VACCINES

Design of vaccine efficacy trials during public health emergencies

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Public health emergencies, such as an Ebola disease outbreak, provide a complex and challenging environment for the evaluation of candidate vaccines. Here, we outline the need for flexible and responsive vaccine trial designs to be used in public health emergencies, and we summarize recommendations for their use in this setting.

INTRODUCTION

The recent public health emergencies surrounding the 2014–2016 West African Ebola virus outbreak and the 2015–2016 Zika virus outbreak have demonstrated that the global community is unprepared to evaluate candidate vaccines in affected countries despite decades of research into vaccine development on emerging pathogens (*1*). For example, preclinical and early clinical studies of candidate vaccines for emerging pathogens have not been completed due to inadequate coordination among governments, nongovernmental organizations (NGOs), and the private sector. Infrastructure for conducting clinical research in affected areas is limited and strained by the outbreak response. The timeline for writing, approving, and implementing protocols is dramatically compressed.

Epidemics caused by pathogens with no licensed vaccine will undoubtedly emerge in the future, and the public health community must be prepared to rapidly evaluate experimental vaccines in such circumstances. To address this challenge, the World Health Organization (WHO) convened a group of statisticians, clinical trialists, infectious disease modelers, and researchers as part of its R&D Blueprint Plan of Action (*2*). The mission of this group was to develop a consensus on vaccine study designs for the rapid evaluation of vaccine candidates that would address scientific, ethical, and logistical issues arising during public health emergencies. Discussions were framed on the basis of the Blueprint priority diseases (*3*), which were selected for their likelihood to cause public health emergencies and for the lack of adequate medical countermeasures. The Blueprint priority disease list is to be updated annually by an expert panel. The 2018 list includes Crimean-Congo hemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS), Nipah virus and henipaviral diseases, Rift Valley fever, Zika virus disease, and disease X (a future unknown threat).

The principal goal of a vaccine efficacy trial is to obtain efficacy and effectiveness data that can support broader use of a vaccine under a defined regulatory framework. In the context of a disease outbreak, vaccine evaluation also provides a way to give access in the affected communities to the most promising experimental vaccines and potentially to help control the outbreak should the vaccine prove to be effective. In this process, we need to ensure that the experimental vaccine is demonstrated to be safe and effective and that it is used with an adequate community engagement and delivery strategy. Conducting vaccine evaluation in public health emergencies is associated with methodological and operational challenges (*4*, *5*). The epidemiology of an infectious disease, sociocultural aspects, and outbreak circumstances affect the choices that must be made when designing a vaccine trial or study.

There is limited knowledge about the transmission dynamics and the natural history of the Blueprint priority diseases. These pathogens are prone to cause epidemics where the spatiotemporal incidence of the disease may be highly variable and unpredictable. Unlike endemic diseases, outbreaks end or are contained to a point such that only sporadic cases occur. Furthermore, outbreaks may typically last only a few weeks, and it may take 1 to 2 weeks for an outbreak to be detected and confirmed. In settings with poor surveillance, it may take even longer. These epidemiological and operational aspects make it difficult for studies to identify, enroll, and vaccinate at-risk participants before exposure, as well as to define the appropriate endpoints to estimate vaccine efficacy and effectiveness. Given the urgency, very little may be known about the vaccine candidate in terms of safety and immunogenicity in humans or in terms of thermostability and other properties. Importantly, vaccine evaluation may also take place in a setting with unvalidated and nonstandardized diagnostics and serological assays, which poses considerable challenges for case ascertainment and endpoint measurement.

Outbreak circumstances are complex, and each outbreak has different characteristics. Typically, a public health emergency may trigger the rapid development of a number of vaccine candidates that could be tested in affected countries if the outbreak persists. As a result, trial sponsors may compete for study sites and populations. In addition, research in epidemic management is relatively new. The conduct of research needs to be fully integrated into the international effort to control the disease and should not be performed at the expense of the broader response to a public health emergency. Last, there may be fears and misconceptions among the affected communities.

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Involving communities in the study implementation and complying with good participatory practices for research (*6*) are essential to increase acceptability of the intervention and preserve the integrity of the trial.

Double-blind, placebo-controlled, individually randomized vaccine trials provide robust evidence that may inform licensure and broader use of a vaccine. However, because of the epidemiological situation and the working environment in public health emergencies, trialists may be compelled to consider alternative study designs. As part of the Blueprint working group on vaccine evaluation, we discuss here the major vaccine study designs that should be considered during public health emergencies caused by emerging and reemerging pathogens for which there are no licensed vaccine. We discuss study endpoints, the target population, the randomization strategy, the comparator arm, the primary statistical analysis, and data monitoring from the point of view of challenges and potential trade-offs.

ENDPOINTS FOR VACCINE CLINICAL TRIALS

Clinical study endpoints should be selected to support the broader intended use of a vaccine as described in the WHO vaccine target product profile, which provides a summary of desired characteristics of a target product for a given pathogen. They should be representative of the public health outcome caused by that particular pathogen that must be reduced, usually symptomatic or severe disease (table S1). Two types of commonly desired vaccines are (i) fast-acting vaccines amenable to use reactively during outbreaks to interrupt chains of transmission and terminate outbreaks and (ii) durable vaccines that can be used preventatively in targeted populations to maximize the public health impact of the vaccine. Preventive vaccines are especially valuable for protecting against endemic diseases, such as Lassa fever, and may be prioritized for use in high-risk populations, such as health care workers. For pathogens without a developed target product profile (e.g., for disease X), the same basic principles are expected to apply especially if the new pathogen produces an acute viral disease with a similar pattern of spillover from the animal (zoonotic) reservoir to humans.

In practice, it may not be feasible to implement a vaccine trial with large enough sample sizes using the endpoints that are representative of the public health burden, such as clinical disease. In addition, if the diagnostic assays are poor, or there is limited infrastructure, then endpoints requiring laboratory confirmation may be difficult to obtain. For instance, although cases of microcephaly represent the major public health burden associated with Zika virus infection, the choice of more frequent clinical events as a primary outcome measure for vaccine efficacy trials would likely be necessary to ensure feasible sample sizes (*7*). The justification of a mild, more common endpoint as the primary endpoint in vaccine trials would be predicated on the assumption that the benefit of the vaccine on the selected endpoint is reasonably likely to predict clinical benefit for the endpoint of public health interest.

Methodological options for such vaccine trials include clinical disease endpoints, infection endpoints, or immune correlates of vaccine-induced protection. Clinical disease endpoints, such as severe disease or disease of any severity, may be clinically or laboratory confirmed. A clinical disease endpoint without laboratory confirmation should only be considered for pathogens with a highly distinct clinical syndrome, and these studies should consider laboratory testing of a random sample of cases to internally estimate how frequently cases are misclassified (*8*). For infection endpoints, detection of acute infection in the absence of clinical disease may require frequent laboratory testing and so may be operationally challenging. Detection of seroconversion would require an assay that could distinguish natural infection from vaccine-induced immunity. Vaccine trials are encouraged to collect serological data at baseline and after vaccination to measure potential immunological correlates of vaccine-induced protection (*9*). Where available, validated immunological correlates can be used to infer the efficacy of a vaccine, but they are unlikely to exist for emerging pathogens or for new vaccine platforms. Nonetheless, immune correlate data can be used along with other data sources to demonstrate a reasonable likelihood that the vaccine is efficacious when a clinical disease or infection endpoint is not feasible.

For Zika vaccine efficacy trials, although there are likely many more asymptomatic infections than clinical disease cases, selecting an endpoint related to Zika virus infection would rely on a robust laboratory capacity and active surveillance system. However, licensed diagnostics for Zika virus infection are limited, and serological assays are cross-reactive with other arboviruses such as dengue virus. Virologically confirmed Zika clinical disease is a more feasible primary endpoint for a Zika vaccine efficacy trial because of the challenges of detecting infection endpoints, but Zika clinical disease will require a larger overall trial (*7*). Because Zika disease symptoms are nonspecific and may be mistaken for other arboviral diseases, laboratory confirmation is critical.

The take home message. The demonstration of a vaccine's benefit based on a laboratory-confirmed clinical disease endpoint is the recommended way to evaluate a vaccine because it is often most representative of the public health burden of interest. In some settings, infection or other endpoints may be justified as proxies. The use of immunological correlate data may be necessary if clinical disease or infection endpoints are not feasible. Clinical study endpoints may differ from those desired from a public health perspective in the vaccine target product profile, but the benefit would have to be validated in future studies.

THE TARGET POPULATION FOR VACCINE CLINICAL TRIALS

The vaccine clinical trial population should be representative of the target population defined in the vaccine target product profile or based on what is known about the pathogen's epidemiology. It may not be feasible to obtain a sufficient sample size by targeting a study population representative of the public health burden, for example, prevention of Zika virus infection in women of reproductive age (*7*). Because the incidence of new cases of Zika virus infection is extremely variable in public health emergencies, it may be challenging to identify a predefined population in a given area that is at risk and fully susceptible to disease transmission.

Vaccine clinical studies may target areas at highest geographic risk for disease transmission. Studies may further narrow the target population to those with other risk factors that make them at highest risk of infection, such as occupation or contact with high-risk individuals. For example, individuals and their household contacts who have direct contact with camels are at increased risk of infection with MERS-CoV. A targeted approach to vaccination may require a smaller overall sample size if the incidence is truly higher in these individuals, although it may be harder to identify, enroll, and track such participants compared to the general population.

A responsive target population is a study population in which enrollment and vaccination are triggered by the occurrence of a

new case. For instance, the study population enrolled in the Ebola ring vaccination trial in Guinea (*10*) was a responsive study population enrolling contacts and contacts of contacts of confirmed cases. For vector-borne diseases, such as Zika, the study population may be defined by geographic proximity to a case. A responsive approach is intended to track the epidemic as it progresses and focuses the intervention where the risk is highest. This approach relies on a sensitive and rapid surveillance system to inform the study in real time as well as a mobile vaccine delivery system. Such a study design works best for single-dose vaccines that evoke a quick immune response and for infectious diseases that spread relatively slowly through predictable contact networks. For rapidly spreading diseases, it may be necessary to use broader inclusion criteria to capture later generations of disease transmission. For example, while the typical ring vaccination strategy includes first-order and second-order contacts, one may add third-order contacts or everyone residing within a fixed distance of the case. It may also be advantageous to monitor preselected high-risk sites to speed responsive vaccination. For example, vaccine trials for Lassa fever could include heightened surveillance in areas where cases are most frequently detected, with rapid vaccination of participants when disease transmission is observed.

The take home message. Clinical trials that responsively enroll participants are appropriate in areas where the transmission dynamics are extremely unpredictable. Because they focus the intervention where the transmission and risk exposure are occurring, the statistical power is expected to increase and the required sample size is expected to decrease. Computational disease modeling can be used to predict trial participant accrual rates and to inform sample size selection (*11*).

RANDOMIZATION OF VACCINE CLINICAL TRIALS

Clinical trial randomization of study participants to receive vaccine or a comparator (e.g., placebo or a vaccine targeting an unrelated but geographically relevant disease) provides assurance that the groups being compared are similar except for the intervention being studied. The use of randomization has been strongly debated in the context of the West African Ebola outbreak (*12*–*14*) because its use may deny persons an opportunity to have access to a potentially effective vaccine in a situation with high mortality and lack of adequate medical countermeasures. Experts argued that randomized trials are the most reliable and rapid way to identify the relative benefits and risks of investigational products and that every effort should be made to implement clinical trial designs with random group assignments during outbreaks and epidemics (*5*, *13*). Our group concurs with this recommendation. Randomized clinical trials are the study design of choice in public health emergencies, and deviation from the use of randomized clinical trial designs should occur only under exceptional circumstances after a robust risk-benefit analysis. For instance, if there is sufficient evidence of the safety and effectiveness of an investigational vaccine and there is no satisfactory alternative, then the use of randomization may raise ethical concerns and acceptability among the affected populations.

METHODOLOGICAL OPTIONS FOR RANDOMIZATION

There are different forms of appropriate randomized vaccine trials (Fig. 1). The unit of randomization can be at the individual or cluster level with various levels of stratification as needed.

Randomization at the individual level. In an individually randomized controlled trial (iRCT), participants are randomized within each study site (Fig. 1). Sites could be defined responsively or from natural groupings of people at high risk of infection (e.g., health care workers). The iRCT is a statistically efficient design, especially when there is substantial heterogeneity in incidence across study sites. The primary analysis estimates the individual-level reduction in susceptibility to disease or infection ("direct vaccine effect" or sometimes "vaccine efficacy"). Population-level effects of vaccination, including indirect protection, are typically not estimated (*15*). If indirect vaccine protection is high, then one concern is that transmission within the study site could be dramatically reduced in both the vaccine and comparator arms of the trial such that it becomes difficult to measure vaccine efficacy (*16*). More than one vaccine candidate may be suitable for efficacy testing, in which case, multi-arm trials sharing a single placebo or comparator vaccine arm would be possible, requiring fewer resources than multiple, independent two-arm trials (Fig. 1) (*17*). This approach is attractive because it provides a method to simultaneously evaluate multiple vaccine candidates and has the potential to diversify the number and supply of vaccines available. This approach has been determined to be optimal for Zika vaccine trials where future disease transmission will probably occur in different geographic clusters in pockets of still susceptible populations.

Factorial trials permit simultaneous evaluation of a vaccine and an innovative non-vaccine intervention (e.g., vector control) targeting the same disease. For example, participants may be individually randomized to vaccine or placebo, and the non-vaccine intervention may be individually randomized or cluster-randomized (Fig. 1). For diseases that spread in the environment, such as cholera in contaminated water sources, sites could be cluster-randomized to water, sanitation, and hygiene interventions. Factorial trials (individual randomization for vaccination with either individual or cluster randomization to the non-vaccine intervention) conserve resources by using the same population and trial infrastructure (*18*). Where the non-vaccine intervention is effective at reducing disease in the study population, however, the power to detect vaccine efficacy will also be reduced.

Randomization at the cluster level. In cluster trials, all participants within a cluster are assigned to the same intervention. In parallel cluster randomized controlled trials (cRCTs), study sites (e.g., high-risk communities) or small groups (e.g., households) are randomized as a unit to receive vaccine or a comparator (Fig. 1). Clusters may be defined responsively, for example, the contact-based rings in the Ebola ring vaccination trial (*10*), such that they naturally capture infectious disease transmission networks (*19*). The primary analysis estimates total vaccine effectiveness, which measures the individual-level benefit of the vaccine resulting from the combination of direct and indirect (e.g., herd immunity) vaccine effects (*15*). If data collection is expanded to include nonparticipants, then the trial can generate estimates of indirect and overall effects of vaccination. A form of this strategy was used in the Ebola ring vaccination trial (*20*). Parallel cRCTs are subject to a number of biases that can reduce interpretability of the results (*19*). Furthermore, clustered design trials are less statistically efficient than individually randomized design trials, especially when there is great heterogeneity across clusters.

In stepped wedge cRCTs, the vaccine is delivered to all clusters but in a randomized order. In public health emergencies, these trial designs have important disadvantages, primarily because they are complex to plan, implement, and analyze (*19*). Stepped wedge cRCTs are inflexible because all of the participants and

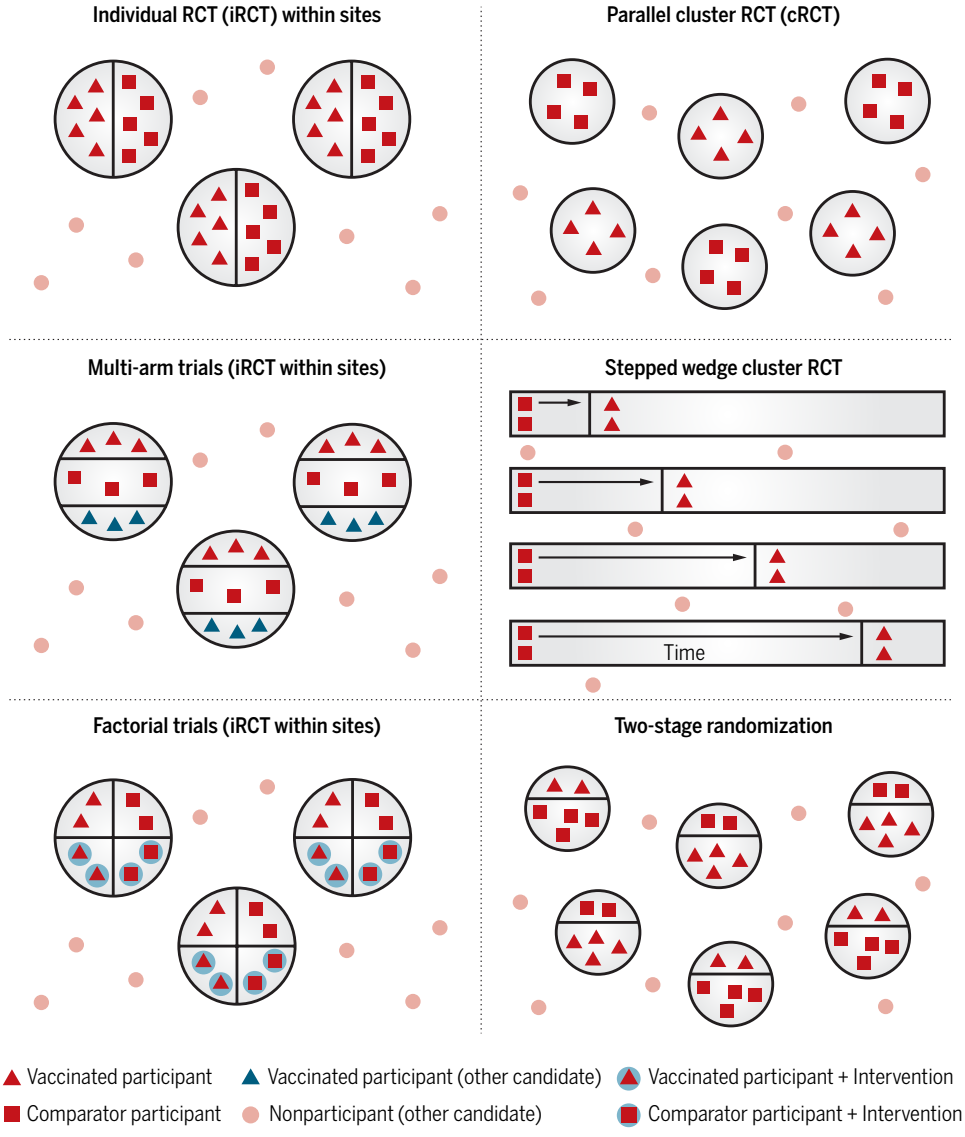

Fig. 1. The different forms of randomized clinical trials for testing experimental vaccines. (**Left**) Shown are different forms of iRCTs. In iRCTs, randomization can be of individual participants within sites (**top**). iRCTs also can be multi-arm trials where two or more vaccine candidates are evaluated against a common comparator (**middle**); they also can be factorial trials where a vaccine and another non-vaccine intervention are evaluated simultaneously (**bottom**). (**Right**) Randomized controlled trials can also be clustered (cRCTs). In parallel cRCTs, study sites (e.g., high-risk communities) or small groups (e.g., households) are randomized as a unit to receive vaccine or a control comparator with randomization at the cluster level (top). In stepped wedge cRCTs, vaccine is administered in a random order (middle). cRCTs can also have a two-stage randomization in which clusters are randomized to high or low vaccine coverage followed by individual randomization (bottom).

facilities must be enrolled before the first dose of vaccine can be administered. Stepped wedge cRCTs probably result in the slowest trials and are not well suited for endpoints with a spatiotemporally variable incidence (*21*).

Two-stage randomized trial designs, in which clusters are randomized to a level of vaccine coverage (e.g., 20 or 80%) and participants are individually randomized to achieve this coverage (Fig. 1), are one of the only designs to support relatively unbiased estimation of both direct and indirect vaccine effects (*22*). An important disadvantage of the study design is its complexity, and there is no precedent for such a design in vaccine trials.

The take home message. Despite the challenging circumstances of a public health emergency, trial randomization, whether at the individual or cluster level, remains a key principle in vaccine evaluation. Deviation from the use of randomized designs should occur only under exceptional circumstances. For public health emergencies, we recommend randomized trial designs that are compatible with the enrollment of a responsive target population. For estimating vaccine efficacy, individual randomization within responsively defined sites will typically require the smallest overall sample size. Cluster randomization trials can provide an individual-level measure of vaccine efficacy by measuring total vaccine effectiveness as well as population-level indirect effects, whereas individual randomization trials only measure direct vaccine effects (*15*).

COMPARATOR CONTROLS FOR VACCINE TRIALS

A common model for evaluating and deploying a new vaccine against a disease for which there is no existing vaccine is that it is first tested in a clinical trial with a placebo as a control or with an unrelated vaccine as a control. The use of blinding (or masking) as is required with the use of a control reduces the potential for selection bias, detection bias, and performance bias (23). As with randomization, the use of a placebo has been strongly debated in the context of the West African Ebola outbreak (*24*) and will likely be debated in future public health emergencies.

Researchers should consider whether the risks associated with use of the placebo, that is, the risks of the placebo intervention itself and those of withholding or delaying a vaccine with evidence of efficacy and effectiveness, are minimal, preventable, or reversible. Risks greater than these may constrain the use of a placebo.

During public health emergencies, a delayed vaccination arm as the comparator may be adopted in which individuals or clusters of individuals are allocated to either immediate or delayed vaccination. A delayed vaccination approach was used as a comparator arm and implemented in the Ebola ring vaccination trial in Guinea in 2015–2016 (*20*, *25*) and in the Ebola iRCT trial in Sierra Leone in 2015–2016 (*26*). Motivations for the use of a delayed comparator include improved acceptability, providing vaccine to individuals whose need is greatest, and

promoting control of the epidemic if the vaccine is efficacious. However, if the vaccine is ineffective or unsafe, then more people are exposed to the vaccine than in a trial that has a placebo or unrelated vaccine control. Trials using delayed vaccination are expected to have lower power than placebo-controlled trials, and the vaccine efficacy estimates may be biased (*27*). To reduce bias, the length of the delay should be relatively long compared to the disease incubation period and the time required for the immune response to develop to the vaccine.

In settings where an existing vaccine has already been established to provide a clinically meaningful benefit, an experimental vaccine may have potential advantages other than efficacy; such as a more favorable tolerability or safety profile; more convenient storage, transport, or administration, or lower cost. It might be sufficient for the experimental vaccine to have similar rather than superior efficacy relative to the existing vaccine, which can be evaluated in a non-inferiority trial (*28*). A non-inferiority trial is designed to assess whether an experimental product is at least as effective as an existing product. Depending on the size of the non-inferiority margin (minimum threshold for an unacceptable loss of efficacy), non-inferiority trials may require large sample sizes that make them challenging in the setting of a public health emergency.

The take home message. Although the use of a placebo or an unrelated control vaccine provides a robust methodological standard and can allow for blinding to protect against many real or perceived biases, the use of delayed vaccination as a comparator can be explored under certain circumstances.

PRIMARY STATISTICAL ANALYSIS OF VACCINE CLINICAL TRIALS

The estimated effects of a vaccine may be sensitive to the primary statistical analysis used, especially the inclusion of cases with illness onset shortly after vaccination. Cases that occur immediately after vaccination are likely to be the result of infection before vaccination or before the development of a robust immune response. For responsive vaccination strategies, the period of highest incidence in the target population may be around the time of vaccination.

The primary statistical analysis can be conducted in three ways: per protocol, intention to treat, or modified intention to treat. The per protocol analysis restricts the population for analysis to fully compliant participants receiving all vaccine doses as allocated per protocol. The primary statistical analysis often includes a delay and usually starts after the final dose of the vaccine plus the maximum incubation period. The goal of the per protocol analysis is to estimate the intrinsic efficacy of the vaccine to support licensure decisions and planning, but it is subject to post-randomization biases such as differential loss to follow-up. Alternatively, an intention-to-treat analysis includes all cases occurring after randomization or all cases occurring after the first dose of vaccine or placebo. The intention-to-treat analysis yields a practical, although more context-specific, estimate of vaccine effectiveness because it includes cases who may have been infected before the vaccine induced an immune response, as well as individuals who fail to comply with the protocol, potentially for reasons relating to the vaccine itself. As a result, the intention-to-treat estimate of vaccine efficacy tends to be attenuated compared to the per protocol estimate, and the difference between the intention-to-treat and per protocol estimates of vaccine efficacy may be especially large if many infections occur during the per protocol analysis delay (*27*). In the modified intention-to-treat approach, a sensitive test is used to retrospectively exclude individuals infected at baseline (*29*), although this requires the availability of both baseline samples and a reliable test. Although an intention-to-treat statistical analysis is generally regarded as the preferred approach in other types of clinical trials, vaccine efficacy trials frequently conduct a per protocol primary statistical analysis because compliance is typically high (*30*).

The take home message. Although only a single primary analysis may be selected, both intention-to-treat and per protocol estimates of vaccine efficacy should be reported.

DATA MONITORING IN VACCINE CLINICAL TRIALS

It is essential to rapidly identify safe and efficacious vaccines so that they can influence the course of the disease outbreak. It is also important to discard futile or unsafe vaccines at the earliest opportunity so that limited resources can be rededicated to other promising candidates. In outbreaks, disease transmission among humans may decline to extremely low levels or stop entirely, precluding accrual of further evidence to directly evaluate vaccine efficacy.

Independent Data and Safety Monitoring Committees should be in place to safeguard the interests of study participants and to enhance the integrity and credibility of the vaccine trial (*31*). The trial should include specification of data monitoring boundaries allowing for early termination for benefit or for futility while controlling the type 1 error rate and preserving power. Group sequential guidelines, such as an O'Brien-Fleming boundary, provide a widely implemented approach; the number and timing of interim analyses can be flexibly defined (*32*). If a trial is terminated early for efficacy, then the protocol should include a plan for next steps, such as vaccinating all eligible, consenting, unvaccinated participants with continued monitoring for safety. After the promising results of the rVSV-ZEBOV vaccine against Ebola disease (*25*), ring vaccination with immediate vaccination only (no control comparator arm) was implemented in Guinea in response to a flare-up of Ebola disease transmission several months after West Africa was declared Ebola-free. The vaccine was deployed under compassionate use criteria (*33*). Ring vaccination with the rVSV-ZEBOV vaccine has been used during Ebola outbreaks in the Democratic Republic of Congo (*34*).

The clinical trial protocol should clarify how study data would be analyzed if the full sample size is not reached. A waning epidemic could trigger study closure with a final analysis, study pause until the next outbreak occurs in that area, or study continuation to collect additional safety and immunogenicity data. Keeping the study open would be desirable in case there is an unexpected surge in disease transmission. This decision could be guided by an evaluation including disease transmission modeling to assess the probability of future cases in the current outbreak or future outbreaks in the study area (*35*). We recommend pausing the study protocol until the next outbreak occurs to accumulate evidence for the efficacy of a vaccine intervention. Thus, the trial would continue into the next outbreak under a single "master protocol." Any individual outbreak may be too small to fully power a trial, especially for diseases with limited person-to-person transmission that primarily spill over from an animal reservoir. Where such a master protocol approach is not feasible, at minimum, there should be a prospectively defined strategy for merging separate trials of the same intervention, such as a meta-analysis. Research protocols should be aligned as much as possible, with central coordination of the ministries of health in the affected countries by WHO.

The take home message. The study protocol should include a flexible data monitoring strategy for efficacy and futility, and it should prespecify plans for a waning epidemic. It is recommended that this include planning to continue the trial into a future outbreak.

CONCLUSIONS

Here, we have outlined major study designs and design elements to be considered for vaccine trials in public health emergencies. We have underscored the need for responsive and flexible study designs while maintaining the highest scientific and ethical standards possible. Study endpoints should be selected to support the broader intended use of a vaccine and should reflect the public health burden of interest. The study population can be responsively defined or can target high-risk individuals to increase statistical power. Individual or cluster randomization can be implemented, and trials can evaluate multiple experimental vaccines simultaneously to use limited resources more efficiently. Placebo control or the use of an unrelated vaccine control is recommended, with trials blinded whenever possible, although delayed vaccination can be considered as a comparator in certain settings. Both a per protocol and an intention-to-treat statistical analysis should be reported. Trials should prespecify a monitoring strategy that is robust to changing disease epidemiology.

A key principle is that randomized designs should be used whenever possible. Observational studies [e.g., cohort studies and test-negative designs) (*15*, *36*)] should only be considered in limited settings because the quality of inference will always be inferior relative to a randomized design. A setting where observational studies may be useful is when the product has received conditional licensure but requires further evaluation. As in any observational study, collection of and adjustment for potential confounders are critical. Results of observational studies are easiest to interpret when the effect of the intervention is large enough to overshadow random error and bias (*37*).

In rare settings, where deemed ethical, human challenge studies in which participants are intentionally exposed to the pathogen may be used to support regulatory decisions, provided that the human challenge model is adequately predictive of vaccine protection from natural exposure to the pathogen (*38*). Human challenge studies can use classical experimental designs and relatively small sample sizes to directly assess efficacy, safety, and immunogenicity of an experimental vaccine.

To navigate through the various study design elements and options outlined here and to promote scientific discussion among methodologists, an interactive, web-based decision support tool has been developed and is freely available at vaxeval.com (*39*). Our work on vaccine study design is one component of the larger Blueprint effort at WHO. Other workstreams include establishing a Global Coordination Mechanism to facilitate dialogue among relevant stakeholders. The Coalition for Epidemic Preparedness Innovations (CEPI) is one partner engaged in this work. CEPI aims to support the early development of experimental vaccines for prioritized pathogens, which is important for advancing vaccine candidates to efficacy testing (*40*).

Many of the principles described here for vaccine studies can be expanded to therapeutic and prophylactic antimicrobial agents. Advance planning for vaccine trial designs is critical for a rapid and effective response to a public health emergency and to advance knowledge to address and mitigate future public health emergencies. By expanding these study designs and plans for all potential emerging infectious disease threats on the Blueprint priority disease list, we will be able to rigorously evaluate vaccine and antimicrobial efficacy and effectiveness at the earliest opportunity when an outbreak occurs to mitigate current and future outbreaks.

SUPPLEMENTARY MATERIALS

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Table S1. WHO vaccine target product profiles for priority pathogens.

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