

Influenza Virus Evolution, Host Factors and the Assessment of Influenza Vaccine Effectiveness

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Abstract

For over 10 years, the test-negative case-control design is used for a timely and reliable estimation of seasonal influenza vaccine performance. Influenza vaccine effectiveness (VE) varies significantly by influenza type and subtype. Therefore, the calculation of type/subtype specific VE estimates is essential, as the calculation of an overall protective effect could be misleading if several types are circulating. Besides viral factors, also host and environmental factors influence the protective effect of influenza vaccines considerably. Rising evidence suggests that repeated vaccination using the identical vaccine in successive seasons combined with the circulation of relevant drift variants negatively interferes with the protection provided by the vaccine. For a better understanding of factors influencing VE, it is important to combine genetic, antigenic, epidemiologic and clinical data with agent-host factors for optimizing VE estimates.

Short Communication

Influenza virus vaccines are the main prophylactic strategy for reducing the burden of influenza morbidity and mortality [1]. Nevertheless the currently available influenza vaccines induce a narrow and strain specific immunity and their protective effect is limited by the continuous evolution of influenza viruses associated with rapidly evolving mutations in key antigenic sites of the hemagglutinin surface protein [2-5]. Besides viral factors, also host and environmental factors considerably influence the protective effect of influenza vaccines considerably [6-8]. Assessment of vaccine effectiveness (VE) using the test-negative case-control design has revolutionized VE monitoring and has contributed to a better understanding of suboptimal VE of seasonal influenza vaccines [9]. This methodology first described for the 2004/05 influenza season in Canada [10,11] is now the preferred observational study design to reliably calculate the effectiveness of seasonal influenza vaccines against medically attended influenza virus infections [12]. The method relies on a sentinel surveillance network of physicians collecting clinical data and specimens from patients with influenza like illness. Its prospective nature allows early interim estimates of VE during the season [13-15]. Linking the clinical data of the participating patients to data of the antigenic and genetic characterization of viruses recovered from these study patients have revealed substantial variations in VE estimates across types and subtypes [11,12,16-18].

Although it is appealing to report an average protective effect of influenza vaccination, evidence suggests that estimates of an overall influenza vaccine effectiveness can be misleading especially in seasons with a heterogeneous mix of strains and/or influenza virus strains of different types and subtypes evolving during a season [12,19,20]. The findings of our study [17] on estimates of influenza vaccine effectiveness in 2014/15 in Austria, where influenza vaccine provided substantial protection against A(H1N1)pdm09 and influenza B viruses,

but only very limited protection against A(H3N2) viruses, underscore the importance to perform type/subtype specific VE estimates.

This is particularly important for the A(H3N2) viruses because they are the most rapidly evolving influenza viruses and it is therefore not surprising, that their rapid antigenic drift regularly contributes to reduced VE [18,21-23]. Another aspect in this context is the decrease of the protective effect of seasonal influenza vaccines against A(H3N2) virus infections during the season as indicated by reduced VE estimates in the second part of the season reported in some studies [24-26]. One possible explanation provided by the authors of these studies was the waning of vaccine-induced immunity during the season. In these studies detailed monitoring of the evolution of the influenza A(H3N2) virus strains collected from study participants has not been performed and therefore the significant influence of viral changes during the season on VE estimates has not been addressed. The changing dynamics of circulating strains with variable matches to the vaccine strains during the season on VE estimates is further substantiated by our recently published assessment of VE in Austria [17]. The results of our study clearly demonstrate that the calendar week of infection was the factor that influenced VE estimates most. The increasing VE estimates in the second part of the season correlated with the increased circulation of influenza virus strains with a better match to the vaccine strains as only revealed by detailed genetic monitoring of the circulating virus strains. Antigenic characterization by conventional hemagglutination inhibition (HI) assay failed to detect the relevant A(H3N2) drift variants in time, due to the unavailability of antisera during the season against the newly evolving viruses. In addition A(H3N2) viruses increasingly fail to agglutinate red blood cells [27] and so the development of alternative methods for antigenic characterization becomes crucial. Meanwhile, only the genomic analyses can provide timely and reliable virus characterization data for A(H3N2) viruses, but reliable genetic correlates for relevant antigenic

mutations have still to be defined. This shows again the importance of the inclusion of genetic data in VE-estimate studies.

In addition, the performance of seasonal influenza vaccines is not only influenced by viral diversity and evolution, but also by different host factors like the patient's age, concomitant and underlying diseases. Also the individual history of infections and/or vaccinations plays an important role in the patient's immune response [3,6-8,28-31]. In particular, several studies have recently reported that frequent prior vaccination is associated with sub optimal vaccine effectiveness [3,29,30,32]. In these studies, a negative interference from prior immunisation with current vaccine protection was observed. This was especially pronounced in seasons with the circulation of relevant drift variants and repeated immunisation with an identical (but mismatched) vaccine antigen. This negative interference with current vaccine protection is impressively demonstrated by the recent study for the 2014/15 season in Canada of Skowronski et al. [3]. In this study patients without vaccination in season 2013/14 had significant protection against A(H3N2) illness, whereas patients that had received the identical vaccine in 2013/14 and 2014/15 had a significantly reduced protection against A(H3N2) infections.

In our study, we were not able to reliably address this issue, since the majority of the participants (94%) had not received influenza vaccination for the previous season 2013/14 and therefore the group of participants immunized in both season was too small to allow further analyses.

Nevertheless investigating the influence of previous vaccination with seasonal influenza vaccines on the protective effect of the current influenza vaccine is a very important issue. To our knowledge only, one recently published study on VE estimates using the test-negative case-control design did stratify by the type of influenza vaccines used (inactivated vs. live attenuated influenza vaccines) [33]. Since the immune response induced by live attenuated vaccines differ significantly in many aspects (immune repertoire, its functionality, magnitude and longevity) from the immune response induced by inactivated vaccines [34-36] the type of vaccine used may be an important influencing factor on VE estimates. Detailed comparative analyses on the protective effect of inactivated and live attenuated influenza vaccines in different age groups are required for a better understanding of influenza vaccine performance and interference. Regarding the increasing use of live attenuated influenza vaccines in children and young adults, this will become all the more important, especially in the context of interference of prior immunization with current vaccine protection. In future it will become necessary to stratify VE estimates by type of influenza vaccine used (inactivated vs. live attenuated influenza vaccines) to increase our knowledge on influenza vaccine performance.

In addition to the type of vaccines used a variety of host, epidemiological and viral factors exert an influence on the assessment of influenza VE. Therefore, standardised recommendations for test-negative design studies as summarised in Table 1 are required to minimise biases and to obtain precise and comparable results for influenza vaccine performance. Furthermore, increasing sample sizes will allow more precise estimates of age group and subtype specific VE and will pave the way to estimate the performance of different types of vaccines used.

In summary, the test-negative design is currently the most reliable approach for routine assessment of influenza VE against medically attended influenza virus infection. It is much less susceptible to bias

due to misclassification of infection and to confounding by health care seeking behaviour compared to traditional cohort studies or case-control studies.

Viral factors
Definition of standard procedures for:
- Sample collection
- viral detection in clinical samples (culture and method for PCR testing)
- antigenic and genetic virus characterization
Epidemiological factors
Standardisation of ILI/ARI* case definition
Limitation of the study period to the period of influenza virus circulation
Standardised definition of age groups
Standardised definition of possible confounders (underlying diseases,...)
Standardised definition of inclusion/exclusion criteria for study participants
Host factors
Reporting of source of data used
Reporting of date of vaccination and of type of vaccines used*
Reporting of history of vaccination in previous season(s) and of type of vaccines used
Reporting of date of birth, sex, pregnancy, underlying diseases, ...
Reporting of calendar week of ILI/ARI*
Vaccine effectiveness (VE) reporting
Reporting of subtype (clade) specific VE estimates
Reporting of age group specific VE estimates
Reporting of vaccine type* specific VE estimates
Reporting of VE estimates adjusted for calendar week of vaccination and infection
*ILI/ARI: Influenza like Illness /Acute Respiratory Infection
*type of vaccine used: live attenuated, inactivated, vaccine product used

Table 1: Recommendation for the standardization of influenza vaccine effectiveness studies using the test-negative case control design concerning factors that should be considered.

It is a feasible and easily to implement approach to obtain influenza VE estimates. An additional advantage of this study design is that vaccine performance can be prospectively as well as retrospectively assessed. The statistical methods used to estimate VE in test-negative case control studies have also been developing from crude estimates as used in the first studies to the now applied methods of multivariate logistic regression and propensity score models [37]. In addition, the use of conditional logistic regression matching on time can provide better fit especially if vaccine uptake extends over a season [38]. Further research, however, is needed for optimizing the set of confounders to be considered. Special attention should be payed to the number and type of present and previously received vaccinations and the time since last vaccination. Another aspect that needs further study is the test of the assumption that the incidence of non-influenza

respiratory infections is equal between vaccinated and unvaccinated groups within strata of care-seeking patients [19].

Conclusion

For a better understanding of factors influencing the protective effect of influenza vaccines, it is crucial to combine detailed genetic, antigenic, epidemiologic data and information on vaccine type used with agent-host factors for optimizing VE estimates.

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