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Assessing Vaccine Efficacy in Influenza Clinical Trials - Challenges and Difficulties

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Title: Assessing Vaccine Efficacy in Influenza Clinical Trials - Challenges and Difficulties

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Summary

The efficacy assessment of an investigational influenza vaccine often requires conducting large and expensive clinical trials. Specificities of influenza make singular such an evaluation and increase the complexity of the study designs and the analysis of the efficacy endpoints. Among others, these specificities are low attack rate, seasonality, multiplicity of the flu viruses, potential mutations, heterogeneity of the virus circulation in different region of the world, prediction of the vaccine composition, etc. This paper discuss how all those factors may impact the design, the conduct and the analysis of a vaccine efficacy trial and explains why such trials could fail whatever the true level of vaccine efficacy. Based on this, we argue that extending the length of such studies to several consecutive seasons could be an interesting alternative to the frequently-used one-year design, and we propose refinements of the statistical models to be explored.

Keywords: Design, Efficacy, Influenza, Statistics, Study, Vaccine

1. Introduction

Influenza vaccination is used to limit the circulation of the influenza viruses, and to prevent infection as much as possible\(^1\). The frequent antigenic changes impose the recommendation of an annual immunization with strains identified by predictive models of virus circulation. The current standard seasonal vaccine contains three inactivated antigens associated to the three virus subtypes that circulate in human since 1977, i.e. A/H1N1, A/H3N2 and B. Since the Northern Hemisphere (NH) and Southern Hemisphere (SH) have winter at different periods of the year, there are actually two flu seasons each year, November to April in NH and May to October in SH, and therefore two vaccine formulations as well\(^1\).
As for other types of medication, the clinical development of a new influenza vaccine takes place in three phases to seek registration\(^3\). The goal of the first two ones is to identify, in small cohorts, a formulation (vaccine components and their dosage) sufficiently safe, well tolerated and inducing an immune response. The clinical vaccine efficacy (VE) is then assessed in a large phase III trial where the enrolled subjects are randomized to receive either the experimental vaccine or a comparator, active or not, just before the influenza season. The objective of these VE trials is to estimate the fraction of disease that the investigational vaccine would prevent with respect to the comparator during the period of investigation. The incidence rates in both groups are compared to assess, most of the time, superiority based on a pre-specified threshold of success\(^4\).

Although the principle is quite simple, designing, conducting and analyzing such Phase III VE trials raise numerous difficulties, require the inclusion of a very large number of subjects and take years of effort. Table 1 summarizes the main VE trials conducted in the last 15 years, several of them leading to a failure.

After a short overview about design and analysis in the specific setting of influenza VE trials, the objective of this paper is to identify and discuss the main sources of difficulties that the clinical teams have to face in their long walk to the success and addresses some challenging questions related to this type of trials. Our points will be illustrated using results from a detailed analysis of the main influenza VE trials published and/or referenced on CTR over the last fifteen years (Table 1).

2. **Design and Statistical Analysis**

Most of the recent influenza VE trials took the form of a randomized prospective double-blind controlled multi-center study, run usually in a particular age category and over one or eventually two influenza seasons (Table 1). Subjects are vaccinated with the investigational vaccine or the control and then actively followed during the subsequent influenza season. When some influenza symptoms appear (influenza-like illness), swab samples are taken to confirm the presence of influenza virus.
After the season, the confirmed cases are recorded in each arm and there should be evidence that the investigational vaccine does prevent more influenza events than the control to claim efficacy.

The control arm could be either a placebo or an active vaccine with or without an established efficacy against influenza. An influenza-efficacious vaccine should be used when its administration is recommended in the target population in some participating countries, as it is the case for example for VE trials targeting the elderly population run in the United States\textsuperscript{5}. An influenza non-efficacious active control could be envisaged to provide some benefit to the target population, for example using a Hepatitis A vaccine as control in a paediatric population (NCT01218308\textsuperscript{6} and NCT01439360 in Table 1).

Though usually conducted over one or two consecutive seasons, these trials do sometimes cover more of them (NCT00644059\textsuperscript{7} and NCT01439360 in Table 1), a cohort being enrolled by season. A reason could be the difficulty to recruit enough subjects, as all the study participants should ideally be enrolled before the start of the season to take benefit of the whole period. Another reason is an expected low incidence rate in the target population that would not permit to accumulate enough cases over the entire season. Interestingly, the characterization of the efficacy variations based on the circulating strains and their matching level is never mentioned as a justification for running the trial over several seasons. This point will be addressed later in the discussion.

Regarding the statistical analysis, the comparison of the risk of influenza disease after vaccination between the study groups is based on the VE parameter expressing the prevented fraction of disease\textsuperscript{8}. The VE parameter is defined as one minus the ratio $\Psi$ of the risks between the two groups.

A (one-sided) hypothesis test can be written equivalently in term of $\text{VE}$ or $\Psi$\textsuperscript{9}:

\[
\begin{align*}
&\quad \{ \begin{array}{c}
H_0 : \text{VE} \leq \psi_0 \\
H_A : \text{VE} > \psi_0 
\end{array} \iff \{ \begin{array}{c}
H_0 : \Psi \geq 1 - \psi_0 \\
H_A : \Psi < 1 - \psi_0 
\end{array} \}
\end{align*}
\]
where \( \nu_0 (=1-\Psi_0) \) is the clinically-relevant threshold of success. \( \nu_0 \) should be substantially larger than 0 when the superiority over an influenza non-efficacious comparator is assessed. When the test is performed at the \( \alpha \) level of significance, efficacy is statistically demonstrated when the lower limit of the two-sided \((1-\alpha)100\%\) confidence interval of the estimated VE is larger than \( \nu_0 \).

In case of homogeneous length of follow-up, the risk is defined as the proportion of subjects with an event (NCT00192413\textsuperscript{11}, NCT00133523\textsuperscript{12}, NCT00128167\textsuperscript{13}, NCT00133523\textsuperscript{14}, NCT00197223\textsuperscript{15}, NCT00216242\textsuperscript{16}, NCT00363870\textsuperscript{17}, NCT00538512\textsuperscript{18} in Table 1) and the ratio \( \Psi \) as a relative risk\textsuperscript{19}. A variety of methods can be used to estimate \( \Psi \) and one of the most frequently used is the logistic regression that produces an estimated odds ratio (OR) which can be used to approximate the relative risk when the risks are sufficiently small\textsuperscript{20}. In case of heterogeneous follow-up time, \( \Psi \) can be defined as a ratio of incidence rates associated to either the conditional exact test\textsuperscript{3,21} or to the Poisson regression including the follow-up time as offset\textsuperscript{21,23} (NCT00192205\textsuperscript{22}, NCT00644059\textsuperscript{7} in Table 1).

Another approach, allowing also for heterogeneous follow-up times, is to consider hazard functions to estimate the conditional instantaneous risks of event and to estimate the ratio \( \Psi \) by fitting a semi-parametric Cox regression model\textsuperscript{24}. It has to be noted that the logistic regression, the Poisson regression and the Cox regression models can include other covariates while the conditional exact method cannot.

3. **Sources of Difficulties**

3.1. **Low attack rate and heterogeneity of study participants**

The VE assessment requires a sufficient number of influenza cases to have enough power to meet the study objectives. The incidence rates of confirmed influenza cases are generally small and imply thousands of subjects to enroll and follow. As a consequence, such trials are conducted in many
centers, from several countries and sometimes continents, meaning that the participants may have quite different ways of living and behaviors, and that they may be exposed to distinct strains inducing different immunogenicity.

Therefore the risk of confounding the treatment effect of interest with the effect of any other factor is not negligible and it should be properly controlled as much as possible at the time of randomization to avoid any detrimental bias that could jeopardize the study conclusions\textsuperscript{25,26}.

Stratifying the randomization according to the center and other factors and/or using a minimization algorithm to allocate the study participants to the treatment groups have to be envisaged in such a context\textsuperscript{26}.

Some influenza-specific confounding factors are well-known and include the age of the vaccinees (at least in case of broad range)\textsuperscript{27}, the history of influenza vaccination (especially in the countries without any recommendation of vaccination where a variety of different vaccination behaviors could be observed), the country of residence (the politics regarding vaccination are not the same around the world and vaccination of a significant portion of a population provides protection of non-vaccinated individuals through herd immunity\textsuperscript{28}), the general medical conditions, the smoking habits, the social environment, the frequency of individual contacts, etc. One difficulty is that these factors are frequently associated to each other, e.g. the rate of vaccination is usually higher in elderly than in young adults.

3.2. Exposure to Several Virus Strains

Different strains of both type-A and type-B influenza viruses do circulate from one hemisphere to the other causing the seasonal epidemics. These strains have different infectiousness levels and consequently imply different severity levels of the disease. Strains A are also more prone to
mutations than strains B as the formers can affect several species while the latters do circulate among humans only.

In such a context, the heterogeneity in exposure could be huge, especially from one region to another. By looking at the WHO FluNet surveillance database, the following situations are frequently observed: an important circulation of influenza viruses in some countries though almost nothing in others, co-circulation of several viruses in some countries and circulation of a single strain in others, different rates of co-circulation from a country to another, the occurrence of several epidemic peaks (two most of the time) associated to the circulation of different viruses at different moments, etc. Stratifying the statistical analysis by geographical region should then definitely be considered as a way to manage this source of heterogeneity.

In addition, a mutation inducing a major antigenic change could, at any time, generate a pandemic outbreak, that may jeopardize any on-going vaccine efficacy study. The 2009 H1N1 pandemic was a recent illustration as it did not allow to gather the targeted influenza cases in study NCT00976027 (Table 1).

3.3. Vaccine Composition

The current seasonal vaccine contains three strains: one sub-type A/H1N1, one sub-type A/H3N2 and one type B from one of the two main lineages. Those vaccine strains are annually recommended by the World Health Organization based on their likelihood to circulate and cause significant human suffering in the coming season. In this challenging exercise of prediction, it has already happened that the recommendation does not perfectly fit to actual circulation (mismatch) impacting the ongoing VE assessment. This explains why in most of the studies VE assessment is restricted to the matching cases, i.e. those induced by a strain contained in the vaccine.

3.4. Lack of Validated Correlate of Protection (CoP)
Due to the small attack rates, the influenza VE trials are often huge in sample size, expensive and challenging on a logistic point of view. An alternative could be to demonstrate efficacy based on an immunogenicity data package (Hemagglutination Inhibition and Virus Neutralisation assays) considering them as predictive of the protection against influenza illness\textsuperscript{9,30}. However, more and more influenza experts challenge such a material as sufficiently predictive\textsuperscript{31,32} in addition of its reliability\textsuperscript{33}. As a consequence, the regulatory authorities consider approval of a CoP-based registration file only in case of an urgent medical need (annual vaccination and any pandemic outbreak). In absence of such an emergency, the regulatory authorities request to conduct a VE trial based on a clinical endpoint but advice to take these large trials as an opportunity for contributing to the CoP identification.

4. Discussion

4.1. How many influenza seasons?

As previously mentioned, the efficacy of influenza vaccine is usually assessed over one and more occasionally over two seasons (Table 1). The reasons are mainly to rapidly generate the necessary information to apply for a licensure and to reduce the costs. However such a one-season design can be detrimental for the success of the trial as no matter the real efficacy of the vaccine, a low influenza season will significantly reduce the statistical power, while a mismatch will make the VE evaluation meaningless. Such a situation has already led to a failure or an early termination for futility\textsuperscript{15,16}. An additional issue is that a low attack rate seems to be frequently associated with a small VE estimate, although no definitive explanations are available to fully understand this phenomenon\textsuperscript{16}.

In addition, from a scientific point of view, the relevance of such a one-season trial is questionable. Indeed, the frequent antigenic changes due to the mutations might potentially make the vaccine
composition completely different from one year to another. In the last five years, WHO has recommended to change each of the northern hemisphere vaccine strains at least twice. The early phase studies provide evidence of significant variations in the immunogenicity to these different virus types and strains. Consequently, we could also consider that the efficacy against each of them would also vary to some extent without knowing by how much. As a result, there is little value in estimating VE over a single season where we don’t have cases for all the vaccine strains most of the time. It could be more interesting to cover several seasons, accumulating data from a variety of strains and describing the efficacy of the vaccine by an interval covering most of the strain-specific VE estimates instead of a single value. Of course, the subsequent questions would then be how many seasons and how many strains are necessary to obtain relevant information.

In order to conciliate both aspects, i.e. rapidity of submission and relevance of information content, innovative study designs splitting the study over several years could certainly be identified and proposed. This, in our opinion, is an interesting subject for discussion with the regulatory authorities in order to find a win-win way to move forward.

4.2. Which statistical model?

In the previously-mentioned models, the observations are assumed to be independent and identically distributed, given the covariate(s) if any. The subject heterogeneity described in the context of a VE trial does raise the question about the validity of such an assumption and about its impact on the VE assessment. For example that the study participants covered by the same politics of vaccination (within a region or a country) might not be considered as completely independent. To overcome with such a potential issue, stratification of the analysis is a frequently-used option but the specificities associated to influenza make it a real challenge. Using all the pre-cited factors could imply small strata, and in addition to the issue of low attack rates, this would lead to very small number of events in most of them. But considering only a part of them could imply large strata that
would include some heterogeneity (on a geographical point of view, different viruses could circulate (or not) within the same stratum).

An alternative is to use a shared frailty model developed for the analysis of clustered survival data\textsuperscript{34,35}, by introducing random effect(s) in the model. The value of this random effect (also called frailty) is common to all individuals of a “cluster” or strata and take into account all unmeasured common information shared by these individuals. As this random effect acts multiplicatively on the hazard function, individuals with a higher value will be at higher risk of event (so more “frail”). As far as we know, such a model has never been used in the field of influenza. It is however thought to adequately fit because most of the sources of heterogeneity would cover the different fragility levels of the subjects. Moreover, such models seem to be quite robust as the estimation of fixed effects would not be significantly impacted by a misspecification of the frailty distribution\textsuperscript{36}.

Another aspect that might be worth to address is the potential existence of a population fraction that is not susceptible to the influenza strain considered because of natural or previously acquired (by anterior vaccination or infection) immunity. In the framework of survival models, this has been studied under the name of cure models. Several formulations of these models exist. The most common one is to consider that the overall survival function $S(t)$ consists in a two-term mixture model: a first term modeling the proportion of non-susceptible people and a second term to model how influenza would affect the susceptible persons\textsuperscript{37} over time.

To conclude, different models seem to be applicable to better estimate the efficacy of influenza vaccines but should definitely be deeply investigated in terms of their identifiability, their accuracy and their power.

4.3. Towards huge efficacy trials?
More and more, the vaccine manufacturers develop new generations of vaccines to increase the level of protection. This is particularly true in the field of influenza. So, most of the time, the objective of the trial is to assess the superiority of the new vaccine compared to an efficacious one. The main consequence is a significant increase of the size of the efficacy studies which makes the difficulty level even higher. Indeed, the effect sizes to detect in such a context are usually much smaller than the ones assumed in a placebo-controlled trial. Also, overall attack rates are much smaller as all subjects are vaccinated. As a result, larger trials are required to reach an acceptable power. More subjects imply more sources of variation and of heterogeneity to manage when designing and analyzing the study as well as more difficulties on a logistic point of view.

Two recent trials illustrate that point perfectly. On one hand, a 7000-subject study was designed to reach 90% of statistical power to demonstrate that the absolute efficacy of an influenza vaccine assumed to prevent 70% of influenza events was at least 35%\textsuperscript{17}. On the other hand, 43000 subjects were necessary to ensure a power of 90% to detect the nominal superiority of a novel adjuvanted vaccine when compared to the standard of care, assuming that the new formulation should prevent 30% of the failures of its comparator\textsuperscript{38}.

4.4. CoP in flu – A Far Future Challenge

Addressing the request of the authorities to identify a correlate is far from being easy and is still a matter of discussion. First of all, some ambiguity exists around the concepts, the objectives and the methodologies though there is a trend to harmonize\textsuperscript{39}. If the aim is to predict individual protection, we probably need to take into account the information about the individual exposure. Such an ambitious objective cannot be met in a single trial, as large it could be. A meta-analytical approach could be envisaged with all the risks of confounding and sources of difficulties already mentioned to manage (different age ranges, different vaccine composition, risk of mismatching, variations in virus
circulation ...). The analytical variability in the different assays should not be neglected as another
potential source of difficulty.

What’s the likelihood to get a validated correlate of protection in Flu? Some key opinion leaders
think that we are still quite far from reaching this goal\textsuperscript{33,40}. The good news is that the different parties
involved in this quest, i.e. the regulatory agencies, the vaccine manufacturers, the governmental
research institutes ..., are currently realizing that the best and fastest way to succeed is to join all
their efforts. Nevertheless it will definitely take time.

5. Conclusions

Without caricaturing too much, the question addressed in an influenza VE trial could often be
formulated as follows: how to assess as quickly as possible the efficacy of a vaccine for which the
composition frequently changes, for which the antigens could not always perfectly match the
targeted viruses, in a heterogeneous population that could be exposed to different pathogens? In
our opinion, the current way to manage such studies should change to better characterize the level
of protection the vaccinees could expect from the investigational vaccine and to ensure the efficacy
of a good vaccine will be successfully evaluated to allow the more fragile persons to benefit from it.
As a consequence, let’s prepare our-selves to design and analyze VE trials differently, we need to
find more efficient way to do so, even if they will result in being more challenging than those realized
in the recent past.

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<table>
<thead>
<tr>
<th>Investigational vaccine</th>
<th>Ratio</th>
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<th>Population</th>
<th>Statistical methodology</th>
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<td>1:1</td>
<td>1996-1997 (+ revacc)</td>
<td>15 – 71 months</td>
<td>Relative risk based on the observed proportions of cases, Koopman’s method for the ratio of binomials to estimate 95 percent confidence intervals</td>
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<td>1999-2000 2000-2001</td>
<td>6 – 24 months</td>
<td>Risk of Poisson rates with confidence interval based on the assumption of asymptotic normality of the log ratio</td>
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<td>18 – 46 years</td>
<td>Relative risk based on the observed proportions of cases, confidence intervals were constructed using an exact method; Chi-square test and Fisher’s exact test were used for group comparison</td>
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<td>6 – 59 months</td>
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<td>2005-2006 2006-2007</td>
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<td>18 – 64 years</td>
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<td>Adjuvanted MIV (N &lt; 4000) MIV(N &lt; 4000)</td>
<td>unknown</td>
<td>2009-2010</td>
<td>18 years and older</td>
<td>NA</td>
<td>NCT00979602</td>
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<tr>
<td>QIV (N &lt; 5219) Non-active control (N &lt; 5219)</td>
<td>unknown</td>
<td>2010-2011 2011-2012</td>
<td>3 – 8 years</td>
<td>NA</td>
<td>NCT01218308</td>
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<tr>
<td>QIV (N &lt; 8200) Non-active control (N &lt; 8000)</td>
<td>unknown</td>
<td>2011-2012 (NH) 2012 (subtropical) 2012-2013 (NH)</td>
<td>6 – 35 months</td>
<td>NA</td>
<td>NCT01439360</td>
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<tr>
<td>Study Type</td>
<td>Comparator</td>
<td>Study Period</td>
<td>Age Group</td>
<td>Duration</td>
<td>Trial ID</td>
</tr>
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<td>-----------------</td>
<td>------------------</td>
<td>--------------------</td>
<td>----------</td>
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<tr>
<td>1-dose Adjuvanted MIV (N &lt; 6200)</td>
<td>unknown</td>
<td>2010-2011</td>
<td>6 months – 10 years</td>
<td>NA</td>
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<td>2-dose Adjuvanted MIV (N &lt; 6200)</td>
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<td>MIV (N &lt; 6200)</td>
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<td>2011-2012</td>
<td>65 years and older</td>
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<td>TIV HD (N &lt; 26000)</td>
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<td>2011-2012</td>
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<tr>
<td>TIV (N &lt; 26000)</td>
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<td>2012-2013</td>
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</table>

LAIV Live Attenuated Influenza Vaccine (intra-nasal)

MIV/TIV/QIV: Monovalent/Trivalent/Quadrivalent Inactivated Vaccine

* VE not the primary objective

** Not performed due to H1N1 pandemic