Toward a better understanding of the relationship between influenza vaccine effectiveness against specific and non-specific endpoints and vaccine effectiveness against influenza infection

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ABSTRACT

In influenza vaccination studies assessing vaccine effectiveness (VE), both specific and non-specific endpoints (outcomes) are used. We present a formula for the relationship between VE against influenza-related outcomes (VE_E), specific and non-specific, and that against influenza infection (VE_I). In its simplest form, the formula comprises two additional parameters: the influenza attack rate among unvaccinated subjects, and the relative risk of the outcome for influenza infected subjects versus non-infected subjects. Both parameters may show large between-seasonal variation, which translates to a large between-seasonal variation of VE_E estimates. With the full form of the formula it can be shown that, contrary to popular believe, VE_E may be greater than VE_I. We argue that interpreting VE_E estimates in terms of "low" or "high" is not possible without taking the costs of an outcome case into account. We conclude that the decision to use a non-specific endpoint as surrogate for influenza infection should be taken in the awareness of these limitations.

Key words: influenza; vaccine effectiveness; endpoints; specific and non-specific

INTRODUCTION

Influenza vaccine effectiveness field studies are conducted to assess vaccine effectiveness, i.e. to assess how well vaccinated subjects are protected against influenza infection in the "real world". In such studies, both specific and non-specific endpoints are employed. A specific endpoint is based on a laboratory test for

influenza infection, e.g. the real-time polymerase chain reaction (PCR) test [1]. A non-specific endpoint refers to an influenza-related but not laboratory-confirmed clinical syndrome. An example of such a syndrome is e.g. influenza-like illness (ILI), a respiratory illness characterized by fever, fatigue, cough and other symptoms. Influenza is not the only cause of ILI, it can be caused by other viruses as well, for example by the norovirus (the "winter vomiting bug"), the most common cause of viral gastroenteritis. Because influenza is not the only cause of ILI, the syndrome is non-specific for influenza. One reason for using non-specific endpoints as surrogate for infection in influenza vaccine effectiveness studies is ease of case finding, as usually non-specific endpoint cases are easier to identify than specific endpoint cases (see below.)

It is well-known that both specific and non-specific endpoints may lead to a biased estimate of the underlying vaccine effectiveness against influenza infection, denoted here by VE_I. Vaccine effectiveness is defined as the fraction of influenza cases directly prevented by the vaccination. It can be any value between zero (no cases prevented) and one (100% of cases prevented). A non-specific endpoint as surrogate for influenza infection will, as is generally assumed, underestimate VE_I. The reason for this is that there may be endpoint cases due to other causes than influenza infection, cases that cannot be prevented by influenza vaccination [2]. Assume, for example, that the vaccine effectiveness against influenza is 0.75, but that one-fifth of the endpoint cases is due to other causes. Influenza vaccination will prevent 75% of the endpoint cases caused by influenza, but only 0.75 x 0.8 = 60% of *all* endpoint cases. However, using a specific endpoint as surrogate for influenza infection also may not yield fully accurate results. A laboratory test for influenza infection will usually only be done in case of clinical signs and symptoms, which means that non-symptomatic influenza infections will go undetected. Also, when the PCR test is used to determine infection, a nasopharyngeal swab must be collected. It may not be possible to collect all specimens within a few days of symptoms onset and the laboratory test may be done too late, after viral shedding has stopped, causing a number of influenza cases to be missed and VE_I to be underestimated. This is why specific endpoint are generally more difficult to identify than non-specific ones. Conversely, if less severe influenza cases go undetected by the laboratory test, and the less severe cases are predominantly in the vaccinated group, overestimation of VE_I may occur, as has been pointed out by Nauta [3].

To improve understanding of the relationship between vaccine effectiveness against influenza infection and that against specific and non-specific endpoints, we felt a formula would be helpful. From the formula it follows that, contrary to popular believe, vaccine effectiveness against a non-specific endpoint can be greater than vaccine effectiveness against influenza infection. The added Public Health value of the formula is twofold. First, it may help investigators to better understand the limitations of non-specific endpoints. Second, it may help health care workers to correctly interpret estimates of influenza vaccine effectiveness against serious clinical endpoints such as pneumonia or pulmonary embolism. We will show that these estimates can vary considerably between seasons and require a different interpretation than estimates of influenza vaccine effectiveness against infection.

METHODS

Formula for the relationship between vaccine effectiveness against influenza-related endpoints and vaccine effectiveness against influenza infection

Influenza infection may be defined as the biological process of viral intrusion of upper respiratory cells and replication of new influenza virus particles. The standard measure for vaccine effectiveness against influenza infection is one minus the relative risk of influenza infection for vaccinated versus unvaccinated subjects:

$$VE_I = 1 - R_v(I)/R_u(I) \qquad (1)$$

where $R_v(I)$ and $R_u(I)$ are the respective risks of influenza infection for vaccinated and unvaccinated subjects during the influenza season [4]. These risks are usually called "influenza attack rates" [5]. VE_I is the fraction of influenza cases directly prevented by the vaccination and not by other, indirect, vaccine effects such as herd immunity [6]. VE_I can take on any value between zero (no influenza cases prevented, $R_v(I) = R_u(I)$) and one (all influenza cases prevented, $R_v(I) = 0$.)

Likewise, the standard measure for vaccine effectiveness against an influenza-related endpoint is

$$VE_E = 1 - R_v(E)/R_u(E) \qquad (2)$$

where $R_v(E)$ is the risk of the endpoint for vaccinated subjects during the influenza season, and $R_u(E)$ that for unvaccinated subjects. VE_E is the fraction of prevented endpoint cases. The maximum value for VE_E will be lower than one because there are endpoint cases that are not caused by influenza and which thus cannot be prevented by influenza vaccination.

The derivation of the formula for the relationship between VE_E and VE_I can be followed in the Appendix. In its simplest form, the formula comprises two parameters: $R_u(I)$ (see equation 1), the risk of influenza infection for unvaccinated subjects, and RR(E), the relative risk of the endpoint for *influenza infected* subjects versus *non-infected* subjects:

$$VE_E = \frac{(RR(E) - 1) \cdot VE_I}{(RR(E) - 1) + 1/R_u(I)} \qquad (3)$$

RR(E) is a measure of the strength of the relationship between the endpoint and influenza infection. It is strong for specific endpoints, weaker for non-specific endpoints, and one in case there is no relationship at all between the endpoint and influenza infection (like for the endpoint toothache for example).

Example 1. Consider the use of ILI as surrogate endpoint for symptomatic influenza infection. Because by definition all symptomatic influenza cases develop ILI symptoms, the risk of ILI for influenza infected subjects is 1.0. Jackson et al. [7] find that the risk of ILI for subjects who do not get influenza infected is approximately 0.097. Thus, RR(ILI) ≈ 1.0/0.097 = 10.3, a value implying that the strength of the relationship between ILI and symptomatic influenza infection is only modest. Now, if VE_I = 0.70 and the influenza attack rate between seasons varies between 0.01 and 0.10, then, according to formula (3), VE_E will vary between 0.060 and 0.337, due to this variation in the attack rate. This is a rather wide range and what is more, it shows that with a non-specific surrogate endpoint such as ILI, VE_I (here 0.70) can be considerably underestimated.

From (3) it follows that

$$VE_E \leq \frac{(RR(E)-1)}{(RR(E)-1)+1/R_u(I)} < 1.0 \qquad (4)$$

Thus, VE_E is always smaller than 1.0. This has considerable consequences for the interpretation of VE_E.

Example 2. In influenza VE studies, non-specific endpoints are sometimes employed not as surrogate for influenza infection, but because the endpoint is serious or life-threatening and an investigator wishes to assess the impact of influenza vaccination on its incidence. An example of a serious endpoint would be myocarditis (inflammation of the heart muscle), most often caused by a viral infection. Jackson et al. find RR(*Myocarditis*) = 2.1 [7]. Given that the attack rate of (seasonal) influenza will rarely be larger than 0.15, the vaccine effectiveness against myocarditis will be at most (2.1-1.0)/(2.1-1.0+1/0.15) = 0.14 (14% of myocarditis cases prevented).

Formula (3) rests on two assumptions, namely i.) that the endpoint risk does not differ between vaccinated and unvaccinated *non-infected* subjects, and ii.) that it does not differ between vaccinated and unvaccinated *infected* subjects. Because vaccination state is not likely to influence the risk of developing the endpoint due to other pathogens than influenza virus, the first assumption will usually be met. The second assumption, however, will not be met if *vaccinated* infected subjects become less clinically ill from the infection, making them less susceptible to the endpoint compared to *unvaccinated* infected subjects. We use the symbol γ to express this difference in susceptibility. The full formula for the relationship between VE_E and VE_I then is

$$VE_E = \frac{(RR_u(E)-1)-(\gamma \cdot RR_u(E)-1)\cdot(1-VE_I)}{(RR_u(E)-1)+1/R_u(I)} \qquad (5)$$

If, for example, γ = 0.8, the risk of the endpoint for vaccinated infected subjects is 0.8 times the risk for unvaccinated infected subjects. $RR_u(E)$ is the relative risk of the endpoint for influenza infected unvaccinated subjects versus non-infected unvaccinated subjects.

Example 3. Assume that VE_I = 0.7, $RR_u(E)$ = 9.0, $R_u(I)$ = 0.05 and γ = 1.0. Then VE_E = 0.2 (20% of endpoint cases prevented by influenza vaccination). Next, assume that γ = 0.6. Then VE_E = 0.24 (24% of cases prevented). This is explained by the fact that *vaccinated* endpoint cases are not only prevented by the vaccination but also by being less susceptible to the endpoint when infected.

Interestingly, formula (5) indicates that, contrary to popular believe, VE_E can be larger than VE_I. As a rule of the thumb, this will be the case when γ is not close to 1.0 or when $RR_u(E)$ is large. For example when γ = 0.6, $RR_u(E)$ = 100, $R_u(I)$= 0.11 and VE_I = 0.70, then VE_E = 0.75 > VE_I

DISCUSSION

We hope that our formula will help investigators and health care workers to better understand influenza vaccine effectiveness against other endpoints than influenza infection.

The measure to capture influenza vaccine effectiveness against infection, VE_I, is not a constant of nature. Instead, it shows seasonal variation as it depends, amongst others, on the antigenic match between vaccine component and circulating strain, and pre-seasonal immunity (including the effects of previous vaccinations). This may modulate antibody response. The use of particular non-specific endpoints as surrogate for influenza infection will add to this variation, and, as we saw, the additional variation can be considerable. The most important reason for this additional variation is the between-season variation in influenza attack rate. There are seasons with wide epidemic spread, affecting large parts of the population, and non-epidemic seasons with sporadic outbreaks only. The attack rate itself is a combined parameter consisting of the epidemic strength (risk of exposure) and the natural pre-seasonal immunity in the population (risk of infection in unvaccinated subjects), which may vary independently or in correlation. Thus, estimates of vaccine effectiveness that are based on non-specific endpoints show larger variation than estimates based on specific endpoints. This increase in variability is unavoidable.

If in influenza vaccine effectiveness studies non-specific endpoints are employed not as a surrogate for influenza infection, but because the endpoint is serious or life-threatening, the question arises, how to interpret the

resulting effectiveness estimate. VE_I is easy to interpret: an estimate of 0.35 means a moderate vaccine effectiveness against influenza infection (only 35% of influenza cases prevented), given the maximum possible value of 1.0 (100% of influenza cases prevented.) For VE_E such univocal interpretation in terms of low, moderate or high is less straightforward. The reason for this is that its maximum possible value is as we saw less than 1.0, and usually unknown. An estimate of 0.15 means 15% of endpoint cases prevented, but it is impossible to decide if this is a low or high effectiveness. To be able to use the adjectives low or high, the "costs" of an endpoint case have to be taken into account. For some endpoints, for example death from all causes, 5% of cases prevented [8] may be considered an excellent influenza vaccine effectiveness, while for other endpoints it may imply a low effectiveness.

Finally, as noted in the Introduction, it is often thought that when a non-specific endpoint is employed as surrogate for influenza infection VE_I will be underestimated, that $VE_E < VE_I$. From our formula it follows that this need not be the case. Overestimation of VE_I may occur when vaccinated infected influenza cases are less susceptible to the endpoint than unvaccinated infected cases. This was already known for specific endpoints, when the specificity of the laboratory test is lower for vaccinated infected subjects than for unvaccinated infected subjects [3]. With our formula this can now be generalized to all endpoints, including non-specific ones.

In conclusion: variation in VE_E is unavoidable as it is inherent to the measure, and its extent is such that the results of single studies using specific or non-specific endpoints may not be representative of the performance of influenza vaccines in general. Their use as basis for health care decisions and vaccination policies should be reconsidered.

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APPENDIX – DERIVATION OF THE FORMULA

The risks discussed here are probabilities, the probabilities than certain clinical events –influenza infection, an influenza-related outcome– occur. We investigated the relationship between VE_E and VE_I by applying a basic probability rule to these risks. Before presenting our derivation, we first introduce two other risks/probabilities:

R(E|I): Risk of the outcome *given* being influenza infected

R(E|¬I): Risk of the outcome *given* not being influenza infected (with not denoted by the symbol ¬)

These risks are so-called conditional risks, with the condition given after the symbol |. For the first risk the condition is: being influenza infected, for the second risk the condition is: not being influenza infected. An outcome is influenza-related if R(E|I) >R(E|¬I). The basic probability rule we use is

$$R(E) = [R(E|I) - R(E|\neg I)]\cdot R(I) + R(E|\neg I)$$

Define

$$R_v(E|I) = \gamma\cdot R_u(E|I)$$
$$RR_u(E) = R_u(E|I)/R_u(E|\neg I)$$
$$VEI = 1-R_v(I)/R_u(I)$$

and assume that

$$R_v(E|\neg I) = R_u(E|\neg I) = R(E|\neg I)$$

that is, assume that the risk of the outcome does not differ between vaccinated and unvaccinated *non-infected* subjects. Then, with the basic probability rule and some simple algebra it follows that

$$\begin{aligned}
[R_u(E) - R_v(E)] &= [R_u(E|I) - R_u(E|\neg I)]\cdot R_u(I) + R_u(E|\neg I) - [R_v(E|I) - R_v(E|\neg I)]\cdot R_v(I) - R_v(E|\neg I)\\
&= [R_u(E|I) - R(E|\neg I)]\cdot R_u(I) + R(E|\neg I) - [\gamma\cdot R_u(E|I) - R(E|\neg I)]\cdot R_v(I) - R(E|\neg I)\\
&= [R_u(E|I) - R(E|\neg I)]\cdot R_u(I) - [\gamma\cdot R_u(E|I) - R(E|\neg I)]\cdot R_v(I)\\
&= [R_u(E|I) - R(E|\neg I)]\cdot R_u(I) - [\gamma\cdot R_u(E|I) - R(E|\neg I)]\cdot(1-VE_I)\cdot R_u(I)\\
&= [RR_u(E)\cdot R_u(E|\neg I) - R(E|\neg I)]\cdot R_u(I) - [\gamma\cdot RR_u(E)\cdot R_u(E|\neg I) - R(E|\neg I)]\cdot(1-VE_I)\cdot R_u(I)\\
&= [RR_u(E)\cdot R(E|\neg I) - R(E|\neg I)]\cdot R_u(I) - [\gamma\cdot RR_u(E)\cdot R(E|\neg I) - R(E|\neg I)]\cdot(1-VE_I)\cdot R_u(I)\\
&= (RR_u(E)-1)\cdot R(E|\neg I)\cdot R_u(I) - [(\gamma\cdot RR_u(E)-1]\cdot R(E|\neg I)\cdot(1-VE_I)\cdot R_u(I)
\end{aligned}$$

$$\begin{aligned}
R_u(E) &= [R_u(E|I) - R_u(E|\neg I)]\cdot R_u(I) + R_u(E|\neg I)\\
&= [R_u(E|I)/R_u(E|\neg I) - 1]\cdot R_u(E|\neg I)]\cdot R_u(I) + R_u(E|\neg I)\\
&= (RR_u(E)-1)\cdot R(E|\neg I)\cdot R_u(I) + R(E|\neg I)
\end{aligned}$$

Hence

$$\begin{aligned}
VE_E &= 1-R_v(E)/R_u(E)\\
&= [R_u(E) - R_v(E)]/R_u(E)\\
&= \frac{(RR_u(E)-1) - (\gamma\cdot RR_u(E)-1)\cdot(1-VE_I)}{(RR_u(E)-1) + 1/R_u(I)}
\end{aligned}$$

When $\gamma = 1$, $RR_u(E) = RR(E)$ and the formula above simplifies to

$$VE_E = \frac{(RR(E)-1)\cdot VE_I}{(RR(E)-1) + 1/R_u(I)}$$