Sources of Bias When Assessing Seasonal Influenza Vaccine Performance: A Narrative Review

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Abstract. The best way to prevent influenza infection is through vaccination. Evaluating vaccine performance is essentially done through two types of study: clinical trials and the test negative design, an observational study derived from the case control. While in clinical trials the sources of bias are perfectly identified and there are specific tools for assessing them, in test negative design we find very varied sources of bias and a lot of scattered information without there being a validated tool for assessing the risk of bias. The aim of this narrative review is to identify the most important sources of bias in both types of study and to contribute to the development of a risk assessment tool for test negative design studies, given their major importance in evaluating the performance of the seasonal influenza vaccine.

Keywords: Vaccine · Efficacy · Effectiveness · Test negative design · Bias assessment · Estimation

1 Introduction

Influenza is a respiratory disease resulting from infection with the influenza virus. This condition is more prevalent during cold periods, with peaks of infection between November and April in the northern hemisphere, and between June and October in the southern hemisphere [1]. Influenza virus is highly transmissible in humans, via aerosolized respiratory droplets or direct contact with secretions [2, 3]. The World Health Organization (WHO) estimates that there are one billion cases of influenza worldwide each year, of which 3-5 million are severe cases [4].

An estimated 650000 deaths per year result from influenza infection [5]. Influenza poses a significant burden in global public health and vaccination is the most effective way to reduce it [6]. Seasonal influenza vaccination campaigns represent a major investment for countries and governments. Therefore, it is important to assess the performance of the vaccine. Due to the rapid genetic changes that influenza viruses undergo, seasonal influenza vaccines must be reformulated and re-administered annually to match circulating strains. Two types of studies are essentially used to assess the performance of the flu vaccine: randomized clinical trials (RCTs) and observational studies. Among observational studies, the most commonly used is the case-control study, better known as test negative-design (TND) [7]. The aim of this narrative review is to characterize RCT and TND sources of bias. Thus, Section 2 and Section 3 briefly describe RCT and TND respectively. The last section presents a discussion and a conclusion of how relevant are the source of bias previously identified in the evaluation of the seasonal influenza vaccine performance.

2 Randomized Controlled Trials

RCT is mandatory for the marketing authorisation of the vaccine for the year in question [8, 9]. It can be said that this type of study is the gold standard experimental procedure when it comes to scientific evidence [10, 11]. In order to assess the performance of a certain drug or, in this case, vaccine, two groups of people are formed. One group is inoculated with the vaccine and to the other a placebo is given. In RCT, the assessment of the performance of an intervention with a dichotomous outcome can be assessed using different measures: relative risk (RR), relative and absolute risk reduction (RRR and ARR) and the number needed to treat (NNT). The RRR is a measure of the proportional reduction in risk between the intervention and the control group. It is calculated by comparing the relative difference in risk of developing the outcome between the two groups. The formula for RRR is:

$$\text{RRR} = 1 - \frac{\text{Risk in treatment group}}{\text{Risk in control group}} \tag{1}$$

RRR expresses the reduction in risk as a proportion of the risk in the control group. For example, if RRR is 0.50, it means the risk of developing the outcome in the treatment group is reduced by half compared to the control group. The absolute Risk Reduction represents the absolute difference in risk between two groups. It quantifies the reduction in the absolute probability of an event occurring due to the intervention. The formula for ARR is

$$\text{ARR} = \text{Risk in control group} - \text{Risk in treatment group} \tag{2}$$

where the risks can be expressed as a proportion or a percentage. For instance, if ARR is equal to 0.05, it means that the risk of developing the outcome is reduced by five percentage units in the treatment group compared to the control

group. The interpretation of ARR heavily depends on the baseline risk of the outcome in the population being studied. A small absolute reduction in risk may be considered significant in high-risk populations but insignificant in low-risk populations. A common transformation of ARR is $\arcsin(Riskincontrolgroup)^0.5 - arcsin(Riskintreatmentgroup)^0.5$ which is based on a variance-stabilizing transformation. The inverse of the ARR is called the Number Needed to Treat (NNT). It represents the number of patients who need to receive the intervention for one additional patient to benefit compared to not receiving the treatment over a specific period of time. Where Absolute Risk Reduction (ARR) is the absolute difference in risk of experiencing the outcome between the treated and untreated groups over the specified period. A lower NNT indicates that the treatment is more effective, as fewer patients need to be treated to prevent one additional occurrence of the outcome. Conversely, a higher NNT suggests that the treatment is less effective or that the outcome is less common. : The clinical significance of NNT values can be challenging to interpret as it depends on the context, baseline risk and duration of the follow up [12]. The RR is the most common measure and it is employed to gauge the efficacy of the vaccine [13], which is equal to

$$\mathrm{Ef} = 1 - \mathrm{RR} = 1 - \frac{p\left(I|V\right)}{p\left(I|\overline{V}\right)} \tag{3}$$

where RR is the relative risk [14, 15], that is, the ratio between the proportion of infected individuals (I) among the vaccinated (V) over the proportion of infected individuals among the non-vaccinated $\left(\overline{V}\right)$.

RR is a consistent measure across different baseline risks which allow the comparison across studies and populations. It is also more flexible as it can measure both risk reduction and increase. The logarithm transformation is a common transformation applied to RR that can help to approximate RR values to a normal distribution. This is important when dealing with a meta-analysis of RR values. When the risk varies with time the hazard ratio is an alternative as it measures the instantaneous risk of an event occurring in one group relative to another at any given point in time. It is commonly used in survival analysis [12].

RCT are generally double-blind trials, i.e. trials in which neither the participants nor the researchers know which group they are in. These tests are carried out in a controlled manner and in which the administration and control of the individuals' conditions are more rigorous [10, 11]. However RCTs are usually expensive and time-consuming [16] and its application in certain populations is limited (e.g. pregnant women and children) [17]. The following subsections describe some of sources of bias that can affect the estimation of vaccine efficacy computed through the application of (3).

2.1 Selection Bias

Occurs when there are systematic differences between groups that are compared [18, 19]. For example, if groups are not comparable on key demographic factors,

then between-group differences in treatment outcomes cannot necessarily be attributed solely to the study intervention. Randomisation is the most common way of minimising selection bias and has proved to be an effective tool [20, 21].

2.2 Performance Bias

Refers to systematic differences between groups that occur during the study, for instance exposure to factors other than the intervention of interest [22]. For example, if participants know that they are in the active treatment rather than the control condition, this could create positive expectations that have an impact on treatment outcome beyond that of the intervention itself. Blinding is a way to minimize this bias [21, 23].

2.3 Detection Bias

It refers to systematic differences in the way outcomes are determined. This bias occurs if knowledge of a patient's assigned strategy influences outcome assessment [18]. For example, if care providers in a psychotherapy trial are aware of the investigators hypotheses, this knowledge could unconsciously influence the way they rate participants progress. It is crucial that RCTs address this issue by utilizing independent outcome assessors who are blind to participants assigned treatment groups and investigators' expectations.

2.4 Attrition Bias

Attrition bias occurs when there are systematic differences between groups in withdrawals from a study. It's common for participants to drop out of a trial before or in the middle of treatment. The number of withdrawals in the two groups being compared could make the results biased [24]. In order to obtain results that are closer to reality, it is essential to understand the reasons for dropping out and to compare the dropout rates of the groups in comparison with each other [25]. Over-recruitment can help prevent important attrition bias [24].

2.5 Reporting Bias

Refers to systematic differences between reported and unreported data. Studies with significant results are more likely to be published (this issue is known in the context of systematic reviews as publication bias) [26]. To avoid this bias the outcome measures should be clearly identified in the protocol and not chosen during or in the end of the trial.

2.6 Other Bias

The main sources of bias were previously listed, but other sources of bias are possible. This includes bias that can occur when interventions are not carefully applied, or when there is "contamination" between experimental and control groups within a study (for example, participants in different groups discussing the interventions they are receiving) [27].

3 Test Negative Design

In recent years, the effectiveness of the Influenza vaccine has been evaluated mainly by TNDs [16, 28, 29]. People with more or less severe symptoms are admited in a healtcare facility and are tested to confirm the presence of the virus. Individuals who test positive will be the cases, those who test negative will be the controls. The effectiveness of the vaccine (VE) is given by

$$\mathrm{VE} = 1 - \mathrm{OR} = 1 - \frac{p\left(V|I\right) \times p\left(\overline{V}|\overline{I}\right)}{p\left(\overline{V}|I\right) \times p\left(V|\overline{I}\right)} \tag{4}$$

which show the difference in the likelihood of developing a certain condition, whether or not the vaccine has been administered [30–32]. The estimator defined in (4) is the maximum likelihood estimator of the populational VE. Although it is not an unbiased estimator, it's bias is negligible if the sample size is not low [33].

Another popular measure of association between binary outcomes is the phi coefficient ϕ. It is equivalent to the Pearson correlation coefficient r but applies to two binary variables. The ϕ coefficient ranges from -1 to 1 and its interpretation is similar to the interpretation of r for continuous variables [34].

The odds ratio is a measure that compares the odds of an event occurring in one group relative to another, which is more difficult to interpret. However, it is commonly used in epidemiological studies and clinical trials to quantify the association between an intervention and an outcome as it provides a measure of the relative risk between two groups whereas the phi coefficient may be more suitable for exploratory analyses.

In theory, the measures used in RCT could be used in TND. However, observational studies are susceptible to confounding and biases due to the lack of randomization. Hence, odds ratio estimation through logistic regression models can help adjust the estimation for confounding variables and provide valid measures of association in the presence of these biases [34].

One of the great advantages of TND studies is that they can be easily applied to any population, regardless of whether or not they belong to a risk group, and that they can determine whether different influenza viruses circulating in real-world conditions can influence the effectiveness of the influenza vaccine [11]. In addition, it is a quicker and cheaper form of evaluation than other observational studies such as cohort studies [35]. However, TND studies are not free from bias and some of its sources are listed in what follows.

3.1 Match Between the Circulating and Strains Included in the Vaccine and the Ones Most Prevalent in Circulation

The lack of concordance between the virus strains included in the vaccine and those circulating in a given vaccination season is probably the most important source of bias with a major impact in the VE estimation [36]. The WHO has flu surveillance and monitoring systems in place to determine which strains are more prevalent worldwide. Five reference centres, located in the United States, United Kingdom, Australia, Japan and China are responsible for compiling the information issued by each country, pinpointing the strains that are expected to be most prevalent the following year, and these are the ones that should be included in the next seasonal Influenza vaccine [37]. The high rate of viral mutation, includes less marked processes (antigenic drift) and profound alterations (antigenic shift). Thus circulating strains are not always the ones expected, causing a notable detriment of the VE [38].

From the specific point of view of the flu vaccine, the ideal would be for there to always be match between the strains in circulation and those included in the vaccine. The best way to minimise this bias is to compare seasons separately, not mixing data from match seasons with data from mismatch seasons [1].

3.2 Comorbidities

Comorbidities are also a determining factor [39], especially given that vaccination is recommended for those with chronic health problems. The influence of comorbidities can be analysed in two ways: the ability of the interaction with the vaccine to be robust enough for good protection, and comorbidities as a determining influence on resistance to infection, even if attenuated by the use of the vaccine. The presence of disease and conditions that degrade the individual physically and psychologically interfere with the immune system's ability to respond to the vaccine and resist the disease. Thus, the presence of comorbidities may underestimate VE [40]. However when the performance vaccine is measured by the protection against hospitalization or even against death its performance may be overestimated when there is a high rate of vaccination among these individuals [41].

It seems clear that the presence of comorbidities can affect the effectiveness of the flu vaccine, just like any other vaccine. The best way to control this bias is to compare what is comparable, people with comorbidities should be analysed separately [42].

3.3 Outpatients Versus Inpatatients

TND are mainly suitable for outpatients and do not show such robust results for inpatients [43]. Outpatients and inpatients have substantially different characteristics: disease severity, age, frailer and comorbidities. The inpatient population usually presents more severe symptoms. These characteristics that differentiate the hospitalised population from the well-validated outpatient population could

lead to biased estimates of VE. Specifically, the increased prevalence of chronic respiratory and related diseases among hospitalised adults could lead to biased estimates of influenza VE using the TND [44, 45]. Bias in hospital-based TND estimates would occur if individuals with chronic respiratory diseases, such as chronic obstructive pulmonary disease or congestive heart failure, present with symptoms that mimic the symptoms of an acute respiratory infection (ARI) when they are not experiencing a true ARI. These same individuals may seek medical attention more often. If these patients, who are more likely to test negative for the flu and more likely to present themselves at the hospital, are also more likely to be vaccinated, this could bias estimates of the VE upwards in TND studies. Since the influenza vaccine can provide greater protection against severe illness than against mild to moderate illness, it can be difficult to differentiate bias effect from a true increase in VE.

3.4 The Need to Go to a Healthcare Centre

Another of the sources of bias most often mentioned in the literature is the fact that it only uses information of patients that require recourse to health systems. Given that the majority of flu cases do not require hospital treatment, some data will be difficult to generalise [46]. Symptoms of influenza illness are usually referred to influenza like illness (ILI) and ARI depending on the severity of the symptoms. Not all individuals infected with influenza develop ILI or ARI, some remain asymptomatic. The role of asymptomatic individuals is important to consider when assessing disease dynamics and estimating VE. While asymptomatic individuals are less infectious [47], they may have a similar or greater role in perpetuating an outbreak [48] than their symptomatic counter parts because they may make more contacts, as they do not realize they are infected (e.g., they will not stay home from work or school). Estimates of the proportion of asymptomatic individuals in a given influenza epidemic vary widely [48–50]. We can find studies with 0% to 100% of asymptomatics [50]. Current estimates of VE fail to capture asymptomatic individuals as routine surveillance focuses on symptomatic cases (usually, individuals who seek medical care).

To reduce the loss of information it would be useful to combine other observational studies, such as a cohort study, in which there is a greater follow-up of the population [51].

3.5 Pandemic Seasons

In the context of a pandemic, estimation of influenza VE involves additional challenges. Vaccination should occur at the beginning of flu season, which typically begins in October, in the northern hemisphere. It takes approximately 14 days after vaccination for a healthy adult to reach peak antibody protection [52]. It takes approximately 6 to 8 months to identify and predict which influenza strains to include in the upcoming season's vaccine. During this time, the influenza virus occasionally undergoes antigenic shift, in which it changes to a novel virus, creating potential for a pandemic [52]. The outbreak of a pandemic is usually quick.

The vaccine that contains the pandemic strain is only available months after the start of the pandemic (giving rise to the bias already discussed in subsection 3.1). The delayed and gradual timing of vaccination may introduce additional bias into estimates of VE compared to seasonal epidemics, where most people get vaccinated before the outbreak. Moreover, persons infected prior to vaccination are immune to influenza from the infection and not from vaccination. If such people were also more likely to get vaccinated, measurement of effectiveness would be biased toward a higher VE estimate [53].

3.6 Prior Vaccination

Many studies have tried to understand whether and to what extent previous vaccination interferes with the effectiveness of the seasonal vaccine. Natural infection and vaccination will interfere with the individual's immune system. Theoretically, it's expected that there may be some pre-existing immunity, either from previous infection or vaccination [54], which could favour resistance to the disease [55]. The results are not consensual and all point to great difficulty in controlling all the variables that can interfere with the results [56]. Several studies did not find a significant impact of prior vaccination in VE estimation [57–61].

One way of minimising this type of bias is to compute estimates of effectiveness adjusted for previous vaccination [54].

3.7 Pregancy

Pregnant women are a WHO priority group for influenza vaccination, but evidence from observational studies in pregnancy is subject, among others, to the healthy-vaccinee bias, something common when we analyse comorbidities, overestimating the vaccine effectiveness and safety [62]. Vaccinating pregnant women against influenza presents some challenges both in terms of assessing the safety and effectiveness of the vaccine. In addition to the fact that there are not many studies evaluating the two parameters, some of them have problems with impartiality, since some authors have financial relationships with vaccine producers [63].

3.8 Self-Reported Vaccination Status

Most TND studies use the self-report as a basis for confirming the vaccination of a given individual. Information reported by vaccinated people is usually more reliable than information provided by non-vaccinated [64]. VE underestimation occurs when non-vaccinated individuals identified themselves as being vaccinated. Hence, the use of self-reported influenza vaccination history can meaningfully bias influenza VE estimated through TND [65].

3.9 The Time of Vaccine Administration

The choice of the best time for vaccination is a matter of debate and can be a relevant factor in the preventive effectiveness of the vaccine . It was observed minimal, not statistically significant within-season declines in VE [66], so the recommended time for vaccination of the actual guidelines seems to be a good choice.

3.10 Individual Characteristics Such as Age and Gender

Influenza infection remains a significant burden on older populations and often results in catastrophic disability in those who survive infection [67]. The immune response to the Influenza vaccine differs according to age (comorbidities, as addressed in subsection 3.2, are also associated with older age). The amount and type of antibodies counted are not the same and the elderly have a worse immune response [68]. Some countries provide to the elderly people higher doses or adjuvant vaccines to minimize this problem [69]. TND studies commonly report an overall VE estimate by assigning equal weight to each individual within a sample. When a given population - the elderly, adults or children - is over-represented, the effectiveness data obtained is biased [70]. Many studies aim to assess whether the effectiveness of the flu vaccine differs in men and women. The differences found are not significant, e.g. [39].

3.11 Other Bias

Embryonic egg cells have been the main way of developing Influenza vaccines. In recent years, production methods have been developed in which cell cultures replace eggs in this function due to the associated risk of allergies and to the high demand for eggs [71]. Some studies are trying to determine whether the effectiveness of the two techniques differs significantly. The studies observed do not present very different effectiveness data [72]. A study had the objective of determining the effect oral vitamin A supplementation. In a community with vitamin A deficiencies, vitamin A supplementation increased the response to the Influenza vaccine [73]. Other studies intend to see if the administration of probiotics improves the response to the vaccine. Probiotics are seen as agents that improve the performance of the immune system. Although it is likely that this is the case, and many studies point in this direction, there is still a great deal of heterogeneity in the results [74].

4 Discussion

The effectiveness of the Influenza vaccine depends on a complex set of interactions between the host, including vaccination and natural infection, the virus and environmental factors [75], such as the time of year, exposure to places of higher risk and contact with carriers of the disease. Even in years when influenza

VE is modest, vaccination can drastically lower the disease burden. There are a number of factors that interfere with the effectiveness of the Influenza vaccine and which can introduce bias into the estimates.

RCT and TND are the most used study designs to assess the performance of the seasonal Influenza vaccine. There is a lot of information about sources of bias estimating the efficacy/effectiveness of the seasonal influenza vaccine. In RCT studies, the information is systematised and there is a widely used bias assessment tool, Rob 2 [76], which is recommended by the Cochrane's library (available in www.cochranelibrary.com). As far as TNDs are concerned, there are many studies on this subject, but the information is very dispersed and there is no specific tool for assessing bias in TNDs. This paper gathers and compares some information present in the literature on this topic.

Although RCT studies are considered to be the gold standard of the experimental study designs [10, 77], they are not without sources of bias. This work lists problems associated with this study design that con be overcome through randomisation and blindness, which increase the robustness of the results obtained.

All limitations pointed out in RCTs are not exclusive to this type of study. They are even more marked in quasi-RCTs [78].

TND is a derivation of the control case, an observational study. As an observational study, TND has source os bias common to these types os studies (Hammer et al., 2009). In Cohort studies, for example, Self-Reported Vaccination Status would be a source of bias in exactly the same way as in TND. Several sources of bias concerning TND were previously identified. Some bias can overestimate the performance of a vaccine and another ones can underestimate it. While some sources of bias such as comorbidities, pandemic seasons and self-reported vaccination status and age tend to underestimate effectiveness, the match between the strains included in the vaccine and the most prevalent ones in circulation improves the estimation of effectiveness. Studies including only inpatients or inpatients and outpatients tend to overestimate VE because inpatients are often tested to influenza when the symptoms shown are associated with others health problems. Some sources of bias such as pregnancy, vaccination period, gender, mood during the vaccine uptake, vaccine development substrate, probiotics and supplementation do not seem to significantly influence the estimation of VE, or at least results in different studies are inconsistent.

The role of prior vaccination in VE estimation is widely discussed in literature. It is expected that in the unvaccinated it could underestimate VE since it could increase the number of unvaccinated people who are not infected, due to some residual protection from previous vaccines. On the other hand, in individuals vaccinated in the current season, VE may be overestimated as they add to the current vaccination some immunity from previous years of vaccination, which may even include strains that are prevalent in the year in which the effectiveness is being evaluated.

The need to go to a healthcare centre is a source of bias for different reasons. The role of asymptomatic patients stands out, as they have a great influence

on the spread of the disease but are rarely tested. Studies designed to estimate VE against asymptomatic influenza are difficult and expensive as these studies require frequent testing of study participants to capture asymptomatic cases [46]. In addition, factors such as the socio-economic status, lifestyle and health condition of the individuals who visit health centres may not be similar to those of the general population [79]. In order to obtain more reliable and complete results on a given population, it would be useful to use TND-type studies associated with cohort studies, in which information on asymptomatic patients who have contracted the disease and who have not had to resort to health services is not lost and we have data on the effectiveness of disease prevention that is closer to reality [46, 80]. TND studies are a reliable tool for evaluating the Influenza vaccine [81, 1]. This type of study controls bias well and presents robust results [44, 81]. The VE estimated by RCT studies was 10% higher than the VE estimated through the TNDs although the difference was not significant [1]. The lower value of effectiveness obtained by TND studies is not surprising considering the various sources of bias that can underestimate the VE. Of all the factors identified having an impact on VE estimation, the match between the strains included in the vaccine and the most prevalent in circulation is the most determining factor [1, 82], especially in elderly [83, 84]. Hence, it is not relevant to have a high number of strains in a vaccine if they do not match the strains the vaccine aims to prevent [85–87].

5 Conclusion

As VE is an estimate of a causal effect from observational studies, any estimate should be adjusted for potential confounding variables, i.e., variables associated with both vaccination and risk of influenza [88]. It is also interesting to observe that pooled VE obtained from adjusted and non-adjusted estimates were not significantly different in a recent systematic review [1]. This leads to believe that the impact of some of the confounding variables identified in the literature as influencing VE (e.g., prior vaccination) is limited, as some authors have already referred [89]. This discussion about the TND source of bias can contribute to develop a specific quality assessment tool for TND studies taking into account its wide use and relevance in the evaluation of VE.

Acknowledgments This work is partially financed by national funds through FCT – Fundação para a Ciência e a Tecnologia under the project UIDB/00006/2020. DOI: 10.54499/UIDB/00006/2020 (https://doi.org/10.54499/UIDB/00006/2020).

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