A Digression on Covid-19 Vaccine Clinical Trials and its Consequences

Jorge Luis Romeu, Ph.D.
https://www.researchgate.net/profile/Jorge_Romeu
http://web.cortland.edu/romeu/
Email: romeu@cortland.edu

1.0 Introduction

In this short paper we digress about *Covid-19* vaccine *Clinical Trials and its results*. The fact that accelerated trials for several candidate vaccines have made possible its forthcoming (emergency) release by the CDC makes a serious discussion necessary. We assume the reader is familiar with our two previous papers on vaccine research: statistical methods to establish a new *Vaccine Life*: https://www.researchgate.net/publication/344495955_Survival_Analysis_Methods_Applied_to_Establishing_Covid-19_Vaccine_Life and statistical methods to help *accelerate vaccine testing*: https://www.researchgate.net/publication/344193195_Some_Statistical_Methods_to_Accelerate_Covid-19_Vaccine_Testing

We will use, in our discussion, several comments aired in the American Statistical Association *(ASA) Community* List-serve as well as our own thoughts. The ASA is the primary professional statistics organization in the USA and one of the most important in the world.

The mentioned ASA *Community* List-serve can be found in:

https://community.amstat.org/communities/community-home/digestviewer/viewthread?GroupId=2653&MessageKey=aabfc603-56be-442d-975c-967469dae056&CommunityKey=6b2d607a-e31f-4f19-8357-020a8631b999&tab=digestviewer&ReturnUrl=%2fcommunities%2fcommunity-home%2fdigestviewer%3ftab%3ddigestviewer%26CommunityKey%3d6b2d607a-e31f-4f19-8357-020a8631b999

2.0 Covid-19 Vaccine Clinical Trial

Covid-19 Vaccine success rate discussions have been intensive in the past few days. There are, at least, three different vaccines in the final stages of clinical trials, here and in Europe. They have different traits: some are cheaper to produce; others require quite difficult (very low temperature) storage and transportation requirements. And all have been tested for a very limited time.

They will soon be released due to the emergency situation brought up by Covid-19 Pandemic: the risk of early release is considered much lower than the risk of not having a vaccine at all. It is necessary to reduce or eliminate virus infection which results in a high death toll. And a vaccine will produce a result akin to “heard immunization”.

The efforts undertaken by health, governments, and drug manufacturers, to develop vaccines[1] is commendable and include many out-of-the-ordinary events, such as the public release, by some organizations, of their testing protocols. For example the Moderna test protocol can be found in: https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf and Pfizer's in: https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf

There are *some drawbacks on an early release* of a vaccine, stemming from the *limited time* they have been tested. These include failure to *identify certain side-effects*, especially the long-term ones; failure to determine the *time length of the immunization* provided; failure to determine the particular cohorts (e.g. elderly) that each of the vaccines will benefit more (or less), etc.

In the next section, we discuss some of these issues.

3.0 Discussion

The following commentaries, made by statisticians, appeared in said *ASA Community* list-serve:

Moderna's Covid vaccine appears to claim that it is "94.5 percent effective" because their study had 95 positives of which only five were in the treatment group.

The number is based upon the expectation (derived from the unvaccinated group) that 90 people in the vaccinated group should have been diagnosed with COVID. With only 5 actually diagnosed in the vaccinated group, the vaccine was successful in preventing 85 of the 90 expected infections.

Efficacy calculation is based on 1 - 5/90, which is approximately the 94.5% figure as claimed,

For people interested in vaccine statistics for Covid19, NISS has a free webinar on the topic: https://www.niss.org/events/copss-niss-covid-19-data-science-webinar-series-statistics-covid-19-vaccine-trials

Regarding the strata, the protocol says this: Randomization will be stratified based on age and, if they are < 65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 based on CDC recommendation as of Mar 2020. There will be 3 strata for randomization: ≥ 65 years, < 65 years and categorized to be at increased risk ("at risk") for the complications of COVID-19, and < 65 years "not at risk". Risk will be defined based on the study participants' relevant past and current medical history. At least 25% of enrolled participants, but not more than 40%, will be either ≥ 65 years of age or < 65 years of age and "at risk" at Screening.

When you have low event rates, such as covid 19 rates in a trial with approximately equal sample sizes. The best way to think of effectiveness as E= 100(X2-X1)/(X1+X2)=90%. X2-Number of Placebos infected X1-Number of Vaccinated infective. The target parameter is 1-RR RR=Relative risk: Vaccinated to Placebo.Effectiveness=1-RR (Relative risk)

[1] https://www.biopharmadive.com/news/coronavirus-vaccine-pipeline-types/579122/

For a trial with low events like Covid, RR is estimated as the ratio of failures on Vaccine to failures on Placebo. The estimated effectiveness is: 1-(5/95)=94.7% (Not the 90% cited earlier:) (F1-F2)/F1 F1-failures in Placebo F2=Failures on vaccine. My denominator of F1+F2 was incorrect. If F1=F2 the estimated effectiveness is 0%.

Up to here, the main comments from the ASA Community List-serve. My comments follow:

The *sample is composed of volunteers*; it is *not randomly drawn* from the population. *Its large size and its stratification structure* help to *compensate for this lack of randomization*. It is not possible to draw a random sample from the general population, since *people cannot be forced to participate* in clinical trials. This is, therefore, the best we can do so far.

Participants' activities are not similar: different people carry out different activities, in different environments, at different levels. Therefore, *exposure to Covid-19 is not necessarily at the same level*. The *large sample* tends to *compensate* for this lack of homogeneity.

The *sizes of subsamples* Placebo and Treatment *are the same*, but only five of Treatment sub-sample had the virus –whereas *90 of the Placebo* sub-sample did. This *suggests* that the vaccine actually protected 85 of the Treatment sub-sample (that should have also become infected, under the hypothesis of equal chance) and thence, the *vaccine is: 1-5/90 = 0.9444 efficient*.

Infected participants *health and age profiles* are very *important*. For example, if most infected participants of Placebo sub-sample were young, and all five Treatment sub-sample participants were old (or some other such important differences in categories), this would trigger a *different interpretation for the clinical trial results*. This information should be checked and reported on.

There are a number of questions that *the brevity of the clinical trial* does not allow to answer:

How long does the *vaccine protection* last? What are the long-range *side effects*? Which are the human *sub-groups that benefit mostly (or seldom)* from the vaccine?

Results obtained so far show how some vaccines are more expensive than others, or require very special conditions (e.g. very low refrigeration temperatures) that make its use in remote or rural regions difficult or impossible. Having several vaccines with well-known characteristics allows using some vaccines on certain subjects, geographical regions, etc.

Clinical trials will likely continue after the release of the vaccine. Information from subjects that become vaccinated will likely be collected. Such additional information will help answer some of the questions above, and confirm or reject the usage pre-defined.

4.0 Conclusions

Vaccine development, including clinical trials and release decisions are science and not political outcomes. Government intervenes to provide funds, help distribute the final product, etc. When a vaccine is released, it is because the risk analysis has proven it yields more benefits than harm.

Each individual should assess his or her situation, according to their age, co-morbidities, activity, etc. and not on political or other non-scientific basis. If in doubt, consult your physician.

Early release of the Covid-19 vaccine is due to the Pandemic. More than a million deaths have already occurred world-wide, and a quarter of a million in the USA, and counting. We do need to have a working vaccine, even with some (potentially) minor problems.

The objective of this digression is to help people in the process of becoming vaccinated. There will be a schedule: those on the front lines (e.g. doctors, nurses, first line defenders) will be the first. Then, those with high risks (e.g. elderly, people with serious co-morbidities). Others, with a low risk of infection (e.g. the young) will be vaccinated, later, as the vaccine becomes available.

In a couple of years of world-wide vaccination, if we are lucky, we will achieve *herd immunity*. If so, we will then be out of this terrible Covid-10 problem.

Previous Work:

Our Covid-19 work stems from *our proposal to the retired* academic and research communities: https://www.researchgate.net/publication/341282217_A_Proposal_for_Fighting_Covid-19_and_its_Economic_Fallout which pursues *one goal*: to *contribute to defeat Covid-19.*

Previous *work* includes ICUs and hospital staffing using the Negative Binomial distribution: https://www.researchgate.net/publication/345914205_Covid-19_ICU_Staff_and_Equipment_Requirements_using_the_Negative_Binomial screening DOEs: https://www.researchgate.net/publication/344924536_Design_of_Experiments_DOE_in_Covid-19_Factor_Screening_and_Assessment using statistical methods to establish a new *Vaccine Life*: https://www.researchgate.net/publication/344495955_Survival_Analysis_Methods_Applied_to_Establishing_Covid-19_Vaccine_Life as well as to help *accelerate vaccine testing*: https://www.researchgate.net/publication/344193195_Some_Statistical_Methods_to_Accelerate_Covid-19_Vaccine_Testing and a *Markov model to study* problems of *reopening college*: https://www.researchgate.net/publication/343825461_A_Markov_Model_to_Study_College_Re-opening_Under_Covid-19 and the *effects of Herd Immunization*: https://www.researchgate.net/publication/343345908_A_Markov_Model_to_Study_Covid-19_Herd_Immunization?channel=doi&linkId=5f244905458515b729f78487&showFulltext=true as well as of *general survival:* https://www.researchgate.net/publication/343021113_A_Markov_Chain_Model_for_Covid-19_Survival_Analysis about socio-economic and racial issues affected by Covid-19: https://www.researchgate.net/publication/343700072_A_Digression_About_Race_Ethnicity_Class_and_Covid-19 and developing *A Markov Chain Model for Covid-19 Survival Analysis:* https://www.researchgate.net/publication/343021113_A_Markov_Chain_Model_for_Covid-19_Survival_Analysis and *An Example of Survival Analysis Applied to analyzing Covid-19 Data*: https://www.researchgate.net/publication/342583500_An_Example_of_Survival_Analysis_Data_Applied_to_Covid-19, and *Multivariate Statistics in the Analysis of Covid-19 Data*, and *More on Applying Multivariate Statistics to Covid-19 Data*, both of which can also be found in: https://www.researchgate.net/publication/341385856_Multivariate_Stats_PC_Discrimination_in_the_Analysis_of_Covid-19, and the implementation of *multivariate analyses* methods such as: https://www.researchgate.net/publication/342154667_More_on_Applying_Principal_Component

s_Discrimination_Analysis_to_Covid-19 *Design of Experiments* to the Assessment of Covid-19: https://www.researchgate.net/publication/341532612_Example_of_a_DOE_Application_to_Coronavarius_Data_Analysis *Offshoring*: https://www.researchgate.net/publication/341685776_Off-Shoring_Taxpayers_and_the_Coronavarus_Pandemic and *reliability methods* in ICU assessment: https://www.researchgate.net/publication/342449617_Example_of_the_Design_and_Operation_of_an_ICU_using_Reliability_Principles and *Quality Control* methods *for monitoring* Covid-19: https://web.cortland.edu/matresearch/AplicatSPCtoCovid19MFE2020.pdf

About the Author:

Jorge Luis Romeu retired Emeritus from the State University of New York (SUNY). He was, for sixteen years, a Research Professor at Syracuse University, where he is currently an Adjunct Professor of Statistics. Romeu worked for many years as a Senior Research Engineer with the Reliability Analysis Center (RAC), an Air Force Information and Analysis Center operated by IIT Research Institute (IITRI). Romeu received seven Fulbright assignments: in Mexico (3), the Dominican Republic (2), Ecuador, and Colombia. He holds a doctorate in Statistics/O.R., is a C. Stat. Fellow, of the Royal Statistical Society, a Senior Member of the American Society for Quality (ASQ), and Member of the American Statistical Association. He is a Past ASQ Regional Director (and currently a Deputy Regional Director), and holds Reliability and Quality ASQ Professional Certifications. Romeu created and directs the Juarez Lincoln Marti International Ed. Project (JLM, https://web.cortland.edu/matresearch/), which supports (i) higher education in Ibero-America and (ii) maintains the Quality, Reliability and Continuous Improvement Institute (QR&CII, https://web.cortland.edu/romeu/QR&CII.htm) applied statistics web site.