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The ring vaccination trial design for the estimation of vaccine efficacy and effectiveness during infectious disease outbreaks

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Abstract

The ring vaccination trial is a recently developed approach for evaluating the efficacy and effectiveness of vaccines, modeled after the surveillance and containment strategy of ring vaccination. Contacts and contacts of contacts of a newly identified disease case form a ring, and these rings are randomized as part of a cluster-randomized trial or with individual randomization within rings. Key advantages of the design include its flexibility to follow the epidemic as it progresses and the targeting of high-risk participants to increase power. We describe the application of the design to estimate the efficacy and effectiveness of an Ebola vaccine during the 2014–2016 West African Ebola epidemic. The design has several notable statistical features. Because vaccination occurs around the time of exposure, the design is particularly sensitive to the choice of per protocol analysis period. If incidence wanes before the per protocol analysis period begins (due to a slow-acting vaccine or a fast-moving pathogen), power can be substantially reduced. Mathematical modeling is valuable for exploring the suitability of the approach in different disease settings. Another statistical feature is zero inflation, which can occur if the chain of transmission does not take off within a ring. In the application to Ebola, the majority of rings had zero subsequent cases. The ring vaccination trial can be extended in several ways, including the definition of rings (e.g., contact-based, spatial, occupational). The design will be valuable in settings where the spatiotemporal spread of the pathogen is highly focused and unpredictable.

Keywords

Cluster randomized trial; infectious diseases; per protocol; ring vaccination; vaccines

Background

The ring vaccination trial is a recently developed design for evaluating the efficacy and effectiveness of vaccines during infectious disease outbreaks.[1] It is modeled after the surveillance and containment strategy of ring vaccination that was used to eradicate smallpox.[2] In ring vaccination, an index case of an infectious disease is identified by surveillance. For example, this person may seek care at a medical center. Contact tracing

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teams then mobilize to identify the contacts and contacts of contacts of the index case. This group of traced contacts forms a “ring” of the social contact network of the index case, and this ring is targeted for vaccination. Vaccine is offered to individuals at greatest risk of exposure, and, when a sufficiently fast-acting and highly effective vaccine is used, vaccination reduces the likelihood that the pathogen spreads beyond the ring.[3,4]

To evaluate vaccine efficacy and effectiveness, the ring vaccination trial combines ring vaccination with cluster randomization of rings to vaccination versus some control.[1] Randomization could also be within rings, e.g., households within rings, or individuals within rings. For cluster-randomized trials, incidence of disease in vaccinated clusters is compared to incidence of disease in control clusters to estimate total vaccine effectiveness.[5] Outcomes for ring members who are ineligible for vaccination or do not consent to vaccination can be analyzed to estimate indirect vaccine effectiveness. In individually-randomized trials, comparisons are made within rings to estimate direct vaccine effectiveness. In this paper, we introduce the ring vaccination trial design, describe its original application during the West African Ebola epidemic, and then review its unique practical and statistical features.

Application to Ebola

The ring vaccination trial approach was first developed and applied to evaluate the rVSV-ZEBOV Ebola vaccine during the 2014–2016 West African Ebola epidemic.[6,7] The West African Ebola epidemic was over an order of magnitude larger than any historical Ebola outbreak. In total, 28,616 Ebola virus disease cases were reported,[8] whereas the largest outbreak before was 425 reported cases in Uganda in 2000.[9] In late 2014, the World Health Organization affirmed the need to evaluate the efficacy of promising candidate vaccines in Phase III trials.[10] Multiple Phase III trials were planned in the primarily affected countries of Sierra Leone, Liberia, and Guinea, but investigators faced important challenges. One major challenge was unpredictable future time trends. At the time trials were being planned, there was substantial uncertainty about future disease incidence. Though Liberia and Sierra Leone experienced large peaks, incidence waned dramatically by early 2015.[8] In contrast, peak incidence in Guinea was lower overall but with a longer tail. Unpredictable spatial spread presented another challenge. Although large outbreaks occurred in urban centers, clusters were also distributed throughout the region, including in areas with lower population density. Finally, there was very limited existing clinical trial infrastructure, and trials were planned in the midst of an active public health emergency.[11]

The ring vaccination trial design was developed in response to these challenges. The features of the design and its application to the Ebola ça Suffit (“Ebola this is enough”) trial in Guinea are described in detail elsewhere.[1,7] Briefly, the Ebola ça Suffit trial evaluated the efficacy and effectiveness of a single dose of rVSV-ZEBOV vaccine. Eligible contacts and contacts of contacts of laboratory-confirmed Ebola virus disease index cases formed rings. Each ring was randomized as a cluster to be offered either immediate vaccination or delayed vaccination (21 days later). The primary endpoint was laboratory confirmed Ebola virus disease 10 or more days after randomization. Assuming vaccine efficacy of 70%, an average of 50 eligible participants per ring, 2% attack rate, and intracluster correlation coefficient

of 0.05, the trial required an estimated 190 rings (95 per arm) to have 90% power to rule out the null hypothesis of 0% with a two-sided α=0.05 test. A larger sample size would be required to rule out a lower bound of 25% or 30%. An interim analysis was planned for the halfway point using an O'Brien- Fleming alpha spending procedure.

An interim analysis of 90 randomized rings yielded evidence of high vaccine efficacy.[7] In the primary population of immediately vaccinated participants and eligible delayed participants, for symptom onset ≥ 10 days after randomization, there were 16 cases out of 2380 individuals within clusters randomized to delayed randomization; these 16 cases occurred within 7 of the 42 delayed clusters. This was compared to 0 cases out of 2014 individuals in immediate clusters. The estimated vaccine efficacy was 100% (95% confidence interval 68.9 to 100%). The calculated intracluster coefficient was 0.035.[6]

On the basis of the recommendation of the data monitoring committee, randomization to delayed vaccination was discontinued. A final analysis summarized results from 98 randomized (51 immediate vaccination, 47 delayed vaccination) and 19 non-randomized clusters (all immediate vaccination).[6] Results were presented restricting to the randomized clusters only and in combined analyses to capture the "totality of the evidence." Vaccine efficacy remained similarly high as in the interim analysis, with no cases observed at 10 or more days in any immediately vaccinated cluster.

The World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) endorsed deploying the rVSV-ZEBOV vaccine to contacts and contacts of contacts of Ebola Zaire virus disease cases within a ring vaccination strategy, as well as vaccinating at-risk health care and front-line workers.[12] There have been several Ebola outbreaks since where ring vaccination has been used as a control strategy and there has been further evaluation of vaccine effectiveness.[13] This vaccine was licensed by the US Food and Drug Administration in December 2019 as the Merck Ervebo vaccine for the prevention of Ebola virus disease.[14]

Practical features of the design

The ring vaccination trial design has many practical features that make it well-suited for the outbreak context. The central feature is that it is flexible and follows the epidemic as it progresses. Thus, when an outbreak moves into a particular sub-region, the trial moves with it, recruiting the contacts and contacts of contacts of newly identified cases. In the Ebola ça Suffit trial, rings were geographically spread across Basse-Guinée,[7] reflecting dispersed pockets of transmission that would have been difficult to predict in advance.

The design is highly targeted, enrolling individuals based on known exposure, with higher expected attack rate than in a population not defined by exposure. The approach also maximizes the chance that the trial can continue to generate evidence despite low or declining incidence. In Guinea, by the time the pilot phase of the trial started in late March 2015, Ebola incidence had begun to wane. Though weekly numbers of new cases in Guinea were relatively low afterwards, because the design was so targeted, many of these cases contributed to the trial as either index cases or ring members.

The flexibility of the trial design is enabled by mobile teams and innovative cold chain technology to support vaccine delivery. In the Ebola ça Suffit trial, teams visited the rings on days 0, 3, 14, 21, 42, 63 and 84 post-vaccination. The clustered design has logistical advantages in terms of the simplicity of study procedures. The design has a naturally stepped roll-out, with new rings identified over time as the epidemic progresses.[15] The trial can complement, and not interfere with, ongoing contact tracing activities. Contact tracing is a recommended control strategy for Ebola virus disease because of the pathogen's relatively low incidence, spread through tightly connected networks, and sufficiently long incubation period.[16] Ring vaccination can integrate naturally into this process. Importantly, the design has been shown to be feasible even in very challenging circumstances.

Statistical features of the design

The ring vaccination trial has several notable statistical features. One important feature is that recruitment targets a population with an epidemiological link to a known case; thus, some members may be infected prior to randomization. This is always a possibility in vaccine clinical trials, and it is why the majority of trials use a per protocol primary analysis that excludes cases occurring within some window after randomization. The length of this window reflects the incubation period of the pathogen (time from infection to symptom onset) and the immune ramp-up period of the vaccine. In many settings, the intention-to-treat estimate is very similar to the per protocol estimate because relatively few cases occur during this window.[17] The estimates, though, can differ greatly in the context of an outbreak. Horne et al. noticed a 20% difference between the intention-to-treat and per protocol analyses for a hepatitis A vaccine trial conducted during a community outbreak.[18] Though the per protocol analysis starting 50 days after immunization showed 100% vaccine efficacy, many cases were observed at the start of the trial, partly due to the long incubation period of hepatitis A (mean of approximately 4 weeks).[19] These early cases in the vaccination group reflected infections that occurred prior to vaccination or prior to the vaccine conferring full protection.

In the ring vaccination trial, we might expect incidence to be initially high but decline after surveillance and containment procedures are implemented in the affected populations. High infection hazard rates near the time of randomization can yield large discrepancies between intention-to-treat and per protocol estimates because many cases are observed in the vaccination arm before the vaccine is fully protective; this is especially relevant if the pathogen has a long incubation period or if the vaccinee's immune response develops slowly. The impact is that ring vaccination trials are more sensitive to the choice of the analysis window than other types of vaccine trials. This is a type of bias-variance tradeoff, where early events during a period of partial protection bias vaccine efficacy downward but can still improve overall study power. These tradeoffs can be explored analytically[20] or via simulation.[21] For this reason, ring vaccination trials are best suited for slow-moving pathogens and fast-acting vaccines.[22,23] For example, such a trial would not be feasible if incidence was at or near zero by the time the per protocol period began. The ring vaccination approach must be weighed against a design where exposure and enrollment into the trial plus vaccination are not closely linked in time.

Another statistical feature of ring vaccination trials is zero inflation. The spread of infectious diseases can be highly stochastic. For Ebola, as for other pathogens, a large fraction of index cases do not result in secondary cases.[24] Where this occurs, the chain of transmission ends, and unless there are new exposures from outside of the ring, there will be zero subsequent cases. At the interim analysis of the Ebola ring vaccination trial, in the primary analysis of vaccine-eligible individuals with symptom onset 10 or more days after randomization, 0 out of 48 immediate vaccination clusters and 7 out of 42 delayed clusters had subsequent cases. This excludes cases occurring within 0 to 9 days after randomization. When we consider subsequent cases occurring at any time after randomization and include cases in vaccine-ineligible ring members, 9 out of 48 immediate vaccination clusters and 13 out of 42 delayed vaccination clusters had any subsequent cases. Even in this broader analysis, the majority of clusters in either arm had no subsequent cases; in the clusters that had further transmission, the majority of cases occurred within 0 to 9 days after randomization, reflecting high early exposure.[7]

One impact of zero inflation is that it greatly restricts the available analytical methods for estimating vaccine efficacy while still accounting for the clustered nature of the data. For the Ebola ring vaccination trial, the pre-specified analysis plan of a Cox proportional hazards model with a cluster-level frailty was not tractable, so a cluster-level exact test was used for significance testing, along with a confidence interval derived from an inverted likelihood ratio test assuming a beta-binomial distribution.[7] More analytical methods are available when individual-randomization is within rings.

Simulation studies are useful for planning the statistical analysis considering potentially small numbers of non-zero clusters. For the design of infectious disease trials, mathematical modeling is a particularly valuable tool as it allows researchers to replicate key dynamic features while exploring different trial design options.[25] For ring vaccination trials, researchers can input assumptions about the natural history of disease, population network features, the sensitivity of the surveillance system, and the potential impact of the vaccine. This type of modeling has been used to study both the effectiveness of ring vaccination as a public health strategy[3,4] and as a vaccine trial design.[21,26] Investigating the performance of ring vaccination trials using simulation models is highly recommended for future study planning.

Discussion

The ring vaccination trial is a flexible approach for evaluating vaccine efficacy and effectiveness. It has been shown to be feasible even in resource-limited settings during a public health emergency, and, thus, is a valuable tool for evaluating future fast-acting vaccines. It may have an advantage over more traditional vaccine trial designs (i.e., designs where eligibility is not defined based on known exposure) for diseases with intense, unpredictable hot spots but low population-level incidence. The design requires a fast and sensitive surveillance system to detect new cases, and the trial itself is made possible by the use of mobile teams and cold-chain technology. The sensitivity of the trial to the specification of the analysis period is a limitation, and the analysis plan must be robust to zero inflation.

There are many potential extensions to the ring vaccination design. Though originally described as a cluster-randomized approach, individual randomization within rings yields greater statistical power for the same sample size.[27] Eligibility for members of the subsequent ring need not be contact-based, particularly for infectious diseases that are not spread by person-to-person contact. For example, a spatially-defined ring (e.g. everyone living within a fixed distance of the index case's residence) is more relevant for vector-borne or environmentally-borne diseases.[22] Rings could also be pre-existing units, such as work sites or congregate living facilities, where a ring is created following the first case within a unit. Given that the act of interviewing, identifying and enrolling contacts takes time, applying simpler eligibility criteria may be preferable in settings where contact networks are less predictive of risk, where speed is prioritized, or where surveillance systems lack sensitivity or are too strained. There is a wide opportunity for innovation in how the design is applied and optimized to new diseases and new settings.

The value of ring vaccination trials was demonstrated during the 2014–2016 West African Ebola epidemic, and the design has since been considered for vaccines targeting other pathogens. During the COVID-19 pandemic, ring vaccination was explored, but ultimately vaccine efficacy was assessed via traditional, individually randomized trials at a very large scale. Two dose vaccines are not well-suited for ring vaccination, and the COVID-19 trials were able to leverage existing clinical trial networks and infrastructure. Given the intensity and ubiquity of SARS-CoV-2 transmission, the COVID-19 trials were successful in quickly accruing the necessary endpoints. Ultimately, ring vaccination is most advantageous when traditional approaches are not feasible or have a low probability of success. Then, there are context-specific considerations for choosing between these designs, such as how much clinical trial infrastructure exists and how clustered transmission is in the affected region. A promising path forward is a hybrid design that leverages the flexibility of ring trials with the stability of traditional trials. In these responsive trials, sites or populations are pre-selected and monitored, but randomization and vaccination only occurs after transmission is detected.[28] Ring vaccination and other types of "responsive" designs extend our capacity to conduct efficacy trials in emergency settings.

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