully included or fully excluded from the trial to avoid the problems outlined above for the fried-egg design. By excluding some clusters in the study region from the CRT, clusters included in the CRT are ensured to be at least the contamination distance from any other cluster assigned to a different CRT treatment arm. The steps for implementing the approach are summarised as: (1) defining the trial setting; (2) defining optional inclusion criteria; (3) identifying the maximum possible number of clusters; and (4) randomisation.

Defining the trial setting

The trial-specific definitions of cluster and contamination distance must be made by the investigators of the CRT. In the context of vector-borne disease, the contamination distance can reasonably be taken to mean Euclidean distance. In other contexts, a different measure (e.g. a measure based on social connectivity) may be more appropriate, but the same principles hold. Next, the boundary of each cluster should be mapped. We define a connection as any two clusters with boundaries that are within the contamination distance of each other (i.e. if the shortest distance between any two houses, one in each of the two clusters, is less than the contamination distance). Using the map of all clusters, all connections between clusters should be drawn (Figure 2a). Pairs of clusters with connections, by definition, cannot be allocated to different treatment arms of the CRT. As shown in Figure 2b, excluding some clusters from the CRT leaves the remaining clusters without any connections to the other clusters in the CRT.

Defining optional inclusion criteria

Additional inclusion criteria could be defined by the CRT investigators to suit the needs of the trial and study region, but this step is not necessarily required. One option would be to allow clusters with connections (i.e. within the contamination distance of each other) to both (or all) be included in the CRT, with the restriction that they are allocated to the same CRT treatment arm (Figure 2c). This increases the total number of clusters in the CRT and, thus, the statistical power in the analysis of trial outcomes. It is then useful to define a cluster-group as either a single cluster with no connections to another cluster in the CRT, or a group of two or more clusters with connections to each other. For statistical efficiency we should only allow cluster-groups with more than one cluster where doing so does not decrease the total number of cluster-groups included in the CRT. (Figure 2d). This is because the primary

analysis is a randomisation-based test for significant treatment effects that must account for the restricted randomisation, and whose power is therefore primarily dependent on the number of cluster-groups.

An additional option for modifying the inclusion criteria is aimed at potential social expectations of fairness, because in many cases, CRT interventions are perceived as benefits by the communities in the study region. In a typical CRT, people living in clusters allocated to the CRT control arm do not receive the perceived benefit of the intervention. Still, through proper community engagement, these communities should understand that they had a non-zero probability of being allocated to the CRT intervention arm. However, in the method proposed in this paper, excluded clusters are not part of the CRT treatment arm allocation. Therefore, if it is important that every community have a non-zero probability of being included in the CRT, it is possible to set this as an additional inclusion criterion. When identifying the potential randomisation options, it would be stipulated that every cluster is included in at least one set. This also would reduce the risk of subjective bias when selecting clusters. Where this conflicts with other inclusion criteria, it is up to the investigators to determine the optimal balance among competing criteria.

Algorithm for identifying potential randomisation design options

Here, we briefly present an algorithm for identifying potential randomisation design options. Each randomisation design option is a set of clusters that meet all inclusion criteria described above within a specific study setting. The design algorithm is described formally in Supplementary File 1.

Let *n* be the total number of clusters available for inclusion in the randomisation design. Two clusters are connected if there is potential for contamination between them, as defined above. We can represent the set of clusters formally as a *graph*[13] with *n vertices* corresponding to the clusters, and *edges* corresponding to all connected pairs of vertices.

The left-hand panel of Figure 3 gives an example with *n=9* vertices and *11* edges. This graph forms a single *network*, meaning that any two of its vertices can be connected by a path along a sequence of edges; the positions of the vertices are irrelevant, only their connections matter. A set of *k* vertices is a valid *randomisation unit* (cluster-group) if none of its members is connected to any of the remaining *n-k* sampling units. Translating these graph-theoretic definitions into the current context, a valid cluster-group is either a single vertex or a network. Our primary design criterion is to maximise the number of available cluster-groups, whilst a secondary criterion is to minimise the number of excluded clusters. Expressed in graph-theoretic terms, this is equivalent to removing vertices from a graph in such a way as to maximise the resulting number of disconnected vertices plus networks and, within all such solutions, to minimise the number of removed vertices.

Our design algorithm therefore operates on the graph of all *n* clusters by removing vertices and their associated edges in such a way as to simultaneously maximise the number of networks and minimise the number of removed vertices. When these two criteria are in conflict, we prioritise the first, because the networks are the randomisation units. However, to meet the social expectations of fairness described above, we also aim to construct a number of potential randomisation design options that collectively include every vertex. The remaining two panels of Figure 3 illustrate this idea in a simple case. Each shows a design containing three clusters whilst retaining *n-2* vertices, and which together include each of the *n* original vertices at least once.

Randomisation

Depending on the geographic arrangement of clusters in the proposed study region, there may be multiple potential randomisation options that meet the inclusion criteria.

To eliminate the chance of selection bias, the set of clusters that is finally included in the CRT should be selected randomly from all identified potential options (e.g. Figure 4). Finally,

treatment arms can be allocated to the included clusters, remembering that clusters within the same cluster-group are restricted to be in the same treatment arm.

Application: CRT of vector control to reduce malaria transmission

We applied this method to the design of a CRT testing the impact of two vector control interventions in southern Malawi (Trial registration number PACTR201604001501493).[14] The trial site is located near Majete Wildlife Reserve in Chikhwawa District, an area of high malaria transmission in the Lower Shire River Valley region of southern Malawi.[15] The trial is being conducted as part of the Majete Malaria Project (MMP), which considers community engagement and participation as a central focus of its strategy and implements the trial interventions through a community-based approach.

Trial setting

The objective of the trial is to determine the impacts of structural house improvements and larval source management (LSM) on malaria parasite prevalence and entomological inoculation rate (EIR) over a 24-month period, when implemented alone or in combination, in addition to the Malawi National Malaria Control Program interventions. The trial follows a randomised block, 2x2 factorial design, with three blocks of villages situated roughly evenly around the wildlife reserve (Figure 5). Prior to the start of baseline data collection for the trial, the study population was enrolled in a demographic surveillance system, with data managed in the OpenHDS system.[16] Using the geolocations of houses from OpenHDS, we defined the border of each village in the trial catchment area by demarcating a convex hull around the outermost houses of each village, thereby defining the trial clusters. The total population living in the trial catchment area was roughly 25 000 people from 65 clusters. Each block was delineated to cover the same villages as an existing or planned THP

Epicentre, which brings together neighbouring villages as a basis for community-led development.[17]

Standard practice for LSM dictates that implementation of this intervention should account for mosquito dispersal by treating both the target area (in this case a village) and a radius around that target area. To account for this prior to the selection of which clusters were included in the trial, we delineated a zone 400 m beyond the border of each cluster. This distance was based on published records of mosquito dispersal distance and accounting for the relatively high human population density of the trial clusters. In this way, all houses in LSM clusters would have LSM implemented around them out to a distance of at least 400 m. Similarly, houses in clusters not allocated to LSM would be at least 400 m from any implementation of LSM. Therefore, the distance between any house in a given cluster, and a house in another, unconnected cluster (as defined above), was 800 m.

Inclusion criteria for randomisation design options

Because of the importance of community engagement for both the project and the implementation of trial interventions, we determined that every cluster should have a non-zero probability of being included in the trial and stipulated that every cluster was included in at least one randomisation design option. Because of the geography of the clusters, this was only possible after we allowed randomisation design options to have a minimum of $N_{max} - 1$ cluster-groups, where N_{max} is the maximum number of cluster-groups possible in the block. Further, we allowed cluster-groups of any size (as opposed to setting a maximum number of clusters per cluster-group) as long as every potential design submitted to the randomised selection in each block should have at least $N_{max} - 1$ cluster-groups.

Algorithm for identifying potential randomisation design options

In one of the three blocks, referred to as Focal Area B (Figure 5), it was possible to include all thirteen clusters in the trial, and therefore it was not necessary to identify alternative randomisation design options. The maximum possible number of cluster-groups (N_{max}) was six, with cluster-groups (n) ranging in size from one to three clusters per cluster-group.

In the other two blocks, referred to as Focal Areas A and C, the geography of the clusters resulted in many connections between multiple clusters when using the 800-m contamination distance between households within the clusters (Figure 6a). Accordingly, we used the algorithm described above to find N_{max} for each of the two blocks. Within each block, we then used trial and error to identify six different randomisation design options that had between N_{max}-1 and N_{max} cluster-groups, and where the final list of randomisation design options included every cluster in the block at least once (Figure 6b-g).

Randomisation

In Focal Area B, the six cluster-groups were assigned to the four trial arms by drawing lots during a public event in the community. In Focal Areas A and C, allocation of trial arms to clusters was a two-stage process that took place in each respective community. In the first stage, one of the six randomisation design options was selected by drawing lots. In the second stage, trial arms were assigned to the cluster-groups in the selected design, again by drawing lots. In all three blocks, the randomisation unit was the cluster-group, while the sampling unit during data collection was the cluster.

Discussion

The methods presented here provide a novel approach for reducing the risk of contamination in CRTs set in study sites with a well-defined, finite set of sampling units whose spatial arrangement presents a risk of treatment contamination. Contamination risk is reduced by excluding some potential clusters from the CRT, and potential subjective bias (in

the selection of which sampling units are included) is eliminated by choosing at random amongst candidate randomisation design options that collectively satisfy the design criteria in any specific application. Identifying the design (or designs) with the maximum possible number of cluster-groups for a given study site by direct inspection, guesswork or trial-and-error rapidly becomes infeasible as the number of sampling units grows (see Supplementary File 1). The site of the vector control CRT presented here provides one such example. Using the algorithm presented here, investigators can overcome this challenge.

The primary advantage of the approach is that it allows CRT investigators to include full sampling units (e.g. an entire village rather than a portion of the village) in both the implementation of the intervention and the primary analysis of the treatment effects. Including data from all individuals within each randomisation unit increases statistical precision. For example, if the outcome for a cluster is an average of the values from n households, and the correlation between households within a cluster is r, the variance of the cluster average is proportional to $(1+(n-1)r)/n$, which decreases as n increases unless, implausibly, $r=1$. This also reduces the risk that the CRT would otherwise implicitly ignore any systematic spatial heterogeneity (specifically at the cluster scale) in the transmission or burden of the disease being investigated. For example, a common cluster unit of allocation is a village. In a region where streams are a common border between villages, and where the targeted disease burden is higher near streams, consistently placing these outer households in the buffer zone is not an ideal trial design. There may also be consistent differences in socio-economic status and living conditions between the edge and interior of a cluster.

To create the contamination distance between sampling units included in the CRT, some sampling units must be excluded from the CRT. In cases where this impacts the statistical power of the study, investigators may need to compensate for this by expanding the geospatial extent of the CRT site to include additional clusters.

It is important for investigators to understand the drivers of pathogen movement in their specific disease system and how those contribute to contamination risk in their particular CRT setting. Both the approach presented here and the fried-egg design assume that disease system components are stable over time. Nomadic populations or those with specific seasonal movements, for example, would either require additional, or alternative, considerations.

In settings where human settlements are not systematically mapped by the government, the demarcation of cluster borders in the CRT catchment area should be done up front. In our example of the vector control CRT, we geolocated all houses in the trial catchment area during enrolment to a demographic surveillance system, allowing for simple demarcation of the village borders using a convex hull. Alternatively, houses in the catchment area could be geolocated using open source satellite imagery,[18,19] though this may still require input from someone familiar with the area to identify sampling unit boundaries when these are not clear from the image. In situations where social or administrative boundaries are not critical to the study design, then any method of demarcating sampling unit boundaries would be acceptable.

We have described the approach in a way that gives flexibility so that investigators are able to determine the relative importance of the criteria used in selecting randomisation design options. For example, if the design of an intervention requires community participation, it would be more important to ensure that all sampling units have a non-zero probability of being included in the CRT treatment allocation. Conversely, if statistical efficiency is considered more important by the trial investigators than social restrictions, it would be reasonable to prioritise the requirement that all randomisation design options include N_{max} cluster-groups over the potential criterion of including all sampling units in at least one design. Additionally, trial outcomes can be measured in the excluded villages,

allowing for an empirical estimate of the distance a trial treatment effect extends beyond the boundaries of implementation.

CRTs have become increasingly common over the past few decades for the evaluation of complex clinical, public health and health system interventions [20]. Over that time, there have been surprisingly few methods developed to address potential contamination of treatment effects among clusters (but see Delrieu et al.[21] for one example). The approach presented here is applicable to cluster-randomised trials investigating a wide range of infectious disease interventions, including vaccines, drugs, vector control, and behaviour change communication.

Conclusion

Those planning CRTs to evaluate interventions should consider the approach presented here when deciding how to reduce the risk of contamination among the CRT randomisation units. The approach reduces the risk of contamination while recognising the potential for intracluster spatial heterogeneity and maximising the number of units of clusters that can be included. The approach also maintains randomness in the allocation of clusters to either the treatment group or control group, therefore permitting a randomisation-valid test of the primary trial hypothesis.

Abbreviations

CRT, cluster-randomised trial; EIR, entomological inoculation rate; LSM, larval source management; MMP, Majete Malaria Project; THP, The Hunger Project

List of Supplementary Material

Supplementary File 1: Method of identifying potential designs (Supplementary file 1.docx)

Funding

This work was supported by Dioraphte Foundation, The Netherlands. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Acknowledgements

We thank Glory Mzembe and Feiko ter Kuile for their reviews and constructive comments on earlier drafts of this manuscript.

Authors' contributions

All authors contributed to conceptualising the methods presented. RM, AC, EG and PD developed the methods. AC and PD developed the algorithm. RM, AC and PD wrote the first draft of the manuscript. All authors provided critical input to the final manuscript. All authors read and approved of the final manuscript.

Declaration of interest

All authors declare that they have no conflicting interests.

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Figures

Figure 1. Schematic of two generic clusters demonstrating the “fried-egg design”. Red line shows “contamination distance”. Both yellow and blue areas are inhabited. One CRT treatment arm is implemented in the entirety of the yellow area, while another treatment arm is implemented in the entirety of the blue area. The diagonal line pattern represents the “buffer zone”, where households are excluded from the analysis of primary CRT outcome.

Figure 2. (A) Schematic of nine generic clusters showing connections between clusters that are separated by less than the contamination distance from each other. The red scale bar in each panel shows the contamination distance. Blue dotted lines show which clusters have connections. Note that clusters D and F are not directly connected, but that they are indirectly connected through cluster E. (B) One potential design for excluding clusters in such a way that the remaining clusters are not connected and could, therefore, be allocated to different arms of a CRT. Light blue clusters are included in the CRT, while grey clusters are excluded. Note that this would include five of the nine clusters in the CRT. (C) Allowing some connected clusters to be included together in the CRT with the restriction that connected clusters be allocated to the same treatment arm of the CRT. In this example, the number of cluster-groups would remain at five, but the number of total clusters included in the CRT would be seven of the nine clusters. (D) A potential trade-off between the number of cluster-groups and the number of clusters included in the CRT. As compared to (C), this

design would increase the total clusters to eight out of nine, but the cluster-groups would be reduced from five to four.

Figure 3. (A) A graph with n=9 vertices (each representing a cluster) forming a single cluster-group. (B) and (C) Sub-graphs with seven vertices (i.e. two vertices have been removed), each of which forms three cluster-groups and which together include each of the original nine vertices at least once.

Figure 4. Four potential, alternative designs for determining which of the nine generic clusters to include in a CRT. Light blue clusters are included in the CRT, while grey clusters are excluded. This is not an exhaustive list of the all potential designs. Still, the final design to be used could be randomly selected from the this set.

Figure 5. (A) Map of Malawi with location of study site indicated by a black square. (B) Map of Majete Wildlife Reserve showing surrounding community-based organizations (CBOs) and indicating the three blocks of villages (clusters) making up the trial catchment area. (C) Map of one of the three blocks showing all clusters in this area. Connections indicate clusters that were joined into cluster-groups for allocation of the trial treatment arms, based on cluster borders being within 800 m of each other. Two polygons, each indicated by an asterisk (*), are small hamlets (27 and 4 houses, respectively) that are socially connected to the nearest respective clusters and were therefore allocated to the same trial treatment arm as those clusters. The MWR staff housing (polygon indicated in red) was excluded from the trial.

Figure 6. All maps show all 21 clusters in this block of the trial catchment area, with connections indicating pairs of clusters that would potentially be included and are separated

by less than 800 m. (A) If all 21 clusters were to have been included in the trial, this would have left one cluster-group with 19 clusters. (B:G) Six potential, alternative designs for which clusters to include in the trial. All six designs have six cluster-groups. The final design for the trial was randomly selected from among these six designs.