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Review

A Review of the Ring Trial Design for Evaluating Ring Interventions for Infectious Diseases

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In trials of infectious disease interventions, rare outcomes and unpredictable spatiotemporal variation can introduce bias, reduce statistical power, and prevent conclusive inferences. Spillover effects can complicate inference if individual randomization is used to gain efficiency. Ring trials are a type of cluster-randomized trial that may increase efficiency and minimize bias, particularly in emergency and elimination settings with strong clustering of infection. They can be used to evaluate ring interventions, which are delivered to individuals in proximity to or contact with index cases. We conducted a systematic review of ring trials, compare them with other trial designs for evaluating ring interventions, and describe strengths and weaknesses of each design. Of 849 articles and 322 protocols screened, we identified 26 ring trials, 15 cluster-randomized trials, 5 trials that randomized households or individuals within rings, and 1 individually randomized trial. The most common interventions were postexposure prophylaxis ($n = 23$) and focal mass drug administration and screening and treatment ($n = 7$). Ring trials require robust surveillance systems and contact tracing for directly transmitted diseases. For rare diseases with strong spatiotemporal clustering, they may have higher efficiency and internal validity than cluster-randomized designs, in part because they ensure that no clusters are excluded from analysis due to zero cluster incidence. Though more research is needed to compare them with other types of trials, ring trials hold promise as a design that can increase trial speed and efficiency while reducing bias.

disease elimination; emerging infections; postexposure prophylaxis; randomized controlled trials; reactive interventions; ring trials; ring vaccination; targeted interventions

Abbreviations: CRCT, cluster-randomized controlled trial; ICC, intraclass correlation; RCT, randomized controlled trial.

INTRODUCTION

Infectious disease transmission is inherently heterogenous, with a minority of the population responsible for the majority of transmission (1). This is especially the case in settings of emerging infectious disease and disease elimination, where diseases are rare and strongly clustered within space or contact networks (2–4). These epidemiologic features can pose challenges in randomized trials (2).

Strong spatial clustering and unpredictable timing of outbreaks can compromise baseline balance between trial arms, reducing statistical power and face validity (5, 6). This is particularly true in cluster-randomized controlled trials (CRCTs), which are commonly used to evaluate infectious disease interventions and enroll fewer units than individually randomized trials typically enroll. Although adjusting for baseline covariates may address baseline imbalance, substantive differences in adjusted and unadjusted estimates may undermine trial credibility and replicability (6).

In addition, in studies at the early or waning stages of an outbreak or in elimination settings, rare, clustered outcomes require large numbers of clusters to minimize false-negative results, which may be infeasible and cost prohibitive (2, 7). Individually randomized trials are more efficient than CRCTs, but contamination can prevent valid estimation of the estimand of interest—the effect of individual treatment versus control (8, 9). CRCTs are often used when contamination is a concern (10), among other reasons (e.g.,

to evaluate group-level interventions, to increase compliance or feasibility) (8). When buffer zones are established between clusters to maintain independence, CRCTs can minimize contamination (8, 11, 12). However, when disease is highly clustered in space or time, disease cases may only occur in a subset of predefined clusters, which may compromise statistical power in CRCTs (7).

Diseases that can be subclinical or asymptomatic pose another challenge to trials (2). For example, malaria and SARS-CoV-2 can be transmitted without symptoms (13), and asymptomatic Zika infection in pregnant women may result in birth defects. For such diseases, it is critical to evaluate asymptomatic infections, but doing so requires outcome measurement in population-based samples instead of, or in addition to, routine surveillance, which can be difficult and costly.

Ring trials are a type of CRCT that may increase efficiency and minimize bias in emerging infection and disease elimination settings (2). This design is well suited for evaluations of ring interventions (e.g., case-area targeted interventions (14–16), targeted interventions (17), focal interventions (18–21), and reactive interventions), which are delivered to individuals in proximity to or with contact with index cases. Ring interventions have been proposed or implemented for a wide range of diseases, including smallpox (4), malaria (22), and COVID-19 (23). In ring trials, as index cases are detected, each "ring" of individuals around the index case is randomized. This design was used to evaluate ring vaccination for the Ebola vaccine (24) and may be effective for ring interventions for other infectious diseases with asymptomatic transmission and high spatiotemporal transmission heterogeneity.

Here, we review ring trial designs, compare them with traditional trial designs, and discuss optimal settings for their use. We also report the findings of a systematic review of ring trials and trials of ring interventions, including published studies and protocols for ongoing studies.

METHODS

We conducted a narrative review of articles related to ring trials and ring interventions, focusing on methodological papers and simulation studies. To identify empirical studies, we conducted a systematic review to identify all published studies and registered study protocols reporting trials of ring interventions, including ring trials and other types of trials (PROSPERO registration: CRD42021238932). The remainder of this section focuses on the methods we used in the systematic review.

Inclusion and exclusion criteria

We included studies that 1) were reported as a research article or trial protocol; 2) used a ring trial design or other randomized design to evaluate a ring intervention; 3) measured disease or health-related outcomes; 4) evaluated public health intervention(s); 5) enrolled humans; 6) were reported in English; and 7) were published or registered before August 23, 2021. We defined ring interventions as interventions delivered to neighbors, contacts of index cases, or contacts of contacts of index cases. Index cases may be detected through passive surveillance, in which case patients present at health facilities, or active surveillance, in which case patients are detected through population screening. Typically, interventions are delivered within a relatively short period after index-case detection, when onward transmission to ring members is expected. We distinguished ring interventions from reactive interventions, which are delivered in response to an outbreak but are not restricted to individuals in proximity to or contact with index cases (25–32). We defined a ring trial as a study in which researchers enrolled rings of individuals or households in physical proximity to or in contact with an index case and randomly allocated each ring to study groups. We did not consider interventions to be ring interventions if a single contact of an index case was enrolled or if contacts were enrolled who were possibly exposed to an index case, but trial investigators made no attempt to identify or confirm index cases.

Search strategy

We searched PubMed (MEDLINE) and ClinicalTrials.gov in August 2021. We included the search terms "ring trial," "responsive target population," "ring vaccine," "ring intervention," "ring vaccination," "ring treatment," "ring vaccine," "responsive target population," "case area targeted intervention," "permuted locus," "reactive case detection," "reactive focal," "ring prophylaxis," "focal mass drug administration," "targeted mass drug administration," "household contact," and "post exposure prophylaxis" independently and in combination with the terms "trial," "randomized trial," "randomized controlled trial," "randomized control trial," "controlled trial," and "control trial." See additional details in the Web Appendix (available at https://doi.org/10.1093/aje/mxac003).

Article selection

Two investigators independently assessed article titles, abstracts, and full-text eligibility. Investigators logged inclusion and exclusion criteria during abstract and full-text review and resolved discordant classifications between each stage; for discordant classifications during title and abstract review, we erred on the side of including records in the full-text review. For trial registrations, 2 investigators reviewed registration eligibility in a single stage.

Data extraction

We extracted the following data from each selected publication: country, year, primary and secondary outcomes, intervention(s), comparison group(s), study design, rationale for the study design, ring definition, randomization unit, randomization type (e.g., stratified randomization), index-case definition, buffer zones, planned study size, power-calculation assumptions, and eligibility criteria. For completed studies, we also extracted results (e.g., study

size, compliance, mean response time, parameter estimated, analysis method, outcomes per group, measures of effect).

Risk-of-bias assessment

Investigators independently assessed risk of bias using the revised Cochrane risk-of-bias tool for cluster randomized trials (33). For publications in which multiple analyses were reported, we focused on the primary analysis. We classified the risk of bias in each domain and overall as "low risk," "some concerns," or "high risk." We resolved discordant classifications through consensus.

RESULTS

In the following summary of the findings of studies identified in our systematic review, we highlight features of ring trial design and contrast them with alternative designs, drawing on relevant methods and simulation studies.

Trial selection

We performed a title review of all 849 publications, abstract review of 238 publications, and full-text review of 73 publications (Figure 1). We reviewed 322 ClinicalTrials.gov registrations, of which 20 met inclusion criteria. Initial concordance between investigators was 90% after title review, 92% after abstract review, and 93% after full-text review; we resolved all discordances through consensus. Concordance for ClinicalTrials.gov registrations was 96%. In total, 52 trials (n = 50 publications and 20 registrations) met inclusion criteria.

Trial characteristics

Thirty-one trials were completed, 16 were in progress, 3 were registered and had not started, and registrations for 2 had been withdrawn (Table 1). Twenty-five trials used a ring design (Figure 2A), 7 trials individually randomized contacts of index cases (Figure 2B), and 15 others were CRCTs (Figure 2C). Twenty trials were located in low- or middle-income countries, and 31 studies were located in high-income countries. Studies measured infectious diseases in emergency, outbreak, and emerging infection settings (n = 18), epidemics (n = 15), endemic settings (n = 12), and elimination settings (n = 7).

Interventions

The most common type of interventions were postexposure prophylaxis or preventive chemotherapy delivered to household members or nearby residents of index cases (Table 1). These included postexposure prophylaxis for SARS-CoV-2 (n = 12), influenza (n = 9), common cold (n = 1), meningococcal meningitis (n = 1), cholera (n = 1), tuberculosis (n = 1), pertussis (n = 1), and leprosy (n = 1). Studies also applied focal mass drug administration or focal screening and treatment for malaria (n = 7), focal indoor residual spraying for malaria (n = 2), contact or community-based screening and treatment for tuberculosis (n = 2), and household decolonization for *Staphylococcus aureus* (n = 1). In 2 studies, researchers evaluated vaccines for Ebola in contacts of index cases and for hepatitis A in household contacts. In a few studies, nonpharmaceutical interventions were evaluated, including handwashing promotion for contacts of case patients with cholera or diarrhea (n = 2), masks and preventive behavior education for household members of case patients with influenza (n = 2) or tuberculosis (n = 1), conditional cash transfers for household contacts of case patients with tuberculosis (n = 1), and notification of partners of case patients with chlamydia or human immunodeficiency virus (n = 2). Different types of ring interventions were compared in several trials (n = 10); in 2 studies, researchers compared ring interventions with population-wide interventions for malaria because the latter are unsustainable, costly, and/or may contribute to drug and insecticide resistance. Most interventions were delivered to all ring members regardless of infection status (n = 49), and some were only delivered to ring members who tested positive for disease (n = 4).

Trial designs

Three types of randomized designs were used to evaluate ring interventions (Figure 2). A ring trial design was used in 26 studies (Table 1, Figure 2A). In 5 trials, researchers enrolled individuals or households in rings around index cases and then randomly allocated units in each ring to intervention or control, stratifying by ring (i.e., a ring-stratified trial) (Figure 2B). Fifteen studies were CRCTs of ring interventions, in which geographic clusters (e.g., health-facility catchment areas) were defined before index case presentation (Figure 2C). Five trial registrations and 1 published trial did not include sufficient information to determine the trial design. CRCTs were the only design used in elimination settings; ring trials were more common in epidemic and emergency or outbreak settings (Table 2).

In trials in which clusters are solely composed of ring members exposed to index cases, ring trials and CRCTs are equivalent. This was the case in many ring trials in which rings were defined as household contacts of index cases. On the other hand, in several CRCTs, researchers defined clusters on the basis of administrative geographic areas, and rings composed a subset of these areas; in these studies, ring trials were a subset of a cluster-randomized design. To make this distinction clear, hereafter, we use "CRCT" to refer to traditional, cluster-randomized trials in which clusters were enrolled before index case presentation.

In ring trials, the ring was the unit of randomization and the unit of intervention (Figure 2A); in ring-stratified randomized trials, the unit of randomization and intervention was the individual, and randomization was stratified by rings for each index case (Figure 2B). In CRCTs, the units of randomization and intervention were clusters, and a single cluster sometimes contained multiple rings that overlapped in location but not in time (Figure 2C). In individually randomized trials, the unit of randomization was the individual, and randomization did not consider ring membership.

Table 1. Characteristics of Trials Identified in the Systematic Review

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Barnabas, 2021, 2020 (55, 100)	NCT 04328961	United States	Study protocol; article	Completed	Hydroxychloroquine as prophylactic	Ascorbic acid	Ring trial	Household	Study site and type of contact (household member vs. health care worker)	COVID-19	Emergency/emerging infection
Bath, 2021 (17)	NCT 02556242	South Africa	Article	Completed	Reactive, targeted, indoor residual spraying	Standard indoor residual spraying	Cluster RCT	Census ward	Historical malaria and indoor residual spraying coverage, population size and density, and length of waterways	Malaria	Elimination
Bridges, 2017, 2016 (18, 101)	NCT 02654912	Zambia	Study protocol; trial registration	Recruitment complete	Presumptive antimalarial treatment of population within 140 m of index cases	Testing and treatment of positive individuals within 140 m of index cases	Cluster RCT	Health-facility catchment area	None	Malaria	Elimination
Coldiron, 2018, 2017 (48, 102)	NCT 02724046	Niger	Protocol; article	Completed	Ciprofloxacin treatment of index case household or village	Standard of care	Cluster RCT	Village	None	Meningitis	Outbreak

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Cowling, 2008 (75)	NCT 00425893	Hong Kong	Article (preliminary results)	Completed	1) Health education plus mask intervention 2) Health education plus handwashing intervention	General health education	Ring trial	Household	None	Influenza	Seasonal epidemic
Echevarría, 1995 (51)	N/A	Peru	Article	Completed	Single-dose ciprofloxacin	Placebo	RCT	Not indicated	None	Cholera	Endemic infection
Egsmose, 1965 (103)	N/A	Kenya	Article	Completed	1-year course of isoniazid	Placebo	Ring trial	Household	None	Pulmonary tuberculosis	Endemic infection
Eisele, 2015, 2020, 2016 (19, 74, 104)	NCT 02329301	Zambia	Study protocol; article; article	Completed	Household-level focal mass drug administration	Community-level mass drug administration	Cluster RCT	Health-facility catchment area	Low vs. moderate transmission	Malaria	Elimination setting
Fritz, 2012 (105)	NCT 00731783	United States	Article	Completed	Household infection decolonization	Decolonization of infected individual	Ring trial	Household (intervention) or individual (control)	None	*Staphylococcus aureus* infection	Epidemic infection
George, 2021 (106); Masud, 2020 (107)	NCT 04008134	Bangladesh	Article; article	Completed	Mobile health program focused on handwashing promotion, or mobile health program plus home visits	Standard message on oral rehydration	Ring trial	Household	Study site, hospital ward, and treatment location	Diarrhea	Endemic infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Halperin, 1999 (52)	N/A	Canada	Article	Completed	Erythromycin estolate for 10 days	Placebo	Ring trial	Household	None	*Bordetella pertussis* infection	Outbreak
Hayden, 2000 (60)	N/A	United States, Canada, United Kingdom, Finland	Article	Completed	Inhaled zanamivir as prophylactic	Placebo administered through inhaler	Ring trial	Family	None	Influenza	Seasonal epidemic
Hayden, 2004 (68)	N/A	United States, Estonia, United Kingdom	Article	Completed	Oseltamivir as prophylactic	No household treatment except for the index case	Ring trial	Household	Presence of an infant or a second case in the household	Influenza	Seasonal epidemic
Henao-Restrepo, 2017, 2015, 2015 (24, 42, 109)	PACTR 2015–03001 057193	Guinea	Article; article; study protocol	Completed	Ebola Virus vaccination of contacts and contacts of contacts of index cases	Delayed Ebola virus vaccination of contacts and contacts of contacts of index cases after 21 days	Ring trial	Contacts and contacts of contacts of index cases	Location (urban vs. rural), ring size (<21 vs. >20)	Ebola virus disease	Emergency/ emerging infection
Herzog, 1986 (54)	N/A	Switzerland	Article	Completed	Low-dose intranasal recombinant leucocyte IFN-αA, Ro 22–8181 as prophylactic	Placebo	Ring trial	Family	None	Common cold	Seasonal epidemic

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Hsiang, 2020, 2015 (21, 111); Medzihradsky, 2018 (110)	NCT 02610400	Namibia	Article; study protocol; trial registration	Completed	1) Presumptive antimalarial treatment of population within 500 m of index cases; 2) indoor residual spraying within 500 m of index cases	1) Testing and treatment of positive individuals within 500 m of index cases; 2) Indoor residual spraying within 500 m of index cases	Cluster RCT with factorial design	Census enumeration area	Historical malaria incidence, population size and density, and distance from household to health care facility	Malaria	Elimination
Ikematsu, 2020 (56)	JapicCTI-184180	Japan	Article	Completed	Baloxavir as prophylactic	Placebo	Ring-stratified RCT	Individuals	Time from illness onset to enrollment; treatment of index patient; participant age	Influenza	Seasonal epidemic
Iturriaga, 2021 (112)	NCT 04552379	Chile	Study protocol	Recruitment ongoing	Pegylated IFN β-1a subcutaneous treatment as prophylactic	Standard of care	Ring trial	Household	Number of people in household	COVID-19	Emergency/ emerging infection
Kashiwagi, 2013 (57)	JapicCTI-111647	Japan	Article	Completed	Inhaled laninamivir octanoate as prophylactic	Placebo	Ring-stratified RCT	Individuals	Institution; index patient infection with influenza A or B	Influenza	Seasonal epidemic

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Kashiwagi, 2016 (58)	JapicCTI-142679	Japan	Article	Completed	Inhaled laninamivir octanoate as prophylactic	Placebo	Ring-stratified RCT	Individuals	Virus type of index case; participants' influenza vaccination status in 2014–2015 influenza season	Influenza	Seasonal epidemic
Low, 2006 (113)	NCT 00112255	England	Article	Completed	Partner notification immediately initiated by practice nurse	Referral to specialist clinic	Ring trial	Sexual partners of index case	Medical practice	Chlamydia	Endemic infection
Mitjà, 2021 (67)	NCT 04304053	Spain	Article	Completed	Hydroxychloroquine as prophylactic	Usual care	Ring trial	Ring (e.g., household contacts, health care workers, nursing-home residents)	None	COVID-19	Emergency/emerging infection
Murphy, 1983 (114)	N/A	United States	Article	Completed	Rifampin as prophylactic	Placebo	Ring trial	Contact unit (members of index household and nonresident contacts)	None	Influenza	Seasonal epidemic

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Nakano, 2016 (59)	N/A	Japan	Article	Completed	Inhaled laninamivir octanoate as prophylactic	Placebo	Ring-stratified RCT	Individuals	Virus types for the index case patient; participants' influenza vaccination status	Influenza	Seasonal epidemic
Nanni, 2020 (115)	NCT 04363827	Italy	Study protocol	Trial ongoing	1) Hydroxychloroquine treatment for 1 month; 2) hydroxychloroquine treatment for 5–7 days as prophylactic	Observation	Ring trial	Household members and/or contacts)	Province COVID-19 incidence; index case patient is health care worker; index case COVID-19 treatment	COVID-19	Emergency/emerging infection
Okebe, 2021 (49)	NCT 02878200	Gambia	Article	Completed	Presumptive dihydroartemisinin-piperaquine treatment for all compound members of index case	Screening of compound members of index case	Cluster RCT	Village	Previous leprosy incidence	Malaria	Endemic infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Ortuno-Gutierrez, 2019 (37); De Jong, 2018 (116)	NCT 03662022	Comoros and Madagascar	Protocol; trial registration	Active, recruitment complete	Postexposure prophylaxis provided to household members of index case patient, neighborhood contacts within 100 m, or contacts within 100 m who test positive for a serological marker	No postexposure prophylaxis	Cluster RCT	Village	None	Leprosy	Hyperendemic infection
Ram, 2015 (63)	NCT 00880659	Bangladesh	Article	Completed	Intensive handwashing (soap and daily handwashing) behavioral promotion and provision of handwashing station	Standard practices	Ring trial	Household compounds	None	Influenza-like illness	Seasonal epidemic
Sagliocca, 1999 (117)	N/A	Italy	Article	Completed	Hepatitis A vaccine	No vaccine	Ring trial	Household	None	Hepatitis A infection	Endemic infection
Salazar-Austin, 2020 (50)	NCT 03074799	South Africa	Article	Completed	Symptom-based tuberculosis screening of contacts	Skin test–based screening of tuberculosis contacts	Cluster RCT	Clinic	Case notification rate and distance to hospital	Tuberculosis	Endemic infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Seddon, 2018 (118)	ISRCTN 92634082	South Africa	Study protocol	Ongoing	Daily levofloxacin for 24 weeks	Placebo	Ring trial	Household	Study site	Tuberculosis	Endemic infection
Smit, 2020 (76); Calmy, 2020 (119)	NCT 04364022	Switzerland	Study protocol; trial registration	Recruitment complete	Prophylactic lopinavir/ritonavir treatment of households with an asymptomatic index case patient	No treatment of households with an asymptomatic index case patient (standard of care)	Ring-stratified cluster RCT	Household	Study site	COVID-19	Emergency/ emerging infection
Suess, 2012 (65)	NCT 00833885	Germany	Article	Completed	1) Mask/hygiene: households provided with face masks and alcohol-based hand cleaner and information on proper use; 2) mask: households provided with surgical face masks and information on correct use	No masks or hand cleaner provided	Ring trial	Household	None	Influenza	Seasonal epidemic

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Tan, 2021 (77)	NCT 04321174	Canada	Study protocol	Recruitment ongoing	Oral lopinavir/ritonavir course for 2 weeks as prophylactic	No intervention	Ring trial	Ring (e.g., household members, health care workers)	Study site	COVID-19	Emergency/ emerging infection
van der Sande, 2014, 2010 (61, 120)	NCT 01053377; NL92738	Netherlands	Article; trial registration	Completed	Oseltamivir as prophylactic	Placebo	Cluster RCT	Nursing-home unit	None	Influenza	Seasonal epidemic
Vasiliu, 2021 (121)	NCT 03832023	Cameroon and Uganda	Protocol	Recruiting	Community-based tuberculosis screening of household contacts	Facility-based standard of care	Cluster RCT	Health-facility catchment area	Country	Tuberculosis	Endemic infection
Vilakati, 2021 (20); Hsiang, 2014 (122)	NCT 02315690	Eswatini	Article; trial registration	Completed	Presumptive antimalarial treatment of population within 200 m of index cases	Testing and treatment of positive individuals within 500 m of index cases	Cluster RCT	Locality	Malaria history; cluster size	Malaria	Elimination
Wamuti, 2015 (123); Cherutich 2017 (124)	NCT 01616420	Kenya	Protocol	Completed	Assisted partner notification services immediately after index case enrollment	6-week delayed assisted partner notification about services	Cluster RCT	HIV testing site	Country and rurality	HIV	Epidemic infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Wang, 2021 (125)	NCT 04536298	United States	Study protocol	Recruitment ongoing	High-dose vitamin D_3 supplementation as 1) early treatment, and 2) prophylactic	Placebo capsule of identical appearance and taste	Ring trial	Dyads (index case patient plus closest household member)	None	COVID-19	Emergency/ emerging infection
Welliver, 2001 (53)	N/A	Belgium, Canada, Denmark, Finland, Germany, Netherlands, Norway, Switzerland, United Kingdom, United States	Article	Completed	Oseltamivir as prophylactic	Placebo	Ring trial	Household	None	Influenza	Seasonal epidemic
Wingfield, 2017 (126)	N/A	Peru	Article	Completed	Standard of care plus socioeconomic support	Standard of care	Ring trial	Household	None	Tuberculosis	Endemic infection
Agrawal, 2020 (127)	NCT 04342156	Singapore	Trial registration	Withdrawn	Hydroxychloroquine sulfate	No treatment	Ring trial	Household	None	COVID-19	Emergency/ emerging infection
Bardin, 2020 (128)	NCT 04343248	United States	Trial registration	Trial ongoing	Nitazoxanide as prophylactic, with vitamin super B-complex as dietary supplement	Placebo, with vitamin super B-complex as dietary supplement	RCT[c]	Not specified	None	COVID-19 and other viral respiratory illnesses	Emergency/ emerging infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Bennett, 2020 (129)	NCT 04416945	Lao People's Democratic Republic	Trial registration	Not yet recruiting	Testing and treatment of positive individuals in 5 nearest households to index case patient	Standard of care and village-based RACD	Cluster RCT	Health-facility catchment area	None	Malaria	Elimination setting
Borrie, 2020 (130)	NCT 04397328	Canada	Trial registration	Not yet recruiting	Hydroxychloroquine as prophylactic	Placebo	RCT[c]	Not specified	None	COVID-19	Emergency/emerging infection
Bracchi, 2021 (131)	NCT 04842331	United Kingdom	Trial registration	Recruitment ongoing	RESP301 (nitric oxide–generating solution) as prophylactic, with standard of care	Standard of care	Ring trial	Household	None	COVID-19	Emergency/emerging infection
Elvira, 2021 (132)	NCT 04938596	Chile	Trial registration	Not yet recruiting	Combination of mask provision, prevention recommendations, and education about tuberculosis	Standard of care	Cluster RCT	Health care area and corresponding clinics	None	Tuberculosis	Endemic infection

Table continues

Table 1. Continued

First Author,[a] Year (Reference No.)	Registration	Country	Publication Type[b]	Publication Status	Intervention	Control	Study Design	Unit of Randomization	Stratification	Primary Outcome Disease	Study Setting
Gadisa, 2020 (133)	NCT 04241705	Ethiopia	Trial registration	Recruitment ongoing	1) Presumptive antimalarial treatment of population within 100 m of index case patients; 2) testing and treatment of positive individuals within 100 m of index case patients	Standard of care	Cluster RCT	District	None	Malaria	Elimination
Giles, 2020 (134)	NCT 04318444	United States	Trial registration	Recruitment ongoing	Hydroxychloroquine as prophylactic	Placebo	RCT[c]	Not specified	None	COVID-19	Emergency/ emerging infection
Malin, 2021 (135)	NCT 04894474	Not specified	Trial registration	Withdrawn	Antibody BI 767551 medication	Placebo	RCT[c]	Individual	None	COVID-19	Emergency/ emerging infection
McGeer, 2020 (136)	NCT 04448119	Canada	Trial registration	Active, recruitment complete	Favipiravir	Placebo	Ring trial	Long-term care home	None	COVID-19	Emergency/ emerging infection
Sued, 2021 (137)	NCT 04788407	Argentina	Trial registration	Recruitment ongoing	Nitazoxanide as prophylactic	Placebo	RCT[c]	Not specified	None	COVID-19	Emergency/ emerging infection

Abbreviations: HIV, human immunodeficiency virus; N/A, not applicable; RACD, reactive case detection; RCT, randomized controlled trial.
[a] First author's last name for published articles, preprints, or protocols. Principal investigator's last name for trial registrations with no publication.
[b] Includes all types of articles retrieved in the systematic review.
[c] Insufficient information to determine type of trial.

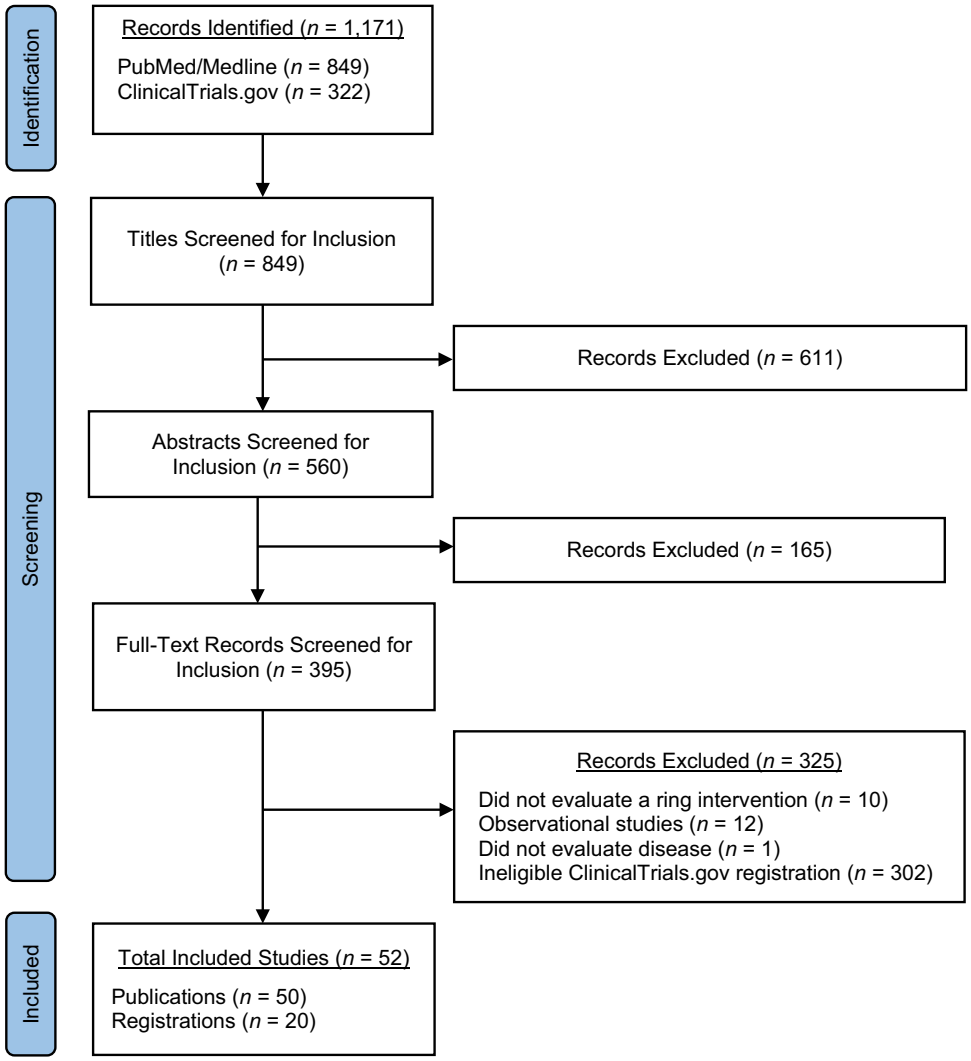

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for systematic review screening and inclusion. All registrations from ClinicalTrials.gov were reviewed in a single stage of full-text review, and records overlapped. "Total included studies" refers to research projects for which 1 or more records were included. Records of studies include trial registrations, published trial protocols, and original research articles.

Index case ascertainment

In all but 2 studies, index cases were identified through passive surveillance, in which index case patients presented at health care facilities, where infection was confirmed with laboratory tests and then reported to surveillance systems (Web Table 1). Passive surveillance effectiveness depends on the extent of health care use and the robustness of the case reporting system (34–36). In 2 trials, researchers used active surveillance to identify index cases. In 1 study, health workers tested all individuals in study communities for malaria with rapid diagnostic tests and treated positive individuals; in the intervention arm, for household members with any positive tests, all individuals were offered treatment regardless of test results (19). A second trial includes an arm in which nonhousehold contacts of leprosy case patients who test positive for a serological marker of infection will receive treatment (other arms deliver postexposure prophylaxis) (37). In principle, active surveillance could also use serologic surveys to detect prior infections, but if prior infections occurred long before serologic assays, interventions may fail to prevent transmission (26).

Ring enrollment

The most common type of ring was household contacts (or nursing home contacts) of index case patients, especially in endemic, epidemic, and emergency settings (Table 2, Web Table 1). Studies of Ebola, influenza, COVID-19, chlamydia, and human immunodeficiency virus defined rings of contacts and/or contacts of contacts of index cases or household members of an index case. The only trials in which rings were defined on the basis of geographic proximity

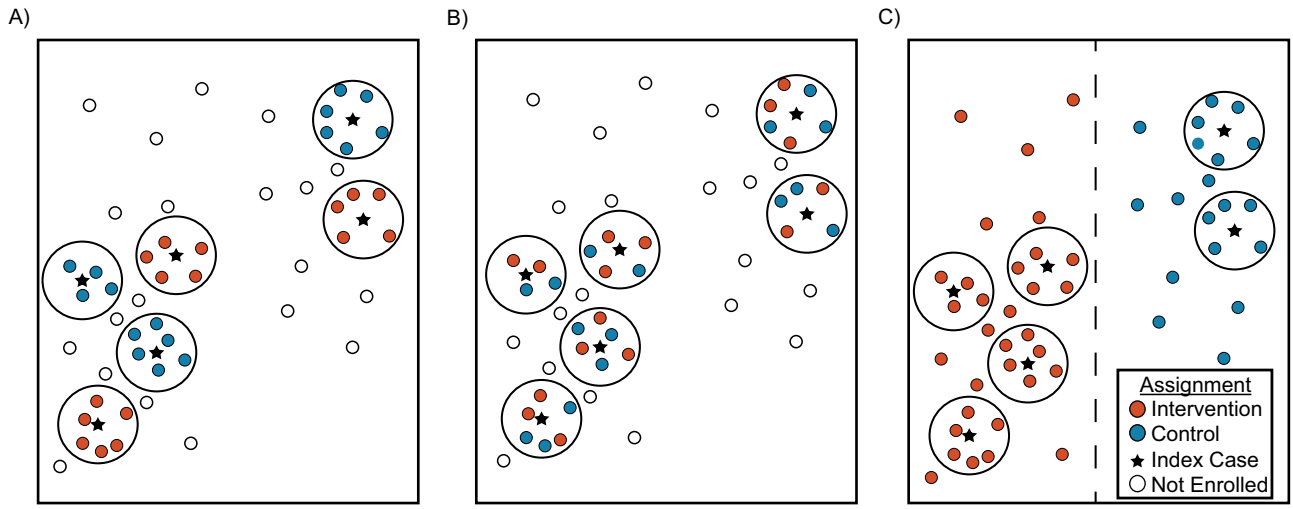

Figure 2. Types of ring intervention trial designs. A) Ring trial design. B) Ring-stratified randomized trial. C) Cluster-randomized trial of ring intervention. The dotted line separates cluster 1 (left) from cluster 2 (right). Whereas all participants in cluster 1 were assigned to the intervention group, only participants inside the 4 rings received the intervention.

(e.g., 100–500 m) of index cases, researchers used cluster-randomized designs (Table 2). In future ring trials of environmentally transmitted or vector-borne disease, researchers could define rings on the basis of geographic proximity to index cases (7). In studies enrolling contacts of index cases, it may be difficult to identify contacts within the desired response window if the contact tracing system is not robust. Complete contact tracing and enrollment may be more difficult for stigmatized diseases, such as human immunodeficiency virus and Ebola (38). In trials in which rings are defined by geographic proximity, it may be difficult to enroll ring members in a timely fashion in the absence of a baseline geographic census identifying the location of all households.

Observation period

Outcomes within predefined observation periods were measured on the basis of the disease incubation period and

Table 2. Number of Included Studies by Study Design, Ring Type, and Study Setting

Study Characteristic	Study Setting							
	Endemic Setting (n = 12[a])		Epidemic Setting (n = 15)		Emerging Infection, Emergency, and Outbreak (n = 18[b])		Elimination Setting (n = 7)	
	No.	%	No.	%	No.	%	No.	%
Trial design								
Cluster-randomized trial	5	45	2	13	1	8	7	100
Ring-stratified cluster-randomized trial	0	0	4	27	1	8	0	0
Ring trial	6	55	9	60	11	84	0	0
Ring type[c]								
Household including index case	8	73	14	93	10	67	1	14
Neighborhood around index case	2	18	0	0	1	7	7	100
Contacts of index case	1	9	2	13	3	20	0	0

[a] Only 11 studies provided sufficient information to determine trial design and ring type.
[b] Only 13 studies provided sufficient information to determine trial design, and 15 provided sufficient information to determine ring type.
[c] If multiple types of rings were used, column percentages exceed 100%.

the expected duration of intervention effectiveness (Web Table 1). For example, observation periods of 10–14 days were used in most influenza and COVID-19 studies, and malaria interventions used observation periods of 35 days or longer for ring mass drug-administration interventions and up to 24 months for reactive, indoor residual spraying, which is expected to have a longer effect duration. In some trials, intervention effects were expected to be transient, and participants could be enrolled in ring interventions more than 1 time. For example, in 2 trials of reactive focal mass drug administration, researchers defined observation periods of 5–8 weeks after the start of an intervention; after this period, if additional index cases occurred in the same area, the intervention was repeated around the new index case (20, 21).

A simulation study of ring trials showed the importance of carefully defining observation periods (39). Starting the observation period before the intervention is effective may attenuate effect estimates toward the null. This is because cases occurring soon after index case presentation may result from transmission prior to intervention. Longer follow-up periods will capture initial intervention effects on recipients as well as reductions in secondary transmission, which may be desired. For interventions with short-lived effects, ending the observation period too late could also attenuate effects toward the null because effects on onward transmission would be expected to be smaller. In vaccine trials, intention-to-treat effects are estimated according to randomized intervention assignment and define the observation period from the time of randomization, which may include the incubation period and time in which vaccinated individuals develop an immune response; per-protocol effects are estimated according to vaccination status, and the observation period starts after the incubation period and development of an immune response (40, 41). For example, in their primary analysis, researchers conducting a ring trial of the Ebola vaccine used a per-protocol approach that included outcomes 10 days or more after randomization (24, 42).

Response time

For infectious diseases with short serial intervals, rapid intervention delivery after index case detection is crucial to ring intervention effectiveness. Trials of influenza and SARS-CoV-2 postexposure prophylaxis typically had response times close to 1 day; response times were longer in other trials (Web Table 2). Response times longer than planned can result in secondary and possibly tertiary transmission before interventions take effect (43, 44). For example, in 2 malaria trials, researchers reported that longer-than-planned response times in some clusters might have limited intervention effectiveness and that response time differed between intervention arms (20, 21). If response time differs between arms, effect estimates may be biased.

Parameter of interest

CRCTs are amenable to estimation of total effects, spillover effects (i.e., indirect effects), and overall effects, each of which provides different information (45–47). Total effects are used to make inferences about effects on intervention recipients, and spillover effects are used to make inferences about untreated individuals in proximity to interventions and may reflect impacts on disease transmission in the study population. Overall effects are used to make inferences about effects on the general population and average across total effects and spillover effects. In all completed CRCTs and ring-stratified RCTs, researchers estimated overall effects, comparing all individuals in treatment clusters (including those outside of rings) with all individuals in control clusters (17, 20, 21, 48–50). In the ring trial of the Ebola vaccine, the primary analysis estimated total effects, comparing outcomes among vaccinated individuals in immediate versus delayed vaccinated groups; a secondary analysis estimated overall effects among all eligible individuals in each arm, including unvaccinated individuals (24). No trials estimated spillover effects among untreated individuals in treatment versus control clusters (45).

In CRCTs, it is common to estimate an overall effect, comparing cluster-level outcomes in treatment versus control clusters. However, when ring members compose a small proportion of study clusters, the overall effect can differ substantially from the total effect because study clusters include a large number of untreated individuals. This result may be more likely in elimination and emergency settings, where index cases typically occur in spatiotemporal clusters. For example, in 2 CRCTs in malaria elimination settings in which researchers estimated overall effects, the proportion of cluster members that participated in ring interventions ranged from 2% (20) to 27% (21). On the other hand, in endemic settings, index cases may be more evenly distributed within the study population, and ring members may compose a larger proportion of the study population; in this case, overall effects and total effects may be more similar. Future trials of ring interventions may benefit from estimating each type of effect (total effect, overall effect, and spillover effect, if possible) to shed light on intervention impacts in different subpopulations.

Internal validity

We assessed the risk of bias of 33 completed studies. There was a low risk of bias in 22 studies, some concerns about 8 studies, and high risk of bias in 1 study (Web Table 3). In the following paragraphs, we highlight potential risks of bias specific to ring trials and CRCTs of ring interventions, some of which were not identified during the formal risk-of-bias assessment.

Blinding. The most common threat to internal validity identified in the risk-of-bias assessment was due to lack of blinding; in 11 trials, participants were blinded to their intervention status (51–61); the remainder were unblinded, typically because of the nature of the interventions. Unblinded studies are often more susceptible to measurement bias, particularly if outcome measurement is subjective, and may have lower retention or compliance (62).

Baseline balance. In all but 2 ring trials (60, 63), all ring-stratified trials, and all but 1 CRCT (20), baseline characteristics were balanced between study arms. In 22 trials, researchers used stratified randomization to support baseline balance (Table 1). In CRCTs, if the number of clusters is relatively small, it can be difficult to account for baseline imbalances, even in covariate-adjusted analyses (64). Ring trials and ring-stratified trials are likely to have better baseline balance than CRCTs because randomization occurs after index case detection. This implicitly stratifies study arms by both location and by time, both of which may strongly influence disease incidence. Performing randomization after ring definition was typical in ring trials and ring-stratified trials, with some exceptions (60), but in all CRCTs, cluster randomization was performed prior to ring enrollment. In settings with strong spatiotemporal clustering, ring trials and ring-stratified trials can deliver interventions in the same geographic area, which can improve balance, whereas CRCTs are more vulnerable to imbalances in the number of index cases that occur during follow-up (Figure 2).

Contamination. If there is inadequate social or physical distance between individuals with different treatment assignments, contamination may bias effect estimates toward the null. No ring trials or ring-stratified trials included social or physical buffer zones; however, contamination between rings may be unlikely in household- or facility-based ring trials. Ring-stratified randomized trials (Figure 2B) may be particularly vulnerable to contamination because individuals in the same ring may have different treatment assignments. In rings defined as households or nursing homes, contamination is more likely. Three of 15 CRCTs included geographic buffer zones between clusters to minimize contamination; none included buffer zones inside rings or clusters (Web Table 1). In 1 CRCT in which buffer zones were not included between clusters, researchers assessed possible contamination and did not find evidence of it (20), and in 1 ring trial in which households with index cases were enrolled, researchers reported contamination in which control households adopted intervention behaviors (65). It may be more feasible to include buffers in ring trials than in CRCTs using fixed geographic areas because ring trials are conducted in a small geographic footprint around index cases, leaving more space for buffers. On the other hand, researchers conducting CRCTs in rare-disease settings may need to enroll participants within very large geographic areas to obtain sufficient statistical power, leaving minimal space for buffers. The same principles apply to studies in which rings of participants are enrolled on the basis of contact networks: rings need to be separated by a reasonable number of network nodes to prevent contamination.

Noncompliance. In practice, compliance with random intervention assignment is often imperfect. In trials of ring interventions, noncompliance included 1) eligible index cases did not trigger interventions (incomplete index case coverage); 2) ring members did not receive their assigned intervention (incomplete target population coverage); and 3) ring members received the incorrect intervention. In CRCTs, the level of noncompliance (cluster vs. individual) affects the magnitude of bias (66). Index case coverage ranged from 58% to 100%, and target population coverage ranged from 27% to 100%; both types of coverage were at least 80%, according to most study reports (Web Table 2). In 3 trials, some participants or clusters received the incorrect intervention, but in 2 of these trials, the proportion receiving the incorrect intervention was very small (20, 67, 68).

Ring trials require nimble implementation teams to deliver interventions to any study site location within a short response time. In CRCTs in which clusters are defined in existing administrative areas, it may be easier to establish intervention delivery infrastructure within each cluster, increasing compliance. Even so, compliance can remain a challenge in CRCTs; for example, in 1 trial report, authors stated that staffing and transportation limitations reduced compliance (20).

When noncompliance depends on participant characteristics or is correlated with loss to follow-up, intention-to-treat estimates that ignore noncompliance are biased (69, 70). Two trials investigated this possibility (20, 21); disease incidence in 1 was inversely associated with target population coverage (21). In any trial, when noncompliance occurs, analysis methods must account for posttreatment measures of compliance (66).

External validity

A common critique of trials is that they have poor external validity (71). Indeed, authors of some of the trial reports included in this review cited the need to evaluate ring interventions in multiple sites because benefits of ring interventions may differ between populations (17, 18, 20). Although CRCTs are often considered to have higher external validity than individual randomized controlled trials (RCTs) (72), this is not necessarily the case for trials of ring interventions, because the interventions are delivered to high-risk individuals. External validity of ring trials may be high when the majority of the study population is susceptible and eligibility criteria are inclusive, as was the case in most of the household postexposure prophylaxis studies and other ring trials, such as the Ebola vaccine trial (42). On the other hand, CRCTs of malaria ring interventions were predominantly conducted in low-transmission elimination settings, where infection occurred in hot spots driven by environmental factors and migration (17, 18, 20, 21). Thus, these trials' findings may generalize only to populations with similar spatiotemporal infection patterns, environmental risk factors, and proportions of immune individuals.

Publication bias

All study registrations for studies that had been completed for at least 1 year had published a corresponding preprint or manuscript, suggesting that publication bias was not present.

Statistical power

Factors that affect statistical power of CRCTs are well established (73). Here, we focus on factors that affect power

of ring trials and CRCTs of ring interventions. For several studies included in this review, researchers described insufficient statistical power (20, 49–51, 61, 74, 75). In CRCTs, the number of clusters required per arm commonly is estimated on the basis of the assumed baseline incidence, intraclass correlation (ICC), and true intervention efficacy. In ring trials, additional factors that affect statistical power include the starting day of the follow-up period, probability of case detection, intervention response time, and the force of infection from individuals outside of the ring (39). In a simulation study in which researchers used a mathematical model to investigate sample size requirements for immediate versus delayed Ebola ring vaccination, the factors that had the strongest effect on sample size were the baseline attack rate and the follow-up start day (39).

Probability of case detection. If all detected cases trigger interventions, increasing probabilities of case detection require larger sample sizes, because more frequent intervention will cause incidence to decline if the intervention is effective (39). However, increasing case-detection probabilities may not require larger sample sizes in trials that do not repeat interventions if subsequent index cases occur during the observation period (20, 21).

Baseline incidence. The assumed baseline incidence in sample-size calculations was low for elimination settings and studies during the late stage of an outbreak and was higher in other settings (Web Table 4). The illness rate of contacts, rather than the baseline incidence rate, was used in the power calculations in some studies of Ebola, influenza, and SARS-CoV-2 (24, 63, 65, 76, 77). An advantage of using ring trials rather than CRCTs when evaluating ring interventions in low-incidence settings is that individuals with the highest incidence in a population are enrolled in the former, which may translate to greater statistical power. In reports on 4 trials, including 3 CRCTs, authors stated that statistical power was low due to lower-than-expected incidence during the study period (49, 51, 61, 74). A shared feature of these trials, in contrast to ring trials, is that researchers enrolled a fixed number of individuals or clusters at baseline instead of at the time of index case presentation. By enrolling rings as index cases occur, ring trials are less susceptible to reductions in statistical power resulting from unexpected decreases in incidence. Simulation studies are needed to investigate whether there is a certain incidence level above which a CRCT is more efficient than a ring trial design.

Compliance. Incomplete intervention coverage, longer-than-intended response time, and incorrect intervention delivery may compromise statistical power (78). Even in analyses that account for noncompliance (e.g., as treated, per protocol, instrumental variables), higher levels of noncompliance reduce statistical power (66). Authors of 1 study cited unexpectedly low intervention coverage as a potential explanation for limited statistical power (20). Authors of a modeling study found that a rapid response time was critical to ring intervention efficacy, especially at higher values of R_0 (44).

Ring size. As in any CRCT, for ring trials, the number of clusters (rings) has a larger impact on statistical power than the number of individuals recruited per ring (8, 39). One consideration unique to ring trials is that increasing the ring size (e.g., diameter around the index case or degree of contact network connections enrolled per ring) may reduce the average risk in ring members. If so, increasing the ring size may have little to no benefit to statistical power. To our knowledge, this has not been formally investigated in simulation studies. More research is needed to evaluate the effect of ring size and membership on statistical power.

Intraclass correlation. In CRCTs, the extent of clustering can have a large influence on required sample sizes (79). Accurate ICC estimates are often difficult to obtain during trial planning, especially in emerging infection or emergency settings (39, 72). For example, in the Ebola ring vaccine trial, the observed ICC of 0.14 was substantially higher than the expected ICC of 0.05 (24). For ring trials, ICCs within the ring around index cases are most relevant and may be especially difficult to obtain. Observational studies in which ICCs are estimated in populations adjacent to index cases would support the design of future ring intervention trials (80, 81).

Network structure within and between rings. In none of the studies included in this review was transmission network structure considered in sample size calculations, but in 1 simulation study, researchers showed that transmission network structure can strongly affect statistical power in CRCTs (82). Statistical power reached 0 as the proportion of network connections shared between treatment and control clusters approached 50% (82). These findings may apply to ring trials as well, particularly for ring trials of directly transmitted diseases, and underscore the value of collecting data on spatial and network structure to support sample size calculations. In addition, studies may benefit from using simulations to inform sample-size selection, because using ICCs alone may overestimate statistical power when individuals share contacts between rings (83).

Ring trials versus CRCTs. We note 3 critical differences between ring trials and CRCTs of ring interventions that we would expect to influence study power. First, the numbers of interventions and ring members per arm are balanced by design in ring trials but may be imbalanced in CRCTs when there is high spatiotemporal clustering and unpredictable fluctuations in incidence (e.g., emergency and elimination settings). In 4 CRCTs of ring interventions in which participants composing village or health-facility clusters were enrolled, the number of interventions per arm was not balanced, because the number of index cases varied between arms (20, 21, 48, 61). In 2 of these studies, researchers noted limited statistical power (20, 61). On the other hand, ring trials tended to have balanced numbers of index cases in study arms.

Second, as noted above, ring members may comprise a much smaller proportion of the study population in CRCTs than in ring trials. This is especially the case when index cases cluster spatiotemporally, as is common in emergency and elimination settings. For example, in a ring trial of the

Ebola vaccine, the proportion of ring members was 76%, whereas in 3 CRCTs conducted in malaria elimination and meningitis outbreak settings, the proportion ranged from 2% to 27% (20, 21, 48).

Third, by definition, all clusters in ring trials include an index case and are included in analyses; in CRCTs, because clusters are randomized before index case detection, some clusters may have 0 index cases during follow-up and must be excluded from analyses. Exclusion of some clusters can reduce power in any setting with a rare outcome. For example, in a CRCT in a malaria elimination setting, only 61% of clusters had at least 1 index case, limiting statistical power (20). In a CRCT of influenza in nursing homes, the small number of outbreaks resulted in many clusters having no index cases, increasing the length of the study and reducing study power (61). We did not identify any simulation studies that directly compared statistical power of ring trials versus CRCTs of ring interventions, and this is an important topic for future research.

Ethics

The ethical guidelines for CRCTs largely apply to ring trials (84). We have outlined some ethical considerations unique to ring trials.

Informed consent. In community-based CRCTs, consent is often required both at the cluster and individual levels (84, 85). In low- and middle-income countries, when the cluster is a community, obtaining group-level consent can be difficult, particularly if there is not an elected community leader to provide consent (86). In ring trials, this is complicated because ring members around each index case often do not compose an extant group, such as a school or village. Of the 8 completed trials in which participants composing village clusters were enrolled, both group and individual consent was obtained in 4 (17, 21, 24, 48). In the Ebola ring vaccine trial, researchers obtained from local leaders consent to administer ring vaccination in potential ring sites prior to enrolling ring members (42). Although it may still be important to obtain the support of local leaders to perform a trial, whether it is ethical to obtain consent from them depends on study circumstances. In addition, in CRCTs, individuals often provide consent to participate after clusters have been randomized for logistical reasons, so it is not possible to obtain consent for randomization (84, 86). In the Ebola ring vaccine trial, investigators sought informed consent from ring members after randomization and notified participants of their treatment assignment after consent was given (24).

Beneficence. In the process of enrolling ring members, ring trials must balance the risk of potentially disclosing index case infection status, which could be harmful for stigmatized diseases, with the potential benefits of the ring intervention. This may be particularly difficult for ring trials in which ring members could be identified through contact tracing. In addition, for ring interventions that involve presumptive treatment of individuals without confirmed infection status (e.g., reactive focal mass drug administration), the potential risk of adverse side effects against benefits must be weighed, considering that some participants who experience such side effects may be otherwise healthy. Investigators frequently cited minimization of adverse outcomes as a potential benefit of ring interventions in comparison with interventions delivered to an entire population, and several studies monitored adverse effects as a secondary outcome.

Equipoise. The comparison group for a ring intervention must be chosen to ensure equipoise, especially when there is evidence of intervention effectiveness if it is delivered at the individual level in a clinical setting. For example, in 3 malaria trials, researchers investigated whether treating all individuals near index cases was more effective than treating individuals near index case patients who tested positive according to a rapid diagnostic test (the standard of care) (18, 20, 21). Even though prior trials demonstrated the effectiveness of antimalarials delivered to individuals (87, 88) or through mass drug administration (89, 90), there was not clear evidence about the effectiveness of the potential ring intervention relative to the standard of care; thus, equipoise was present.

Equity. Because ring trials are particularly useful in emergency settings, after trial completion, investigators may consider offering all participants interventions shown to be effective, to ensure equity. This consideration is particularly important in trials in low- and middle-income countries, where participants may have less access to care and cutting-edge therapies (85). In the Ebola ring vaccine trial, delayed vaccination was provided to the control group to assuage potential concerns of withholding treatment (24, 91). Future ring trials could be used in concert with stepped-wedge designs to ensure equity in study populations. Another potential advantage of ring trials, particularly for outbreak and emergency settings, is that ring interventions can immediately be implemented after trial discontinuation, as was done after the Ebola vaccine ring trial (92).

Extensions

Alternative designs. Ring trials are amenable to additional design modifications, such as adaptive designs (93), as were used in the Ebola ring vaccine trial (42), and stepped-wedge designs (94).

Noncommunicable diseases. Although we only identified ring intervention trials with infectious disease endpoints, in principle, ring trials could also be appropriate for noncommunicable diseases or health behaviors that diffuse through networks (e.g., gun violence (95, 96)). Offering interventions to individuals connected to index cases could be particularly useful for outcomes that are stigmatized or underreported (e.g., opioid-use disorders (97)). In addition, ring trials could be used for noncommunicable, vector-borne or environmentally transmitted diseases that tend to cluster spatially or temporally (e.g., Lyme disease, coccidioidomycosis). The design could be particularly useful for studying interventions in populations where climate change

results in the introduction or reintroduction of diseases with environmental risk factors.

Limitations

Our search strategy may not have included all possible terms used to describe ring interventions, so our results may not encompass all prior trials of ring interventions. In our narrative review, we only identified a small number of simulation studies investigating ring interventions; only 1 investigated a ring trial design (39). We consider the paucity of research on this topic an important finding in itself that motivates future research.

CONCLUSION

Ring interventions are well suited to infectious diseases with asymptomatic and heterogeneous transmission. We identified multiple potential advantages of ring trials over ring-stratified trials and CRCTs for evaluating ring interventions. Although each type of trial has its limitations, overall, we identified in this review more potential threats to validity and statistical power in CRCTs of ring interventions and ring-stratified trials than in ring trials, especially in settings with rare and strongly clustered infections. Additional simulation studies are needed to formally compare design features and statistical power of these trial designs. We believe that ring trials hold promise, particularly for evaluations of ring interventions during public health emergencies, seasonal outbreaks, early or waning stages of an epidemic, and disease elimination or eradication settings. To date, novel trial designs have been adopted slowly, particularly in low- and middle-income countries (98). The COVID-19 pandemic has further underscored the urgent need for novel designs, such as the ring trial, that have the potential to maximize investments, reduce cost, and produce rapid, robust results (99).

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REFERENCES

1. Woolhouse ME, Dye C, Etard JF, et al. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. *Proc Natl Acad Sci U S A.* 1997; 94(1):338–342.
2. Lipsitch M, Eyal N. Improving vaccine trials in infectious disease emergencies. *Science.* 2017;357(6347):153–156.
3. Cotter C, Sturrock HJW, Hsiang MS, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. *Lancet.* 2013;382(9895):900–911.
4. Foege WH, Millar JD, Lane JM. Selective epidemiologic control in smallpox eradication. *Am J Epidemiol.* 1971; 94(4):311–315.
5. Corbett MS, Higgins JPT, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Res Synth Methods.* 2014;5(1): 79–85.
6. Ivers NM, Halperin IJ, Barnsley J, et al. Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. *Trials.* 2012;13(1):120.
7. Dean NE, Gsell P-S, Brookmeyer R, et al. Design of vaccine efficacy trials during public health emergencies. *Sci Transl Med.* 2019;11(499):eaat0360.
8. Donner A, Klar N. *Design and Analysis of Cluster Randomization Trials in Health Research*. 1st ed. London, UK: Arnold; 2000.
9. Hemming K, Taljaard M, Moerbeek M, et al. Contamination: how much can an individually randomized trial tolerate? *Stat Med.* 2021;40(14):3329–3351.
10. Torgerson DJ. Contamination in trials: is cluster randomisation the answer? *BMJ.* 2001;322(7282): 355–357.
11. Campbell MJ, Donner A, Klar N. Developments in cluster randomized trials and statistics in medicine. *Stat Med.* 2007; 26(1):2–19.
12. Hayes RJ, Moulton LH. *Cluster Randomised Trials*. 1st ed. New York, NY: Chapman and Hall/CRC; 2009.
13. Okell LC, Bousema T, Griffin JT, et al. Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. *Nat Commun.* 2012;3:1237.
14. Finger F, Bertuzzo E, Luquero FJ, et al. The potential impact of case-area targeted interventions in response to cholera outbreaks: a modeling study. *PLoS Med.* 2018;15(2): e1002509.
15. Michel E, Gaudart J, Beaulieu S, et al. Estimating effectiveness of case-area targeted response interventions against cholera in Haiti. *Elife.* 2019;8:e50243.
16. Rebaudet S, Bulit G, Gaudart J, et al. The case-area targeted rapid response strategy to control cholera in Haiti: a four-year implementation study. *PLoS Negl Trop Dis.* 2019; 13(4):e0007263.
17. Bath D, Cook J, Govere J, et al. Effectiveness and cost-effectiveness of reactive, targeted indoor residual spraying for malaria control in low-transmission settings: a cluster-randomised, non-inferiority trial in South Africa. *Lancet.* 2021;397(10276):816–827.
18. Bridges DJ, Miller JM, Chalwe V, et al. Community-led responses for elimination (CoRE): a study protocol for a community randomized controlled trial assessing the effectiveness of community-level, reactive focal drug administration for reducing plasmodium falciparum infection prevalence and incidence in Southern Province, Zambia. *Trials.* 2017;18(1):511.
19. Eisele TP, Silumbe K, Finn T, et al. Assessing the effectiveness of household-level focal mass drug

administration and community-wide mass drug administration for reducing malaria parasite infection prevalence and incidence in Southern Province, Zambia: study protocol for a community randomized controlled trial. *Trials.* 2015;16:347.
20. Vilakati S, Mngadi N, Benjamin-Chung J, et al. Effectiveness and safety of reactive focal mass drug administration (rfMDA) using dihydroartemisinin-piperaquine to reduce malaria transmission in the very low-endemic setting of Eswatini: a pragmatic cluster randomised controlled trial. *BMJ Glob Health.* 2021; 6(6):e005021.
21. Hsiang MS, Ntuku H, Roberts KW, et al. Effectiveness of reactive focal mass drug administration and reactive focal vector control to reduce malaria transmission in the low malaria-endemic setting of Namibia: a cluster-randomised controlled, open-label, two-by-two factorial design trial. *Lancet.* 2020;395(10233):1361–1373.
22. Sturrock HJW, Novotny JM, Kunene S, et al. Reactive case detection for malaria elimination: real-life experience from an ongoing program in Swaziland. *PLoS One.* 2013; 8(5):e63830.
23. Xu W, Su S, Jiang S. Ring vaccination of COVID-19 vaccines in medium- and high-risk areas of countries with low incidence of SARS-CoV-2 infection. *Clin Transl Med.* 2021;11(2):e331.
24. Henao-Restrepo AM, Camacho A, Longini IM, 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-randomised trial (Ebola Ça Suffit!). *Lancet.* 2017;389(10068):505–518.
25. Grais RF, AJK C, Ferrari MJ, et al. Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. *J R Soc Interface*. 2008;5(18):67–74.
26. Lessler J, Metcalf CJE, Cutts FT, et al. Impact on epidemic measles of vaccination campaigns triggered by disease outbreaks or serosurveys: a modeling study. *PLoS Med.* 2016;13(10):e1002144.
27. Strebel PM, Cochi SL. Waving goodbye to measles. *Nature.* 2001;414(6865):695–696.
28. Andradóttir S, Chiu W, Goldsman D, et al. Reactive strategies for containing developing outbreaks of pandemic influenza. *BMC Public Health.* 2011;11(1):S1.
29. Chowell G, Fuentes R, Olea A, et al. The basic reproduction number R_0 and effectiveness of reactive interventions during dengue epidemics: the 2002 dengue outbreak in Easter Island, Chile. *Math Biosci Eng.* 2013;10(5–6):1455–1474.
30. Trentini F, Poletti P, Baldacchino F, et al. The containment of potential outbreaks triggered by imported chikungunya cases in Italy: a cost utility epidemiological assessment of vector control measures. *Sci Rep.* 2018;8(1):9034.
31. Ndeffo-Mbah ML, Durham DP, Skrip LA, et al. Evaluating the effectiveness of localized control strategies to curtail chikungunya. *Sci Rep.* 2016;6(1):23997.
32. Hitchings MDT, Coldiron ME, Grais RF, et al. Analysis of a meningococcal meningitis outbreak in Niger – potential effectiveness of reactive prophylaxis. *PLoS Negl Trop Dis.* 2019;13(3):e0007077.
33. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019; 366:l4898.
34. Ohrt C, Roberts KW, Sturrock HJW, et al. Information systems to support surveillance for malaria elimination. *Am J Trop Med Hyg.* 2015;93(1):145–152.
35. Kapesa A, Kweka EJ, Zhou G, et al. Utility of passive malaria surveillance in hospitals as a surrogate to community infection transmission dynamics in western Kenya. *Arch Public Health.* 2018;76(1):39.
36. Owada K, Eckmanns T, Kamara K-BO, et al. Epidemiological data management during an outbreak of Ebola virus disease: key issues and observations from Sierra Leone. *Front Public Health.* 2016;4:163–163.
37. Ortuno-Gutierrez N, Younoussa A, Randrianantoandro A, et al. Protocol, rationale and design of PEOPLE (post ExpOsure prophylaxis for LEprosy in the Comoros and Madagascar): a cluster randomized trial on effectiveness of different modalities of implementation of post-exposure prophylaxis of leprosy contacts. *BMC Infect Dis.* 2019; 19(1):1033.
38. Bausch DG, Piot P. Ebola vaccines: biomedical advances, human rights challenges: commentary on: a randomized, blinded, dose-ranging trial of an Ebola virus glycoprotein (EBOVGP) nanoparticle vaccine with matrix-M adjuvant in healthy adults. *J Infect Dis.* 2020;222(4):521–524.
39. Hitchings MDT, Grais RF, Lipsitch M. Using simulation to aid trial design: ring-vaccination trials. *PLoS Negl Trop Dis.* 2017;11(3):e0005470.
40. Dean NE, Halloran ME, Longini IM. Design of vaccine trials during outbreaks with and without a delayed vaccination comparator. *Ann Appl Stat.* 2018;12(1): 330–347.
41. Horne AD, Lachenbruch PA, Goldenthal KL. Intent-to-treat analysis and preventive vaccine efficacy. *Vaccine.* 2000; 19(2–3):319–326.
42. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ.* 2015;351:h3740.
43. Jiang Z, Wang X, Xia J. Considerations on the clinical development of COVID-19 vaccine from trial design perspectives. *Hum Vaccin Immunother.* 2021;17(3):656–660.
44. Kretzschmar M, van den Hof S, Wallinga J, et al. Ring vaccination and smallpox control. *Emerg Infect Dis.* 2004; 10(5):832–841.
45. Benjamin-Chung J, Arnold BF, Berger D, et al. Spillover effects in epidemiology: parameters, study designs and methodological considerations. *Int J Epidemiol.* 2018;47(1): 332–347.
46. Clemens J, Shin S, Ali M. New approaches to the assessment of vaccine herd protection in clinical trials. *Lancet Infect Dis.* 2011;11(6):482–487.
47. Halloran ME, Longini IM, Struchiner CJ. *Design and Analysis of Vaccine Studies*. New York, NY: Springer; 2010.
48. Coldiron ME, Assao B, Page A-L, et al. Single-dose oral ciprofloxacin prophylaxis as a response to a meningococcal meningitis epidemic in the African meningitis belt: a 3-arm, open-label, cluster-randomized trial. *PLoS Med.* 2018;15(6): e1002593.
49. Okebe J, Dabira E, Jaiteh F, et al. Reactive, self-administered malaria treatment against asymptomatic malaria infection: results of a cluster randomized controlled trial in the Gambia. *Malar J.* 2021;20(1):253.
50. Salazar-Austin N, Cohn S, Barnes GL, et al. Improving tuberculosis preventive therapy uptake: a cluster-randomized trial of symptom-based versus tuberculin skin test-based screening of household tuberculosis contacts less than 5 years of age. *Clin Infect Dis.* 2020;70(8): 1725–1732.
51. Echevarría J, Seas C, Carrillo C, et al. Efficacy and tolerability of ciprofloxacin prophylaxis in adult household contacts of patients with cholera. *Clin Infect Dis.* 1995; 20(6):1480–1484.

52. Halperin SA, Bortolussi R, Langley JM, et al. A randomized, placebo-controlled trial of erythromycin estolate chemoprophylaxis for household contacts of children with culture-positive *Bordetella pertussis* infection. *Pediatrics.* 1999;104(4):e42.
53. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA.* 2001;285(6):748–754.
54. Herzog C, Berger R, Fernex M, et al. Intranasal interferon (rIFN-α a, Ro 22-8181) for contact prophylaxis against common cold: a randomized, double-blind and placebo-controlled field study. *Antiviral Res.* 1986;6(3):171–176.
55. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection. *Ann Intern Med.* 2021;174(3):344–352.
56. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med.* 2020;383(4):309–320.
57. Kashiwagi S, Watanabe A, Ikematsu H, et al. Laninamivir octanoate for post-exposure prophylaxis of influenza in household contacts: a randomized double blind placebo controlled trial. *J Infect Chemother.* 2013;19(4):740–749.
58. Kashiwagi S, Watanabe A, Ikematsu H, et al. Long-acting neuraminidase inhibitor laninamivir octanoate as post-exposure prophylaxis for influenza. *Clin Infect Dis.* 2016;63(3):330–337.
59. Nakano T, Ishiwada N, Sumitani T, et al. Inhaled laninamivir octanoate as prophylaxis for influenza in children. *Pediatrics.* 2016;138(6):e20160109.
60. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med.* 2000;343(18):1282–1289.
61. van der Sande MA, Meijer A, Sen-Kerpiclik F, et al. Effectiveness of post-exposition prophylaxis with oseltamivir in nursing homes: a randomised controlled trial over four seasons. *Emerg Themes Epidemiol.* 2014;11:13.
62. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet.* 2002;359(9307):696–700.
63. Ram PK, DiVita MA, Khatun-e-Jannat K, et al. Impact of intensive handwashing promotion on secondary household influenza-like illness in rural Bangladesh: findings from a randomized controlled trial. *PLoS One.* 2015; 10(6):e0125200.
64. Hernández AV, Steyerberg EW, Habbema JDF. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. *J Clin Epidemiol.* 2004;57(5): 454–460.
65. Suess T, Remschmidt C, Schink SB, et al. The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009-2011. *BMC Infect Dis.* 2012;12:26.
66. Moerbeek M, van Schie S. What are the statistical implications of treatment non-compliance in cluster randomized trials: a simulation study. *Stat Med.* 2019; 38(26):5071–5084.
67. Mitjà O, Corbacho-Monné M, Ubals M, et al. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. *N Engl J Med.* 2021;384(5):417–427.
68. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis.* 2004;189(3): 440–449.
69. Lee YJ, Ellenberg JH, Hirtz DG, et al. Analysis of clinical trials by treatment actually received: is it really an option? *Stat Med.* 1991;10(10):1595–1605.
70. Frangakis C, Rubin D. Addressing complications of intention-to-treat analysis in the combined presence of all-or-none treatment-noncompliance and subsequent missing outcomes. *Biometrika.* 1999;86(2):365–379.
71. Stuart EA, Bradshaw CP, Leaf PJ. Assessing the generalizability of randomized trial results to target populations. *Prev Sci.* 2015;16(3):475–485.
72. Dron L, Taljaard M, Cheung YB, et al. The role and challenges of cluster randomised trials for global health. *Lancet Glob Health.* 2021;9(5):e701–e710.
73. Rutterford C, Copas A, Eldridge S. Methods for sample size determination in cluster randomized trials. *Int J Epidemiol.* 2015;44(3):1051–1067.
74. Eisele TP, Bennett A, Silumbe K, et al. Impact of four rounds of mass drug administration with dihydroartemisinin-piperaquine implemented in Southern Province, Zambia. *Am J Trop Med Hyg.* 2020;103(2_Suppl): 7–18.
75. Cowling BJ, Fung ROP, Cheng CKY, et al. Preliminary findings of a randomized trial of non-pharmaceutical interventions to prevent influenza transmission in households. *PLoS One*. 2008;3(5):e2101.
76. Smit M, Marinosci A, Nicoletti GJ, et al. Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomised trial. *BMJ Open.* 2020; 10(11):e040110.
77. Tan DHS, Chan AK, Jüni P, et al. Post-exposure prophylaxis against SARS-CoV-2 in close contacts of confirmed COVID-19 cases (CORIPREV): study protocol for a cluster-randomized trial. *Trials.* 2021;22(1):224.
78. Jo B, Asparouhov T, Muthén BO. Intention-to-treat analysis in cluster randomized trials with noncompliance. *Stat Med.* 2008;27(27):5565–5577.
79. Cornfield J. Randomization by group: a formal analysis. *Am J Epidemiol.* 1978;108(2):100–102.
80. Hsiang MS, Ntshalintshali N, Kang Dufour M-S, et al. Active case finding for malaria: a 3-year national evaluation of optimal approaches to detect infections and hotspots through reactive case detection in the low-transmission setting of Eswatini. *Clin Infect Dis.* 2020;70(7): 1316–1325.
81. Smith JL, Auala J, Tambo M, et al. Spatial clustering of patent and sub-patent malaria infections in northern Namibia: implications for surveillance and response strategies for elimination. *PLoS One.* 2017;12(8): e0180845.
82. Staples PC, Ogburn EL, Onnela J-P. Incorporating contact network structure in cluster randomized trials. *Sci Rep.* 2015;5(1):17581.
83. Halloran ME, Auranen K, Baird S, et al. Simulations for designing and interpreting intervention trials in infectious diseases. *BMC Med.* 2017;15(1):223.
84. Weijer C, Grimshaw JM, Eccles MP, et al. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. *PLoS Med.* 2012;9(11): e1001346.
85. Choko AT, Roshandel G, Conserve DF, et al. Ethical issues in cluster randomized trials conducted in low- and middle-income countries: an analysis of two case studies. *Trials.* 2020;21(1):314.
86. Osrin D, Azad K, Fernandez A, et al. Ethical challenges in cluster randomized controlled trials: experiences from

public health interventions in Africa and Asia. *Bull World Health Organ.* 2009;87(10):772–779.
87. Zani B, Gathu M, Donegan S, et al. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst Rev.* 2014;2014(1):CD010927.
88. WorldWide Antimalarial Resistance Network (WWARN) Lumefantrine PK/PD Study Group. Artemether-lumefantrine treatment of uncomplicated *Plasmodium falciparum* malaria: a systematic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data. *BMC Med.* 2015;13:227.
89. Poirot E, Skarbinski J, Sinclair D, et al. Mass drug administration for malaria. *Cochrane Database Syst Rev.* 2013;2013(12):CD008846.
90. Newby G, Hwang J, Koita K, et al. Review of mass drug administration for malaria and its operational challenges. *Am J Trop Med Hyg.* 2015;93(1):125–134.
91. Rid A, Miller FG. Ethical rationale for the Ebola "ring vaccination" trial design. *Am J Public Health.* 2016;106(3): 432–435.
92. Gsell P-S, Camacho A, Kucharski AJ, et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. *Lancet Infect Dis.* 2017;17(12):1276–1284.
93. Chow S-C, Chang M. *Adaptive Design Methods in Clinical Trials*. 2nd ed. Boca Raton, FL: Taylor & Francis; 2012.
94. Bellan SE, Pulliam JRC, Pearson CAB, et al. Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis. *Lancet Infect Dis.* 2015;15(6):703–710.
95. Larsen DA, Lane S, Jennings-Bey T, et al. Spatio-temporal patterns of gun violence in Syracuse, New York 2009-2015. *PLoS One.* 2017;12(3):e0173001.
96. Tracy M, Braga AA, Papachristos AV. The transmission of gun and other weapon-involved violence within social networks. *Epidemiol Rev.* 2016;38(1):70–86.
97. Kumar N, Oles W, Howell BA, et al. The role of social network support in treatment outcomes for medication for opioid use disorder: a systematic review. *J Subst Abuse Treat.* 2021;127:108367.
98. Park JJH, Grais RF, Taljaard M, et al. Urgently seeking efficiency and sustainability of clinical trials in global health. *Lancet Glob Health.* 2021;9(5):e681–e690.
99. Park JJH, Mogg R, Smith GE, et al. How COVID-19 has fundamentally changed clinical research in global health. *Lancet Glob Health.* 2021;9(5):e711–e720.
100. Barnabas RV, Brown E, Bershteyn A, et al. Efficacy of hydroxychloroquine for post-exposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among adults exposed to coronavirus disease (COVID-19): a structured summary of a study protocol for a randomised controlled trial. *Trials.* 2020;21(1):475.
101. Bridges DJ. Community-Led Responses for Elimination: controlled trial of reactive case detection versus reactive drug administration (CORE Zambia). ClinicalTrials.gov identifier NCT02654912. 2016. Last updated February 4, 2021. https://clinicaltrials.gov/ct2/show/NCT02654912. Accessed April 1, 2021.
102. Coldiron ME, Alcoba G, Ciglenecki I, et al. Ciprofloxacin for contacts of cases of meningococcal meningitis as an epidemic response: study protocol for a cluster-randomized trial. *Trials.* 2017;18(1):294.
103. Egsmose T, Ang'awa JO, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bull World Health Organ.* 1965;33(3): 419–433.
104. Eisele TP, Bennett A, Silumbe K, et al. Short-term impact of mass drug administration with dihydroartemisinin plus piperaquine on malaria in Southern Province Zambia: a cluster-randomized controlled trial. *J Infect Dis.* 2016; 214(12):1831–1839.
105. Fritz SA, Hogan PG, Hayek G, et al. Household versus individual approaches to eradication of community-associated *Staphylococcus aureus* in children: a randomized trial. *Clin Infect Dis.* 2012;54(6): 743–751.
106. George CM, Monira S, Zohura F, et al. Effects of a water, sanitation and hygiene mobile health program on diarrhea and child growth in Bangladesh: a cluster-randomized controlled trial of the CHoBI7 mobile health program. *Clin Infect Dis.* 2021;73(9):e2560–e2568.
107. Masud J, Islam Bhuyian MS, Kumar Biswas S, et al. Diarrhoeal disease knowledge among diarrhoea patient housholds: findings from the randomised controlled trial of the cholera-hospital-based-intervention-for-7-days (CHoBI7) mobile health program. *Trop Med Int Health.* 2020;25(8):996–1007.
108. Kaiser L, Henry D, Flack NP, et al. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. *Clin Infect Dis.* 2000;30(3): 587–589.
109. Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet.* 2015; 386(9996):857–866.
110. Medzihradsky OF, Kleinschmidt I, Mumbengegwi D, et al. Study protocol for a cluster randomised controlled factorial design trial to assess the effectiveness and feasibility of reactive focal mass drug administration and vector control to reduce malaria transmission in the low endemic setting of Namibia. *BMJ Open.* 2018;8(1): e019294.
111. Hsiang MS. Evaluation of Reactive Focal Mass Drug Administration (rfMDA) +/− Reactive Focal Vector Control (RAVC) in Namibia. ClinicalTrials.gov identifier NCT02610400. 2015. Last updated July 17, 2020. https://clinicaltrials.gov/ct2/show/NCT02610400. Accessed April 1, 2021.
112. Iturriaga C, Eiffler N, Aniba R, et al. A cluster randomized trial of interferon β-1a for the reduction of transmission of SARS-Cov-2: protocol for the Containing Coronavirus Disease 19 Trial (ConCorD-19). *BMC Infect Dis.* 2021; 21(1):814–814.
113. Low N, McCarthy A, Roberts TE, et al. Partner notification of chlamydia infection in primary care: randomised controlled trial and analysis of resource use. *BMJ.* 2006; 332(7532):14–19.
114. Murphy TV, Chrane DF, McCracken GHJ, et al. Rifampin prophylaxis v placebo for household contacts of children with *Hemophilus influenzae* type b disease. *Am J Dis Child.* 1983;137(7):627–632.
115. Nanni O, Viale P, Vertogen B, et al. PROTECT trial: a cluster-randomized study with hydroxychloroquine versus observational support for prevention or early-phase treatment of coronavirus disease (COVID-19): a structured summary of a study protocol for a randomized controlled trial. *Trials.* 2020;21(1):689.

116. de Jong B, Hasker E, Assoumani Y, et al. Post ExpOsure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE). ClinicalTrials.gov identifier NCT03662022. 2018. https://ClinicalTrials.gov/show/NCT03662022. Accessed August 25, 2021.
117. Sagliocca L, Amoroso P, Stroffolini T, et al. Efficacy of hepatitis a vaccine in prevention of secondary hepatitis a infection: a randomised trial. *Lancet.* 1999;353(9159): 1136–1139.
118. Seddon JA, Garcia-Prats AJ, Purchase SE, et al. Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP). *Trials.* 2018; 19(1):693.
119. Calmy A, Labhardt ND. Efficacy of Pragmatic Same-Day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP). ClinicalTrials.gov identifier NCT04364022. 2020. https://clinicaltrials.gov/ct2/show/NCT04364022. Accessed April 1, 2021.
120. van der Sande MA. A Randomised Controlled Trial on the Effect of Post-Exposure Oseltamivir Prophylaxis on Influenza Transmission in Nursing Homes (PEPpIE). ClinicalTrials.gov identifier NCT01053377. 2010. Updated January 21, 2010. https://ClinicalTrials.gov/show/NCT01053377. Accessed August 25, 2021.
121. Vasiliu A, Eymard-Duvernay S, Tchounga B, et al. Community intervention for child tuberculosis active contact investigation and management: study protocol for a parallel cluster randomized controlled trial. *Trials.* 2021;22(1):180.
122. Hsiang MS. Evaluation of Reactive Focal Mass Drug Administration for Malaria Elimination in Swaziland (fMDA). ClinicalTrials.gov identifier NCT02315690. 2014. https://clinicaltrials.gov/ct2/show/NCT02315690. Accessed April 1, 2021.
123. Wamuti BM, Erdman LK, Cherutich P, et al. Assisted partner notification services to augment HIV testing and linkage to care in Kenya: study protocol for a cluster randomized trial. *Implement Sci.* 2015;10:23.
124. Cherutich P, Golden MR, Wamuti B, et al. Assisted partner services for HIV in Kenya: a cluster randomised controlled trial. *Lancet HIV.* 2017;4(2):e74–e82.
125. Wang R, DeGruttola V, Lei Q, et al. The Vitamin D for COVID-19 (VIVID) Trial: a pragmatic cluster-randomized design. *Contemp Clin Trials.* 2021;100:106176.
126. Wingfield T, Tovar MA, Huff D, et al. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. *Bull World Health Organ.* 2017;95(4):270–280.
127. Agrawal R. Safety And Efficacy of Hydroxychloroquine for At Risk Population (SHARP) Against COVID-19 (SHARP COVID-19). ClinicalTrials.gov identifier NCT04342156. 2020. Updated October 8, 2020. https://ClinicalTrials.gov/show/NCT04342156. Accessed August 25, 2021.
128. Bardin M. Trial to evaluate the efficacy and safety of nitazoxanide (NTZ) for post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (LTCF). ClinicalTrials.gov identifier NCT04343248. 2020. Updated April 1, 2021. https://ClinicalTrials.gov/show/NCT04343248. Accessed August 25, 2021.
129. Bennett A, Vanisaveth V. Targeting high risk populations with enhanced reactive case detection in Southern Lao Peoples Democratic Republic (COMBAT). ClinicalTrials.gov identifier NCT04416945. 2020. https://clinicaltrials.gov/ct2/show/NCT04416945. Accessed April 1, 2021.
130. Borrie M. COVID-19 PEP- high-risk individuals in long-term and specialized care - Canada. ClinicalTrials.gov identifier NCT04397328. 2020. Updated May 21, 2020. https://ClinicalTrials.gov/show/NCT04397328. Accessed August 25, 2021.
131. Bracchi A, Flego M. PREvent Viral Exposure aNd Transmission Study: a SARS-CoV-2 PEP Study (PREVENT). ClinicalTrials.gov identifier NCT04842331. 2021. Updated April 13, 2021. https://ClinicalTrials.gov/show/NCT04842331. Accessed August 25, 2021.
132. Elvira M. Airborne Preventive Measures to Reduce New TB Infections in Household Contacts (TBMask). ClinicalTrials.gov identifier NCT04938596. 2021. https://ClinicalTrials.gov/show/NCT04938596. Accessed August 25, 2021.
133. Gadisa E. Evaluation of targeted mass drug administration for malaria in Ethiopia. ClinicalTrials.gov identifier NCT. 2020. Updated June 12, 2020. https://clinicaltrials.gov/ct2/show/NCT04241705. Accessed April 1, 2021.
134. Giles J. Hydroxychloroquine post exposure prophylaxis for coronavirus disease (COVID-19). ClinicalTrials.gov identifier NCT04318444. 2020. April 27, 2020. https://ClinicalTrials.gov/show/NCT04318444. Accessed August 25, 2021.
135. Malin R. A study to test whether BI 767551 can prevent COVID-19 in People who have been exposed to SARS-CoV-2. ClinicalTrials.gov identifier NCT04894474. 2021. https://ClinicalTrials.gov/show/NCT04894474. Accessed August 25, 2021.
136. McGeer A. Control of COVID-19 outbreaks in long term care. ClinicalTrials.gov identifier NCT04448119. 2020. https://ClinicalTrials.gov/show/NCT04448119. Accessed August 25, 2021.
137. Sued O. Efficacy and safety of nitazoxanide for post exposure prophylaxis of COVID-19 in household contacts (PENTZ). ClinicalTrials.gov identifier NCT04788407. 2021. Updated July 2, 2021. https://ClinicalTrials.gov/show/NCT04788407. Accessed August 25, 2021.