4.3 Cluster Randomized Trials

Authors

Matthew Coldiron, Epicentre, Paris, France.

Rebecca F. Grais, Epicentre, Paris, France.

4.3.1 Learning objectives

To understand the role that cluster randomized trials can play in health emergency and disaster risk management (Health EDRM), including:

1. The advantages and disadvantages of the cluster randomized trial methodology.
2. Situations in which cluster randomized trials could be used.
3. Potential difficulties in the implementation of cluster randomized trials and solutions for overcoming them.

4.3.2 Introduction

Chapter 4.1 discussed the role of individually randomized trials in resolving uncertainties about the effects of interventions, actions and strategies, and focused on studies in which the allocation to groups is determined at the level of each individual participant. However, in cases where this is not possible or appropriate, studies may be designed to randomize groups of participants ("clusters") rather than individuals, in what are called cluster randomized trials – sometimes also known as group-randomized trials or place-randomized trials – and these are the focus of this chapter.

In a cluster randomized trial, the intervention is directed at a group of people, which makes this design well-adapted for performing research in Health EDRM situations. Common examples of clusters include villages, schools, doctors' offices, and different wards or services of a hospital. A variety of designs have been used *(1)*. For example, cluster randomized trials have been used to evaluate the effectiveness of:

- Mass vaccination *(2)*
- Mass antibiotic prophylaxis during epidemics *(3)*
- Water and sanitation packages designed to prevent diarrhoeal disease *(4–5)*
- Population-based interventions aimed at decreasing the incidence of acute malnutrition *(6)*.

4.3.3 Design of cluster randomized trials

Most people are more familiar with individually randomized trials (Chapter 4.1) than with cluster randomized trials. However, many of the same considerations apply to their design. These include:

- ensuring that there is not already evidence that would support the hypothesis being tested (ensuring "equipoise", or genuine uncertainty about the potential effects of an intervention);
- conducting a scoping review (Chapter 3.6) or systematic review (Chapter 2.6) if needed;
- defining relevant outcomes;
- estimating the expected effect size of the intervention;
- developing an appropriate strategy for randomization and, if appropriate and necessary, for blinding participants and others involved in the trial to a person's allocated group.

There are however some important differences between cluster randomized trials and individually randomized trials. For example, the risk of an imbalance in potential confounding factors may be higher in a cluster randomized trial, because the number of clusters included is usually smaller than the number of individuals included in an individually randomized trial. Identifying and mitigating selection bias can also be more difficult in cluster randomized trials, where the study intervention is allocated at cluster level, but some individuals within the clusters may choose not to participate. It is also usually impractical (and often impossible) to keep study participants and researchers blinded to intervention allocation in a cluster randomized trial.

There are several additional considerations specific to the cluster randomized trial design. The first concerns the timing of the interventions in the different groups. Clusters are most commonly randomized in parallel, with group allocation happening at the same time. However, in some cases it is not desirable or feasible to carry out parallel randomization. If an intervention takes a long time to put into place (for example, a sanitary system or a new monitoring system in a hospital ward), researchers will sometimes perform what is called a stepped-wedge cluster randomized trial *(7)*. In this type of trial, the different clusters receive the intervention sequentially, and the outcomes of interest are compared across the different clusters, taking into account when the intervention was implemented, with all clusters having received the intervention by the end of the trial.

Secondly, crossover between individuals in different clusters needs to be minimized. The potential for individuals not in a given cluster to receive the intervention, or to have second-hand or spillover benefit from it, must be considered when designing a cluster randomized trial. If clusters are physically distant and there is little contact between them, significant crossover (or contamination) effects are unlikely. Separation of clusters can be integrated into trial design from the beginning, as was done in a trial of emergency room care for acute stroke in which hospitals were purposefully selected to minimize movement of physicians between emergency departments *(8)*. However, if clusters are contiguous

neighbourhoods of a city, or if there are important cultural links between two distinct villages, it is reasonable to expect that some crossover may occur. Researchers should strive to reduce this risk as much as possible.

Thirdly, the effects of clustering need to be accounted for during statistical analysis. In an individually randomized trial, participants receive their intervention (medication, vaccine and so on) and are evaluated individually. In a cluster randomized trial, the intervention is performed at the cluster level, but the outcome of interest is often measured at an individual level. For instance, in a cluster randomized trial evaluating village-level sanitation interventions, where the outcome of interest is diarrhoea, inherent characteristics of the villages, such as socioeconomic level and proximity to a floodplain, might play an important role in the risk of developing diarrhoea. Quantifying the similarities between individuals in a cluster in the intra-cluster correlation coefficient is an essential factor when calculating the sample size and the results of a cluster randomized trial *(9–10)*. Finally, it is important to recognize that inferences made from results of cluster randomized trials are often applied at an individual level, despite the cluster-level randomization. This has important consequences for data analysis, and for communication of trial results. Case Study 4.3.1 describes a novel cluster randomized trial of Ebola vaccines.

Case Study 4.3.1
A novel cluster randomized design for evaluating Ebola vaccines *(2)*

A relatively novel cluster randomized design was used to evaluate experimental vaccines early during the 2014 West Africa Ebola outbreak. The trial was a cluster randomized trial modelled on the ring vaccination approach used in the 1970s to eradicate smallpox. Ring vaccination involves vaccinating individuals who are socially or geographically connected to a confirmed case of an infectious disease, thereby creating a "ring" around infected individuals to prevent spread. In the ring trial, contacts of Ebola cases were enrolled and randomized into two groups, one of which was vaccinated immediately with an experimental vaccine, while the other was assigned to receive the vaccine 21 days after enrolment. The delay of 21 days was based on Ebola's maximum incubation period of 21 days after infection and on the fact that it takes some time for vaccine-induced protection to develop. The design was chosen because the time delay provided a non-placebo comparator group. Incidence of Ebola was compared between the rings (clusters) vaccinated immediately and those vaccinated with a 21-day delay. This design was controversial among scientists and ethicists, but was seen as an acceptable compromise between scientific rigour and providing hoped-for benefits of an unproven vaccine.

4.3.4 Advantages of cluster randomized trials

The most obvious advantage of cluster randomized trials over individually randomized trials is that they allow the evaluation of study interventions that cannot be directed toward selected individuals. This may be because of feasibility (for example, radio advertisements about smoking cessation,

or nursing protocols in a hospital ward), or biological mechanisms (such as interventions that aim to induce herd protection in a population). In certain situations, they may also be easier to implement than an individual-level intervention. For example, providing an intervention about hand hygiene to mothers in a rural village would reasonably be expected to have indirect spillover effects to other members of her household *(11)*.

4.3.5 Disadvantages of cluster randomized trials

The disadvantages of cluster randomized trials compared with individually randomized trials include the greater complexity of their design, as discussed above, as well as the need to include larger numbers of individual participants to obtain the same statistical power *(11)*. Specifically, the intra-cluster correlation coefficient is the main driver of the differences in sample size and clustering must also be considered during analysis of trial data. An example would be an educational intervention in which schools are randomized to one of several new teaching methods. When comparing differences in outcome achieved under the new methods, researchers must account for the fact that two students sampled from the same school are more likely to be similar in terms of outcomes than two students sampled from different schools. Multilevel or other similar statistical models are typically used to correct for non-independence of this kind.

On a more practical level, the hierarchical nature of cluster randomized trials can lead to a duplication of upstream preparation and sensitization efforts – first at cluster-level, and then among individuals in the clusters. This may have cost and time implications for researchers.

Cluster randomized trials are generally not designed to show individual-level effectiveness as a primary objective because the interventions happen at population level. For this reason, it is unusual to use a cluster randomized design with non-licensed products. Nonetheless, in some cases, it is possible to estimate individual effectiveness of an intervention by comparing outcomes among persons who are known to have received the intervention with those who are known not to have received it.

4.3.6 When to use a cluster randomized trial design

Cluster randomized trials are best suited for testing interventions intended for a group of people. Any population-based, mass distribution or administrative activity, such as those used in Health EDRM, lends itself well to cluster-based randomization. Health promotion activities and other interventions aiming to change behaviour are often tested in cluster randomized trials. This is also the case for interventions with a high risk of contamination. In this context, the term “contamination” refers to when individuals randomized to different comparison groups are in frequent contact with one another and thus may be influenced (contaminated), in either or both directions. Contamination is likely to occur in comparisons of interventions within the same community, but randomizing at community-level is an effective solution to this problem.

4.3

Cluster designs can also have practical advantages over individual randomization. They are easier to understand conceptually for policymakers who may be less familiar with the statistical and scientific properties of different trial designs, because they mirror more closely how interventions are implemented at scale. This is one of the reasons they are also a design that should be considered in an emergency, disaster or public health crisis. The design provides easy-to-understand information for groups of people and policy-makers, and can reach more participants due to the larger sample size. It is also important to consider that cluster randomization can capture both direct and indirect effects of an intervention. This is important when assessing effectiveness in a population and means that cluster randomized trials are well-suited to infectious diseases, when there might be direct benefits to those who receive the intervention as well as indirect benefits to those around them, who may benefit from a reduction in exposure *(12)*.

Case Study 4.3.2 describes how a cluster randomized trial was used to test village-wide antibiotic prophylaxis for meningococcal meningitis.

Case Study 4.3.2
Testing a strategy of village-wide antibiotic prophylaxis during a meningococcal meningitis outbreak *(3)*

Mass vaccination campaigns have been part of the standard response to meningococcal meningitis outbreaks in the African meningitis belt for decades, but vaccine supply is not always guaranteed. Antibiotic prophylaxis for contacts of cases is recommended in high-income countries but is not recommended in the meningitis belt because of a lack of evidence. As meningitis epidemics are seasonal, a cluster randomized trial protocol was prepared to test whether a village-wide prophylaxis strategy would work in this setting. When an epidemic hit the Madarounfa District of Niger, the trial started. After the first case was notified in each village, that village was randomized to receive either no prophylaxis, prophylaxis with single-dose ciprofloxacin for household contacts of meningitis, or a village-wide distribution of single-dose ciprofloxacin. The primary outcome was overall meningitis attack rate in the villages at the end of the epidemic. Household prophylaxis did not reduce attack rates, but village-wide prophylaxis reduced attack rates by 60%.

This trial is an example of research performed in an emergency setting. Not all emergencies can be predicted in advance, but in this setting, it was reasonable to be prepared for a meningitis epidemic. The advance preparation, including ethical review, meant that the trial could start very quickly after the beginning of the epidemic. A cluster randomized design was appropriate because the village-wide distributions were implemented across an entire population. Clustering within the individual villages was weaker than expected, which allowed for greater statistical power to discern differences in the meningitis attack rate. Because the villages included in the trial had a reasonable degree of separation, there was little evidence of spillover, which added to the reliability of the main results. If the villages had been closer to each other or there had been more social contact between them, it is likely that more persons from villages randomized to no prophylaxis or household-prophylaxis would have received prophylaxis, which could have influenced the results.

4.3.7 Informed consent in cluster randomized trials

Ethical issues relating to informed consent for participation in research are discussed more fully in Chapters 3.4 and 6.4. In an individually randomized trial (Chapter 4.1), a researcher approaches a potential study participant, explains the nature of the study, potential harms and benefits of participation, and underscores the potential participant's freedom to choose whether to participate in the study without negative consequence. If the participant provides informed consent, they are randomized and receive the study intervention and follow study procedures.

However, this procedure can be difficult – or even impossible – to replicate in cluster randomized trials, which generally take place at a larger scale, and in which many participants will not directly receive the study intervention which is to be given at the cluster level. Researchers and ethicists have therefore established a set of guidelines for the ethical conduct of cluster randomized trials, including issues related to obtaining informed consent from participants: the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials *(13)*.

The guidelines require that trial protocols be reviewed by ethics committees, and address some of the inherent challenges with trials where the level of intervention (cluster level) may differ from the level of outcome ascertainment (individual level). All individuals living in participating clusters are considered to be research participants, which may prove problematic given the size of some cluster randomized trials. Crucially, the guidelines lay out specific criteria for justifying the use of "gatekeepers" who may provide permission for a cluster to participate in a trial (such as a village chief or a nurse manager of a hospital ward). The permission of a gatekeeper should not be confused with proxy consent for individuals to participate, but does allow for most cluster randomized trial interventions to proceed without the individual-level informed consent that is required in individually randomized trials.

Nonetheless, even if a gatekeeper provides permission to participate, researchers have an obligation to communicate openly with individuals in the randomized clusters about the objectives of the research, their individual risks and benefits, and their autonomy to decide whether to participate in study activities, including simply being counted as a study participant. The Ottawa Statement is very clear that any derogation of individual consent must be reviewed and approved by ethical review committees (Case Study 4.3.3).

If unlicensed or investigational medicines or vaccines are used in a cluster randomized trial, it is likely that individual written informed consent would be required from all participants, just as in an individually randomized trial. Given the comparatively larger size of most cluster randomized trials, researchers should consider this during trial design and when they are planning the number of staff that they will need.

Case Study 4.3.3
Permission to participate and informed consent process in a cluster randomized trial

In the antibiotic prophylaxis trial described in Case Study 4.3.2, 49 villages were included in the trial over the course of only 27 days. The total population of these villages was 71 308, including 22 177 who lived in villages that were randomized to receive village-wide distributions of antibiotic prophylaxis.

Even without the emergency situation caused by the ongoing epidemic, it would have been impossible to obtain individual written consent from all persons living in the randomized villages over that brief time period. During study protocol development, the researchers reviewed the Ottawa Statement, and after consultation with the ethical review committees, determined that the criteria for the waiver of individual consent were met. During the trial, village chiefs served as "gatekeepers" and were asked to provide permission for the randomization of their villages.

At the same time, community health workers shared information about the trial in all participating villages. In villages allocated to receive ciprofloxacin distributions, the same community health workers passed through the village before the distribution to give information about the potential harms and benefits of single-dose ciprofloxacin prophylaxis and underscored that there was no obligation to take the prophylaxis. During the village-wide distributions, 77% of the target population received ciprofloxacin. The researchers believed that this was partly due to absences and partly due to individuals choosing not to participate, suggesting that the overall informed consent process of the trial was successful.

4.3.8 Special design and analysis considerations

Cluster randomized trials require careful reflection during their design and analysis. This is primarily because data collected about individuals in clusters are almost always correlated. The outcomes of an individual within a cluster may be likely to be the same as that of other individuals in the same cluster. This needs to be accounted for in the analyses, and subsequent interpretation of the results must consider both intra-cluster correlation and between-cluster variability. Between-cluster variability can be summarized using the coefficient of variation between clusters, and the intra-cluster correlation coefficient. These intuitive statistical properties require the guidance of a researcher experienced in these techniques who can help guide the design of the trial.

4.3.9 Conclusions

Cluster randomized trials have become more common and have been implemented for a variety of Health EDRM issues. Although they are similar to individually randomized trials, cluster randomized trials have important design differences that have implications for data analysis and interpretation of results.

4.3.10 Key messages

- **Cluster randomized trials are interventional studies well-adapted for many emergency situations, and are ideal for evaluating population-level interventions.**
- **Compared to individually randomized trials, cluster randomized trials usually require larger numbers of participants and can be more complex to design and analyse.**
- **Cluster randomized trials can be parallel randomized or sequentially randomized, such as in a stepped-wedge design *(7).***
- **The fundamental ethical principles are similar to those in individually randomized trials, but the Ottawa guidelines consider the particularities of cluster randomized trials** *(13)***.**
- **Design and analysis of cluster randomized trials requires careful reflection and the guidance of experienced researchers.**

4.3.11 Further reading

Campbell MK, Elbourne DR, Altman DG, CONSORT group. CONSORT statement: extension to cluster randomized trials. BMJ 2014: 328: 702–8.

Coldiron ME, Assao B, Page A-L, Hitchings MDT, Alcoba G, Ciglenecki I et al. Single-dose oral ciprofloxacin prophylaxis as a response to a meningococcal meningitis epidemic in the African meningitis belt: a three-arm, open-label, cluster-randomized trial. PLoS Medicine 2018: 15: e1002593.

Hayes R, Moulton L. Cluster randomized trials (2nd edition). Boca Raton, Florida, USA: Chapman and Hall/CRC Press; 2017.

Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomized trial (Ebola Ça Suffit!). Lancet 2017: 389: 505–18.

Isaakidis P, Ioannidis JP. Evaluation of cluster randomized controlled trials in sub-Saharan Africa. American Journal of Epidemiology; 2003: 158(9): 921-6.

4.3.12 References

1. Crespi CM. Improved designs for cluster randomized trials. Annual Review of Public Health. 2016: 37(1): 1-16.
2. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomized trial (Ebola Ça Suffit!). Lancet 2017: 389: 505-18.

3. Coldiron ME, Assao B, Page A-L, Hitchings MDT, Alcoba G, Ciglenecki I, et al. Single-dose oral ciprofloxacin prophylaxis as a response to a meningococcal meningitis epidemic in the African meningitis belt: a three-arm, open-label, cluster-randomized trial. PLoS Medicine 2018: 15: e1002593.

4. Lin A, Ercumen A, Benjamin-Chung J, Arnold BF, Das S, Haque R, et al. Effects of water, sanitation, handwashing, and nutritional interventions on child enteric protozoan infections in rural Bangladesh: A cluster-randomized controlled trial. Clinical Infectious Diseases 2018: 67(10): 1515–22.

5. Lindquist ED, George CM, Perin J, Neiswender De Calani KJ, Norman WR, et al. A cluster randomized controlled trial to reduce childhood diarrhea using hollow fiber water filter and/or hygiene-sanitation educational interventions. American Journal of Tropical Medicine and Hygiene. 2014: 91(1): 190–7.

6. Dewey KG, Mridha MK, Matias SL, Arnold CD, Cummins JR, Khan MSA, et al. Lipid-based nutrient supplementation in the first 1000 d improves child growth in Bangladesh: A cluster-randomized effectiveness trial. American Journal of Clinical Nutrition. 2017: 105(4): 944–57.

7. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomized trial: Rationale, design, analysis, and reporting. BMJ. 2015: 350: h391.

8. Weston VC, Meurer WJ, Frederiksen, SM, Fox AK, Scott PA. Prevention of emergency physician migratory contamination in a cluster randomized trial to increase tissue plasminogen activator use in stroke (the INSTINCT trial). American Journal of Emergency Medicine. 2014: 32(12): 1460-63.

9. Donner A and Klar N. Statistical considerations in the design and analysis of community intervention trials. Journal of Clinical Epidemiology; 1996: 49(4): 435–9.

10. Rutterford C, Copas A, Eldridge S. Methods for sample size determination in cluster randomized trials. International Journal of Epidemiology; 2015: 44(3): 1051–67.

11. Campbell MK, Piaggio G, Elbourne DR, Altman DG. CONSORT 2010 statement: Extension to cluster randomized trials. BMJ; 2012: 345: e5661.

12. Hayes R, Moulton L. Cluster randomized trials (2nd edition). Boca Raton, Florida, USA: Chapman and Hall/CRC Press; 2017.

13. Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, Brehaut JC, et al. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLoS Medicine; 2012: 9(11): e1001346.