Statistical Considerations in the Design of COVID-19 Vaccine Trials Using Real-World Data and Evidence

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Design Considerations for Vaccine Trials with a Special Focus on COVID-19 Vaccine Development

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Real World Data and Evidence: An Interdisciplinary Approach and Applications to Precision Medicine and Healthcare

Outline

Outline II

1. Introduction

1.1. Background

COVID-19 global pandemic

- The most recently discovered coronavirus, a novel SARS coronavirus 2 (SARS-CoV-2), causes coronavirus disease (COVID-19) which became a global pandemic affecting millions of people in over 210 countries worldwide (WHO, 2020c) with fatality rates ranging from 0.3% to 11.4% (Oke and Heneghan, 2020)
- Active research: Epidemiology (e.g., distribution, transmission, control and prevention), clinical management, sequence and synthesis of viral DNA/RNA for vaccine development, and clinical trials for anti-COVID-19 drugs and anti-SARS-CoV-2 vaccines.
- To date, there are no specific antiviral drugs to treat COVID-19 or vaccines to prevent SARS-CoV-2 infection.
- According to the World Health Organization (WHO), as of April 30, 2020, there are at least 102 ongoing COVID-19 candidate vaccine development programs worldwide, the majority of which are in preclinical development, five are in phase I clinical trial, and three are in phase I/II clinical trial (WHO, 2020b)

1.2. Biological Mechanisms and Vaccine Types

How does a vaccine work?

- A vaccine works on the human immune system to elicit immune responses to prevent infection and the disease caused by certain pathogens such as SARS-CoV-2 and/or to reduce the disease severity.
- In order to better design a vaccine clinical trial, it is essential to understand the biological mechanisms of different types of vaccines and their main features including immunogenicity and safety.
- Recent scientific and technological advances have brought much insight in understanding the mechanism of microbes causing human diseases and have helped the development of various types of vaccines.

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1.2. Biological Mechanisms and Vaccine Types

Vaccine types

According to the National Institute of Allergy and Infectious Diseases (NIAID), there are three types of vaccines (https://www.niaid.nih.gov/research/vaccine-types)

- Whole-pathogen vaccines: Consisting of entire pathogens or microbes such as viruses that are inactivated or weakened so that they cannot cause diseases when entering into the body.
  - This type of vaccines includes inactivated vaccines and live-attenuated vaccines.
  - Examples of whole-pathogen vaccine candidates against SARS-CoV-2 infection are the inactivated candidate vaccine by Beijing Institute of Biological Products/Wuhan Institute of Biological Products and the live-attenuated vaccine by Codagenix/Serum Institute of India, both are under preclinical evaluation (Chen et al., 2020; WHO, 2020b).

1.2. Biological Mechanisms and Vaccine Types

Vaccine types

  - The main concerns over live-attenuated vaccines are the possibility of reverting to a non-attenuated, pathogenic phenotype in vaccinated individuals, particularly those with compromised immune system, and possible spread of the vaccine virus in the population (Robert-Guroff, 2007).

- Component vaccines: Comprising only a specific component (subunit) or antigen (protein or carbohydrate) from the virus, that can best stimulate the human immune system.
  - Adjuvants are required to elicit strong protective immune response.
  - A few SARS-CoV-2 component vaccine candidates based on the so-called S protein, a spike protein that can be directly recognized by the host immune system, e.g., the recombinant protein nanoparticle vaccine candidate by Novavax and COVID-19 XWG-03 truncated S proteins vaccine candidate by Innovax/Xiamen Univ./GSK, both are in preclinical evaluation (WHO, 2020b).

1.2. Biological Mechanisms and Vaccine Types

Vaccine types

  - Low incidences of adverse reactions due to administration of component vaccines
  - antigens stimulating the immune system must be pre-identified and broad enough to cover the majority of the pathogenic virus (Vartak and Sucheck, 2016).

- Nucleic acid vaccines: Containing an injection of a few pieces of a microbe's messenger RNA (mRNA) to encode antigens or DNA strands that can instruct the cells to produce antigens against which an immune response is induced.
  - Theoretically, nucleic acid vaccines would in general be efficient, producing a stimulation of long-term immune response.
  - Many of such vaccines are still under investigation and none of them have been licensed for human use.
  - The vaccine co-developed by Moderna and NIAID against SARS-CoV-2 in phase I/II trial is an mRNA vaccine that encodes S protein (`clinicaltrials.gov`, NCT04283461).

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1.3. Human Vaccines

Requirements

- For a virus vaccine to be used in humans, it has to be safe, immunogenic, stable, and capable of inducing sufficient immunity.
- To meet these requirements, a vaccine development program must provide a comprehensive understanding of
  1. virus molecular and structural biology and pathogenesis,
  2. the complexity and plasticity of major viral antigens,
  3. the protective role of antiviral B- and T-cell mediated immune responses, and
  4. any potential side effects that may be associated with excessive immune response, adjuvants, manufacturing processes, and administration routes (Enjuanes et al., 2016)

2. General Considerations in Vaccine Development

2.1. Vaccines Differ from Drugs

Safety, population, dev. process, regulation and logistic

- High safety standard: Prophylactic vaccines are usually given to healthy populations, some of whom may be vulnerable children, older adults, and/or special populations (e.g., service men and women).
- Immune responses as surrogate markers: The immune responses are usually measured by biological assays for the amount, classes or subclasses, and functionality of specific antibodies, in order to determine their degree, duration and scope.
- Vaccine efficacy. Efficacy for vaccines is defined in terms of risk reduction, which can only be observed after proof of concept studies (phase IIa/IIb trials). The use of quantitative methods to establish correlates of protection in terms of vaccine efficacy is important for early decisions.

2.1. Vaccines Differ from Drugs

Safety, population, dev. process, regulation and logistic

- Varying observational time: The impact of active vaccination on the immune system is virtually life-long through memory B and T cell generation. The observational time to establish the safety profile could vary substantially for different vaccines.
- Step-down and -up development strategies: Early safety evaluation starts with adult healthy volunteers and then steps down to adolescents and pediatric populations and steps up to geriatric populations if there are no major safety concerns. This step-down and step-up strategy may be more appropriate for COVID-19 vaccine development as these vaccines will be administered to different age groups.
- High variations in immunogenicity: Vaccines are biologically derived and variations in biological activities can occur, which can be further complicated by biological manufacturing process such as formulation, fermentation, and virus sensitivity to storage condition.

INVENTING FOR LIFE

2.1. Vaccines Differ from Drugs

Safety, population, dev. process, regulation and logistic

- Vaccine adjuvants: Adjuvants are commonly used in component vaccines to produce an immune response strong enough to protect people. However, adjuvanted vaccines can cause more local reactions (e.g., redness, swelling, and pain at the injection site) and more systemic vaccine-related adverse reactions (e.g., fever, chills, and body aches) than non-adjuvanted vaccines (Marciani, 2003; WHO, 2017).
- Logistical challenges: Special conditions (e.g., temperature) during manufacturing, transportation and on-site storage. Another consideration is that the number of people receiving a vaccine is typically orders of magnitude larger than the number of people receiving any single prescription drug $\longrightarrow$ substantial capacity for rapidly scale-up manufacturing in a robust and reliable manner. This could be especially important for rolling a COVID-19 vaccine out as quickly as possible during this pandemic.

2.2. Cautionary Notes

Unique development process

- Given the above considerations, vaccine development is generally complex, lengthy, and costly, and has its own development pathway (Plotkin, 2015; Cunningham et al., 2016; Plotkin et al., 2017).
- Some experts urge not to rush COVID-19 vaccine development (Callaway, 2020a; Jiang, 2020; Peeples, 2020), not only because the knowledge about SARS-CoV-2 virus is lacking (albeit rapidly accumulating), including the virus epidemiology, genomic structure, mechanism of pathogenesis, pathological immune response, but also because scientists need time to fully understand how the immune system responds to SARS-CoV-2, how long the immune response can last, and most importantly, how safe the vaccine will be, when it is widely deployed to the public.

2.2. Cautionary Notes

Unique development process

- Testing vaccines on an accelerated schedule without taking the time to fully understand safety risks could bring unwarranted setbacks during the current pandemic and into the future (Jiang, 2020) and public health urgency does not override the need of scientific rigor which demands reliable results (Ellenberg et al., 2018).
- However, under the current pandemic paradigm, some careful design considerations, such as, master protocol, human challenge trials, appropriate choice of endpoints, study population, and adaptive design strategies (e.g., group sequential design, seamless design), could potentially help shorten the overall development time without compromising the high standard of vaccine development, which is the purpose of this paper.
- In addition, the key statistical considerations discussed below can also be applied to other vaccine development programs in general.

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3. Trial Design Considerations

3.1. Novel Trial Design

To expedite clinical development

- A large number of ongoing COVID-19 vaccine development programs worldwide suggests that novel clinical trial design such as master protocol can be considered to screen out candidate vaccines that are unsafe or ineffective and to continue assessment of promising vaccines based on early data.
- There are at least two advantages associated with master protocols:
  - the use of trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing, and
  - the use of a common protocol that incorporates innovative statistical approaches to trial design and analysis (Woodcock and LaVange, 2017).
- Master protocols are more often used in cancer drug studies for targeting and accelerating clinical development, and they have attracted some interest in non-oncology fields, e.g., infection diseases (Dodd et al., 2016).

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3.1. Novel Trial Design

To expedite clinical development

- Given the current COVID-19 pandemic situation, they may be even more appropriate to accelerate early-phase trials and/or mid- to late-phase trial conduct for vaccine registration.
- A master protocol can accommodate different types of candidate vaccines with specific safety features and hypotheses, different route of administration, and different doses.
- The protocol usually uses adaptive design strategies with pre-defined criteria for dropping out or keeping candidate vaccines already in the trial or adding new candidate vaccines based on pre-specified endpoints which can be correlates of protection (e.g., antigen-specific antibodies) or laboratory-confirmed clinical disease of infection.
- The primary endpoint can be immune correlates of risk, pre-identified serious adverse events such as immunologically enhanced disease, correlates of protection, and laboratory confirmed clinical disease and/or its severity.

INVENTING FOR LIFE

3.1. Novel Trial Design

To expedite clinical development

- Short-term vaccine efficacy can be assessed based on clinical disease of infection due to a short incubation time of SARS-CoV-2 infection.
- The long-term protection of a vaccine cannot be established as it requires data on long-lasting immune responses and protection against infection.
- Multiplicity may occur due to multiple opportunities to make a positive claim on vaccine efficacy for a candidate vaccine.
  - The impact of multiplicity depends on the type of master protocol, the trial design, and the research questions to be answered (Collignon et al., 2020).
  - If a master protocol comprises multiple candidate vaccines with a common control group, multiplicity adjustment may be required to control the protocol-wise type I error rate (PWER).

3.1. Novel Trial Design

To expedite clinical development

- If a master protocol contains multiple candidate vaccines, each of which targets its own population with its own control group, no multiplicity adjustment is necessary because this trial design is similar to conducting separate, independent trials and decisions are made for individual candidate vaccines without referring to other vaccines.
- The degree of multiplicity adjustment depends on the research question.
  - For early-phase screening trials using a master protocol, the PWER can be controlled at a higher-level, e.g., 0.1 or 0.15, in order to allow for more candidate vaccines or doses to enter into the next phases of clinical development.
  - For a confirmative trial with product registration purpose, the PWER should be controlled at level 0.05 (two-sided) with appropriately chosen multiplicity adjustment methods; see Dmitrienko and D'Agostino (2017) for general discussion on statistical approaches to multiplicity issues in clinical trials.

3.2. Vaccine challenge studies

Unique development process

- Protective effects of a vaccine can be evaluated by vaccine challenge studies in which vaccinated and unvaccinated individual can be compared after direct challenge with the target pathogen under controlled experimental conditions (Knight-Jones et al., 2014).
- Challenge studies often start from animal models for initial evaluation of human vaccines and then move to humans with effective vaccines.
- Potential benefits of human challenge trials may include, among others, proof of concept for candidate vaccines, clearer understanding of the pathogenesis of and immunity to a pathogen, and identification of potential correlates of protection (WHO, 2016).

3.2. Vaccine challenge studies

Unique development process

- Human challenge studies may not always be generalizable as the challenge population has always been healthy adults who may be very different from those at risk for natural disease. In addition, challenge trials are often designed to assess short-term protection (Shirley and McArthur, 2011).
- Eyal et al. (2020) argue that human challenge trials of SARS-CoV-2 candidate vaccines could accelerate the clinical development and potential rollout of effective vaccines.
- Given the current pandemic situation of COVID-19, many people try to be self-isolated and a phase III trial may take a much longer time to have interpretable results.
- A human challenge trial may use much fewer volunteers to get meaningful results in a much shorter period of time (Callaway, 2020b).

3.2. Vaccine challenge studies

Unique development process

- Eyal et al. (2020) outline a challenge study design that includes healthy volunteers from "previously uninfected individuals at relatively low risk of complications or mortality from SARS-CoV-2 infection... and who are at substantial risk of natural exposure to SARS-CoV-2."
- These healthy volunteers should be young adults with no chronic health conditions living in areas with high transmission rates. See WHO (2016) for more discussion on study design, operational aspects and ethical considerations of human vaccine challenge trials. A large scale, phase III trial can be conducted if a human challenge trial shows that a candidate vaccine is efficacious.

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

- Suppose that the interest is to test the null hypothesis $H_0 : \text{VE} \leq \text{VE}_0$ against the alternative hypothesis $H_1 : \text{VE} \geq \text{VE}_1$.
- Since VE is measured as the reduction of infection cases of the vaccinated group relative to the unvaccinated group, the number of infection cases in the unvaccinated (or vaccinated) group can be treated as a conditional binomial random variable, given the total number of observed infection cases from both groups.
- In other words, testing $H_0 : \text{VE} \leq \text{VE}_0$ against $H_1 : \text{VE} \geq \text{VE}_1$ is equivalent to testing $H_0 : \pi \leq \pi_0 = 1/\left(2 - \text{VE}_0\right)$ against $H_1 : \pi \geq \pi_1 = 1/\left(2 - \text{VE}_1\right)$, where $\pi = n_{\text{U}}/(n_{\text{V}} + n_{\text{U}})$, n_{V} and n_{U} denote the numbers of infection cases from the vaccinated and unvaccinated groups, respectively.

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

- Using the algorithm described in Chapter 12 of Jennison and Turnbull (1999) and EAST® 6 software, the sample sizes, O'Brian-Fleming-like boundaries for efficacy and futility, and boundary crossing probabilities under H_0 and H_1 of three sequential designs with six interim analyses and one final analysis are calculated for $\text{VE}_0 = 0.3$ and $\text{VE}_1 = \{0.55, 0.60, 0.65\}$ (Tables 1–3).
- For example, if seven analyses are planned with the first interim analysis taking place at information fraction 0.4, a total of 115 infection cases is needed to reject $H_0 : \text{VE}_0 = 0.30$ at significance level 0.025 (one-sided) and power 0.90 if the true $\text{VE}_1 = 0.60$.
- The O'Brien-Fleming-like efficacy and futility bounds are expressed in terms of n_{U}, the number of infection cases from the unvaccinated group.

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

- If the observed number of infection cases from unvaccinated group is equal to or greater than the upper bound for efficacy at any analysis, the vaccine can be declared efficacious (e.g., vaccine efficacy is at least at VE_1); on the other hand, if the observed number of infection cases from unvaccinated group is less than the lower bound for futility at any analysis, the vaccine can be said non-efficacious (e.g., vaccine efficacy is no more than VE_0) (Tables 1–3).

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

Table 1: Sample sizes, O'Brien-Fleming-like boundaries for efficacy and futility, and boundary crossing probabilities of sequential designs with seven analyses for testing $H_0 : \text{VE} \leq \text{VE}_0$ against $H_1 : \text{VE} \geq \text{VE}_1$ at significance level 0.025 (one-sided) and power 0.90 with Lan-DeMets spending functions for both type I and II errors.

Look		Total	UBE[2]	LBF[3]	Boundary Crossing Probability (Cumulative)[4]			
#	IF[1]	Cases	($n_U \geq$)	($n_U <$)	P_0(rej H_0)	P_0(acc H_0)	P_1(acc H_1)	P_1(rej H_1)
Scenario 1. $\text{VE}_0 = 0.30$, $\text{VE}_1 = 0.65$, sample size 115 with $E_0(N)$[5] $= 60$ and $E_1(N)$[5] $= 78$								
1	0.400	46	39	27	0.000	0.498	0.080	0.009
2	0.504	58	46	36	0.001	0.699	0.251	0.020
3	0.600	69	52	44	0.003	0.821	0.448	0.033
4	0.704	81	59	53	0.007	0.902	0.644	0.049
5	0.800	92	66	61	0.012	0.944	0.776	0.065
6	0.904	104	73	70	0.017	0.969	0.867	0.082
7	1.000	115	79	79	0.021	0.979	0.903	0.098

[1] IF: Information fraction in terms of the total number of infection cases from both groups. [2] UBE: Upper bound for efficacy in terms of n_U, the number of infection cases from unvaccinated group. [3] LBF: Lower bound for futility in terms of n_U, the number of infection cases from unvaccinated group. [4] P_0(rej H_0) denotes the probability of rejecting H_0 given H_0 is true, P_0(acc H_0) the probability of accepting H_0 given H_0 is true, P_1(acc H_1) the probability of accepting H_1 given H_1 is true, and P_1(rej H_1) the probability of rejecting H_1 given H_1 is true. [5] $E_0(N)$ denotes the expected sample size under H_0 and $E_1(N)$ the expected sample size under H_1.

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

Table 2: Sample sizes, O'Brien-Fleming-like boundaries for efficacy and futility, and boundary crossing probabilities of sequential designs with seven analyses for testing $H_0 : \text{VE} \leq \text{VE}_0$ against $H_1 : \text{VE} \geq \text{VE}_1$ at significance level 0.025 (one-sided) and power 0.90 with Lan-DeMets spending functions for both type I and II errors.

Look		Total	UBE[2]	LBF[3]	Boundary Crossing Probability (Cumulative)[4]			
#	IF[1]	Cases	($n_U \geq$)	($n_U <$)	P_0(rej H_0)	P_0(acc H_0)	P_1(acc H_1)	P_1(rej H_1)
Scenario 2. $\text{VE}_0 = 0.30$, $\text{VE}_1 = 0.60$, sample size 172 with $E_0(N) = 90$ and $E_1(N) = 115$								
1	0.401	69	55	40	0.000	0.487	0.091	0.009
2	0.500	86	65	53	0.001	0.682	0.255	0.020
3	0.599	103	75	65	0.003	0.814	0.456	0.033
4	0.698	120	85	77	0.007	0.895	0.637	0.048
5	0.802	138	95	90	0.012	0.944	0.779	0.065
6	0.901	155	105	102	0.017	0.969	0.862	0.082
7	1.000	172	115	115	0.021	0.980	0.900	0.099

[1] IF: Information fraction in terms of the total number of infection cases from both groups. [2] UBE: Upper bound for efficacy in terms of n_U, the number of infection cases from unvaccinated group. [3] LBF: Lower bound for futility in terms of n_U, the number of infection cases from unvaccinated group. [4] P_0(rej H_0) denotes the probability of rejecting H_0 given H_0 is true, P_0(acc H_0) the probability of accepting H_0 given H_0 is true, P_1(acc H_1) the probability of accepting H_1 given H_1 is true, and P_1(rej H_1) the probability of rejecting H_1 given H_1 is true. [5] $E_0(N)$ denotes the expected sample size under H_0 and $E_1(N)$ the expected sample size under H_1.

3.3. Sequential Design

A two-arm randomized trial with a group sequential design

Table 3: Sample sizes, O'Brien-Fleming-like boundaries for efficacy and futility, and boundary crossing probabilities of sequential designs with seven analyses for testing $H_0 : \text{VE} \leq \text{VE}_0$ against $H_1 : \text{VE} \geq \text{VE}_1$ at significance level 0.025 (one-sided) and power 0.90 with Lan-DeMets spending functions for both type I and II errors.

Look		Total	UBE[2]	LBF[3]	Boundary Crossing Probability (Cumulative)[4]			
#	IF[1]	Cases	($n_U \geq$)	($n_U <$)	P_0(rej H_0)	P_0(acc H_0)	P_1(acc H_1)	P_1(rej H_1)
Scenario 3. $\text{VE}_0 = 0.30$, $\text{VE}_1 = 0.55$, sample size 267 with $E_0(N) = 140$ and $E_1(N) = 177$								
1	0.401	107	81	63	0.000	0.471	0.099	0.009
2	0.502	134	96	81	0.001	0.673	0.271	0.020
3	0.599	160	111	99	0.003	0.806	0.468	0.033
4	0.700	187	127	118	0.007	0.891	0.649	0.049
5	0.801	214	143	136	0.012	0.940	0.782	0.066
6	0.899	240	158	155	0.017	0.966	0.863	0.082
7	1.000	267	174	174	0.021	0.978	0.901	0.099

[1] IF: Information fraction in terms of the total number of infection cases from both groups. [2] UBE: Upper bound for efficacy in terms of n_U, the number of infection cases from unvaccinated group. [3] LBF: Lower bound for futility in terms of n_U, the number of infection cases from unvaccinated group. [4] P_0(rej H_0) denotes the probability of rejecting H_0 given H_0 is true, P_0(acc H_0) the probability of accepting H_0 given H_0 is true, P_1(acc H_1) the probability of accepting H_1 given H_1 is true, and P_1(rej H_1) the probability of rejecting H_1 given H_1 is true. [5] $E_0(N)$ denotes the expected sample size under H_0 and $E_1(N)$ the expected sample size under H_1.

3.4. Randomization

Individual randomization and cluster randomization

- Individual randomization or individually randomized controlled trials (iRCT). Participants are individually randomized to the investigational vaccine group or placebo group.
  - In comparison with cluster randomization, iRCT design has at least two major advantages: (1) the measured and unmeasured baseline characteristics can be better balanced between groups, and (2) it generally requires a smaller sample size to show the same degree of vaccine efficacy with the same statistical power.
  - The iRCT can be a one-stage randomization where participants are directly randomized to vaccine or placebo group, or a two-stage (*stratified*) randomization in which participants are first grouped into strata according to, say, clinical sites or neighborhood, and within each stratum (site or neighborhood), participants are then randomized to either vaccine or placebo group.
  - Some drawbacks: logistic inconvenience when randomization is performed in small units, e.g., small community or household, and difficulty to keep blinding when the vaccine causes distinctive AEs (Nason, 2016).

3.4. Randomization

Individual randomization and cluster randomization

- Cluster randomized controlled trials (cRCT). In cRCT, clusters of participants are randomized as a unit to receive the investigational vaccine or placebo. A cluster may be defined as a medical center, hospital, school, or neighborhood, and may be chosen to match the anticipated vaccine delivery system, or defined as groups of individuals at high risk of infection such as frontline healthcare workers or based on their contacts (Campbell and Walters, 2014; Hayes and Moulton, 2017).
  - Ideally, all members from participated clusters should be enrolled into the trial; however, a random sample of subjects from each cluster may also be acceptable if the sample is sufficiently representative of that cluster.
  - The advantages of cRCT over iRCT include (1) cRCT is logistically convenient when clusters are well-defined and stable and (2) cRCT design can help estimate the direct and indirect vaccine effect on the reduction of incidence rate of the infectious disease (Hayes et al., 2000).

3.4. Randomization

Individual randomization and cluster randomization

  - However, there are several disadvantages of cRCT as compared with iRCT: (1) a larger sample size required by a cRCT than an iRCT due to intra-cluster correlation (e.g., similarity in population features and response to intervention and possible interaction among participants within cluster), leading to diminishing returns in power and precision as cluster size increases (Hemming et al., 2017), (2) a high probability of unbalanced baseline covariates between comparison groups resulted from cRCT due to fewer units (clusters) being randomized, and (3) possible contamination of participants due to movement and disease transmission (Hayes and Moulton, 2017).
  - To reduce covariate imbalance, a small set of cluster-level matching variables (e.g., baseline prevalence rate, population demographics) can be used to stratify and match clusters, although this may increase operational complexity.

- There are at least three types of cRCTs that can be considered in vaccine trials:

3.4. Randomization

Individual randomization and cluster randomization

- Parallel cRCT is the simplest cluster randomization in which clusters are randomized to either vaccine or placebo group and intervention does not change until the end of the trial.
- Stepped wedge (or phased) cRCT design starts all clusters with placebo and gradually introduces the investigational vaccine to some clusters at a regular basis during the trial, until all clusters taking the vaccine by the end of the trial. It should be pointed out that the order in which the vaccine is introduced to individual clusters should be chosen at random and that care should be taken when estimating vaccine efficacy by comparing before- and after-vaccination for infectious disease with secular trends.
- Ring vaccination design, a strategy of containing the spread of a disease by vaccinating only those who are at a high risk of infection, was used in the eradication of smallpox (Strassburg, 1982) and in the Ebola vaccine development program (Ebola ça Suffit Ring Vaccination Trial Consortium, 2015; Henao-Restrepo et al., 2017).

3.4. Randomization

Individual randomization and cluster randomization

  - A ring of cluster can be defined based on confirmed cases, representing people at risk of exposure to the pathogens, or geographically defined based on (first- or second-generation) contacts. Subjects within rings can be randomized as a cluster unit (cRCT) or individually in the ring of iRCT.
  - Ring vaccination design is best suitable for an outbreak that is highly localized and vaccines that work quickly enough to protect the infection.

- Some other randomization designs may also be considered for vaccine trials during public health emergencies, such as (1) two-stage randomization in which clusters are randomized to different levels of vaccine coverage and participants within clusters are then individually randomized to vaccine or placebo conditional on the vaccine coverage from the first randomization (WHO, 2020a) and (2) factorial trials that allow for simultaneous evaluation of multiple candidate vaccines, or multiple doses of the same candidate vaccine, and some other prevention interventions such as vector control of pathogens or behavioral risk reduction (Friedman et al., 2010).

4. Assessing Vaccine Effectiveness Using RWD & RWE

4.1. Rationale for using RWD & RWE in vaccine trials

Principles to determine whether RWD & RWE should be used

- Randomized controlled trials have many limitations, such as operational complexity, high costs, deviation from real-world medical practice, and lack of generalizability.
- In contrast, real-world studies are less expensive, logistically convenient, reflective of routine medical practice, and representative of general population, and therefore can be considered as an alternative to assess vaccine effectiveness (Tseng and Sy, 2018).
- Chen et al. (2020) present rationales on whether real-world data and evidence (RWD & RWE) can be used in the design and analysis of clinical trials for an investigational product with the following four considerations:

4.1. Rationale for using RWD & RWE in vaccine trials

Principles to determine whether RWD & RWE should be used

1. Scientific: Is the use of real-world data scientifically valid? What are potential challenges that may impact the scientific integrity of the trial? Can relevant assumptions regarding similarity between vaccinated and unvaccinated groups be reasonably verifiable? From scientific perspectives, using RWD & RWE for vaccine efficacy evaluation may be a promising option, especially during the COVID-19 pandemic, partly because randomization sometimes may not be feasible, and blinding can be very difficult in some randomization schemes (e.g., cluster randomization with small cluster size). All of these may lead to operational difficulty of randomized trials.
2. Regulatory: Does the use of real-world data present potentially substantial challenges for regulatory decision-making or conflict with any regulatory guidelines? Sponsors are strongly recommended to have open communications with regulatory agencies on the use of real-world data and evidence before the design and conduct of any vaccine trials.

4.1. Rationale for using RWD & RWE in vaccine trials

Principles to determine whether RWD & RWE should be used

3. Ethical: What are the possible ethical issues if real-world data are not used in the design and analysis of vaccine trials? Does concurrent control group cause ethical problem in the trial? This may be the case in the COVID-19 pandemic if a vaccine is already shown to be fairly safe and efficacious in preventing SARS-CoV-2 infection.
4. Operational: What are the operational challenges in the design and analysis of clinical trials using real-world data? Is an independent statistician necessary to perform the design and analysis of the trial? How is the statistician blinded to outcome data when searching for a matched control? Yue et al. (2014) point out that it is critical to have a protection mechanism in place to prevent outcome information leaking, especially in the design phase, and such actions and specifications should be submitted to regulatory agencies for review and agreement.

- See also FDA (2018) for a general RWE framework and NMPA (2020) for China National Medical Product Administration's regulatory guidance on the use of RWD & RWE for medical product development and regulatory decision-making.

4.2. Design Options Using RWD & RWE

Population selection and randomization

- Given the above rationale in mind, the vaccine developer may consider a vaccination program in a well-established healthcare system or community for an investigational COVID-19 vaccine that has been demonstrated to be safe and immunogenically responsive in early phase trials.
- The candidate vaccine can be given to a group of participants in the healthcare system or a community, without randomization and a pre-defined placebo group, and vaccine effectiveness can be evaluated by examining reported infection cases in the electronic health records of participants in the same source population.
- A simple design in vaccine effectiveness assessment is the case-control design in which a case can be chosen from the study population and one or more controls are randomly selected, or matched based on some pre-defined variables, from the same population.

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4.2. Design Options Using RWD & RWE

Population selection and randomization

- A variation of case-control design is the test-negative design.
- The test-negative design identifies cases and controls from those who seek healthcare services for COVID-19 related illness, e.g., fever, cough, and shortness of breath.
- It has the advantage of eliminating confounding due to healthcare seeking behavior.
- The test-negative design, in which patients who test positive are the cases and those who test negative are the controls, requires a highly specific test to reduce bias in estimated vaccine effectiveness and an assumption that the vaccine does not provide cross-protection to other diseases with similar symptoms (Ohmit et al., 2014; Nauta, 2020)

4.3. Challenges in Using RWD & RWE in Vaccine Trials

Assessment of vaccine effectiveness using RWD

- First, individuals who are vaccinated may be different from those who are not in terms of their baseline characteristics, e.g., vaccinees may have better healthcare access and healthcare awareness than those who are not vaccinated and some healthcare providers may be more likely to recommend the vaccine than others.
  - This type of imbalance in participant's characteristics is often called confounding which, if not adjusted for, may cause confounding bias in the estimated vaccine effectiveness.
  - To overcome potential confounding bias, a commonly used approach is to match the case with one or more controls based on a set of key baseline covariates.
  - Matching can be performed in a variety of ways, such as nearest neighbor matching and propensity score based subclassification.

4.3. Challenges in Using RWD & RWE in Vaccine Trials

Assessment of vaccine effectiveness using RWD

  - Another commonly used method removing confounding bias is inverse probability of treatment weighting that creates a "pseudo-population" in which the treatment is independent of the measured confounders; see Chen et al. (2020) for an overview of matching and other statistical methods in using RWD & RWE to inform trial design and analysis.

- Second, there may be variations in the criteria and practice of case adjudication, which can lead to inconsistency of case definition and diagnosis and hence have an implication in the estimated vaccine effectiveness.
  - There are currently at least two different types of diagnostic tests available for testing the infection of SARS-CoV-2 – PCR test for detecting viral RNA and antibody test for prior viral infection, e.g., Petherick (2020); see also `https://www.who.int/csr/sars/labmethods/en/` – and many testing kits for each of these two diagnostic tools are produced by different manufacturers and approved for use by different authorities across the world.

4.3. Challenges in Using RWD & RWE in Vaccine Trials

Assessment of vaccine effectiveness using RWD

  - Therefore, a high degree of sensitivity and specificity of the diagnostic tests is desired and a standard operating procedure to conduct the test should be in place.

- Third, if EHR are used for identification of cases and controls, extra effort may be needed to ensure that vaccine exposure, infection (outcome), and some key covariates that are associated with vaccine access, vaccination preference, healthcare behavior, etc., are available in the databases.
  - Some of these variables may require retrospectively tracing back for reliability and validity; see Levenson et al. (2020) for an overview and a general discussion on outcome and study variable in real-world studies.
  - Cases using confirmed infection may be underestimated if patients with minor symptoms don't go to clinics or hospitals for diagnostic test, which may lead to a biased sample for the infected cases and hence incorrect estimate of vaccine effectiveness.

4.3. Challenges in Using RWD & RWE in Vaccine Trials

Assessment of vaccine effectiveness using RWD

- In summary, a clinical trial using RWD & RWE to evaluate vaccine effectiveness has the potential to accelerate clinical development, to efficiently use existing healthcare and/or vaccine delivery systems, to possibly benefit more participants with an efficacious vaccine, and to save development time and costs. On the other hand, the trial should be designed carefully to handle some known (and unknown) confounding variables in order to correctly estimate vaccine effectiveness with minimum bias.

5. Conclusion and Recommendations

5. Conclusion and Recommendations

- Vaccine perhaps is the best solution for protection against SARS-CoV-2 infection or reinfection. Vaccine development requires full understanding of SARS-CoV-2 virus (e.g., biological and genomic structure, pathogenesis, immunogenicity) and human body responses (e.g., cellular and humoral immune responses to virus infection), both are essential for vaccine design.
- Although this process takes time as scientific research has its own rule of timeline, scientists race against time in searching candidate vaccines that are safe and effective, during which statistical considerations are essential to help the vaccine development at pandemic speed.
- This talk provided a brief background on the immunology of vaccination against infection and presents some key design considerations for vaccine clinical trials from statistical perspective with a focus on phase III vaccine trials.

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5. Conclusion and Recommendations

- Given the current pandemic paradigm, a safe and effective COVID-19 vaccine is in paramount demand. With all the key points discussed in this paper, it is highly recommended that
  1. novel trial design (e.g., master protocol) can be used in early-phase trial to screen out candidate vaccines due to safety concerns or futility and continue evaluation of promising vaccines,
  2. human challenge trials can be performed to accelerate clinical development,
  3. adaptive strategies (e.g., group sequential design, seamless phase II/III design, keep-the-winner or drop-the-loser design with multiple candidate vaccines or doses) be considered to expedite the development,
  4. extensive modeling and simulation be used to establish reliable correlates of protection, threshold, and waning efficacy,
  5. safety endpoints (e.g., enhanced disease, or any other vaccine-induced immunological disease) be thoroughly investigated, both clinically and statistical (some serious adverse events can be used in designing large scale trials),
  6. real-world data and evidence can be considered under certain circumstances for vaccine efficacy and effectiveness evaluation, and

5. Conclusion and Recommendations

7. global collaboration and integration of vaccine development programs, e.g., COVID-19 Clinical Research Coalition (2020), be initiated to more efficiently use resource, expertise, and trial data (e.g., multiple candidate vaccines from different developers can form a joint development program, for which an efficient trial design can be used).

- Finally, open communication with regulatory agencies on trial design is highly recommended to ensure scientific integrity of clinical research and compliance of trial conduct with regulation and to expedite review and approval process.

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