Randomized-controlled trials to identify and establish new correlates of protection for influenza vaccines

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Background

The European Medicines Agency accepts three measures of immunogenicity for the evaluation of inactivated influenza vaccines (IIVs). They are the hemagglutinin inhibition antibody titer (HAI titer) measured by the hemagglutination-inhibition (HAI) assay, anti-influenza virus antibodies measured by the single radial hemolysis assay, and neutralizing antibodies against the influenza virus measured by the virus microneutralization (MN) assay. Among these, only the HAI titer is well established as a CoP for IIVs. As the HAI titer is unable to fully explain or predict the effectiveness of current IIVs, and are unable to predict the effectiveness of live attenuated influenza vaccines, there is a need to identify additional CoPs that predict the effectiveness of existing or new influenza vaccines. Here, we assess the study design considerations, including sample size requirements for studies to assess the independent associations of two or more CoPs with clinical endpoints and their respective contributions to protection from those outcomes.

Methods

Using the anti-neuraminidase (NAI) antibody titer as an exemplar, we conducted simulation studies to estimate the required sample size to achieve adequate statistical power to identify independent associations of HAI and NAI titers with laboratory-confirmed influenza virus infections in randomized controlled trials.

We based our analysis on the hypothesized relationships between influenza vaccination, risk of influenza virus infections, and CoPs such as the HAI and NAI titer (Figure 1). The total effect of vaccination (a+b+c+d+e) was simulated as a composite of the effects of HAI titer (a+c), NAI titer (b+d), and influenza vaccination through non-HAI and NAI pathways (e) on risk of influenza virus infection using data from Hong Kong and the United States [1, 2]. We then assessed the association between the CoPs and laboratory-confirmed influenza virus infections with multivariable logistic regression, and the causal contribution of the CoPs using causal mediation analysis [3].

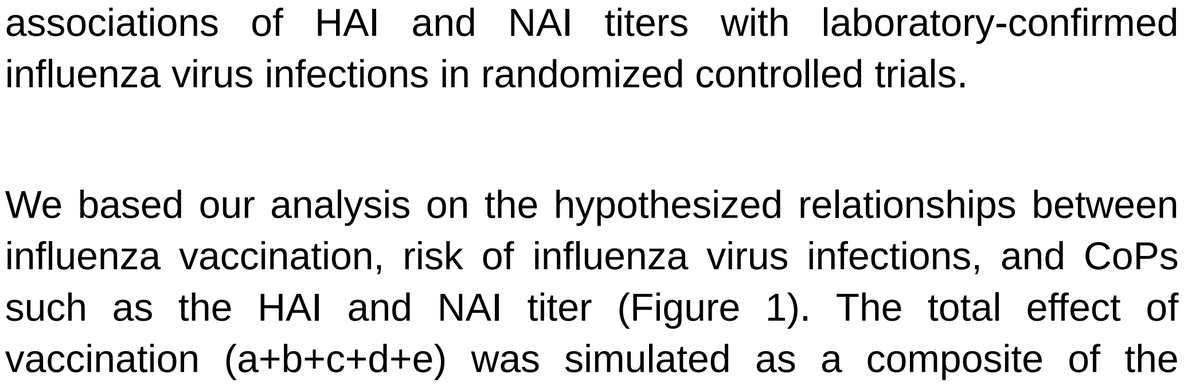

Figure 1. Causal diagram of hypothesized relationships between influenza vaccination, risk of influenza virus infections, levels of correlates of protection (HAI and NAI titer), and age in the context of a randomized controlled trial. Influenza vaccination is hypothesized to reduce the risk of influenza virus infections via the increase in levels of hemagglutination inhibition (HAI) and neuraminidase inhibition (NAI) antibody titers. Age affects risk of infection with influenza virus due to contact patterns and predisposition to disease. However, it does not affect the likelihood of influenza vaccination as this is presumed to be equal in a randomized controlled trial.

Results

In simulations where baseline risk of laboratory-confirmed influenza virus infection for unvaccinated participants with undetectable HAI titers is 10% and unit increases in HAI titer after vaccination reduces the risk of infection by 20% (consistent with 50% protection for a titer of 40) [4], sample sizes of approximately 2,500 are estimated to have a 80% power to identify the HAI titer as a CoP. When unit increases in HAI and NAI titers reduces risk by 20% and 15% respectively with the same baseline risk (i.e. the second CoP has a weaker effect than the HAI titer), our study suggests that at least 4,500 participants may be required for a study to have a 80% power to detect independent associations of both HAI and NAI titers with risk of laboratory-confirmed influenza virus infections and their causal contributions to vaccine-induced protection. If the baseline risk of infection is lower, or if the effect of the second CoP is even weaker, larger sample sizes will be needed.

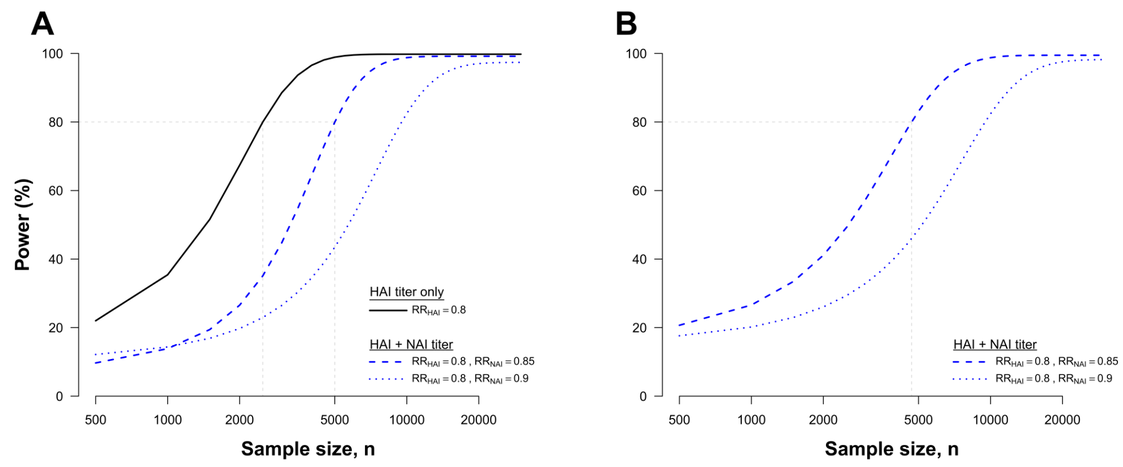

Figure 2. (Panel A) Effect of sample sizes on the statistical power to detect a statistically significant association between HAI titer and laboratory-confirmed influenza virus infections, and an independent association of an additional correlate of protection (e.g. NAI titer) with multivariable logistic regression.
(Panel B) Effect of sample sizes on the statistical power to detect a statistically significant causal contribution of NAI titer to the reduction of risk of influenza virus infections by comparing mediation models of direct effects with HAI titer only and both HAI and NAI titer included.

Discussion

Large sample sizes (beyond that of typical influenza vaccine efficacy trials) may be required to assess the association of a new CoP with clinical endpoints and its causal contribution to protection, particularly when the effect of the new CoP is weak, and when an independent association needs to be established for a new CoP due to correlation with existing CoPs. This indicates the need for independent studies that are specifically designed and adequately powered to achieve this objective.

References

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