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Review

Vaccine effects and impact of vaccination programmes in post-licensure studies

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ABSTRACT

Once a vaccine is licensed and introduced in the population, post-licensure studies are required to measure vaccine effectiveness and impact of vaccination programmes on the population at large. However, confusion still prevails around these concepts, making it difficult to discern which effects are measured in such studies and how their findings should be interpreted. We review from the public health evaluation perspective the effects of vaccine-related exposures, describe the methods used to measure them and their assumptions.

We distinguish effects due to exposure to individual vaccination from those due to exposure to a vaccination programme, as the latter depends on vaccine coverage, other population factors and includes indirect effects as well. Vaccine (direct) effectiveness is estimated by comparing vaccinated and unvaccinated individuals exposed to the same vaccination programme. The impact of a vaccination programme, defined here as the population prevented fraction when exposure is the programme, is measured by comparing populations with and without a vaccination programme, most commonly the same population before and after vaccination. These designs are based on a number of assumptions for valid inference. In particular, they assume that vaccinees and non-vaccinees do not differ in terms of susceptibility and exposure to the disease or in ascertainment of vaccination and disease status. In pre and post-vaccination design, the population is assumed to have similar baseline transmission, case detection and reporting, risk factors and medical practices in both periods.

These principles are frequently violated in post-licensure studies. Potential confounding and biases must be minimized in study design and analyses, or taken into account during result interpretation. It is also essential to define which exposure is evaluated (individual vaccination or vaccination programme) and which effect is measured. This may help decision-makers clarify which type of study is needed and how to interpret the results.

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1. Introduction

Before licensure, a vaccine must demonstrate its immunogenicity and/or protective efficacy in clinical trials, as well as its quality and safety [1,2]. Once the vaccine is authorized by regulatory authorities and used in the population at large, post-licensure studies are required to assess vaccine safety and effectiveness, as well as impact of vaccination programmes [3]. This monitoring of the benefit–risk balance is currently an integral part of the life cycle of vaccines [4].

Vaccine efficacy, and the study designs used to measure it, are clearly defined [3,5,6]. But the distinction from vaccine effectiveness is often ignored [3,5,6]. The term impact of a vaccination programme is widely used in the literature and by international agencies but what it exactly means and how to measure it is usually not described and certainly not standardized [1,2,7–9]. Overall, post-licensure vaccine studies use diverging terms to describe different types of effect. This confusion in terminology implies that the type of post-licensure effects that is expected from a vaccine – or a vaccination programme – is rarely clarified at the level of decision-makers.

Post-licensure studies are mainly observational because the real-life effects of a vaccine administered in a public health programme are difficult to measure in an experimental design. Observational designs are based on a number of assumptions that are rarely met, and their findings are thus prone to biases. Decision-makers in the vaccine world need to know which effect is measured and which are the methodological limitations to be able to interpret and use the findings of post-licensure studies.

Our objective is to review and delineate, among the various evaluations of vaccine intervention, what applies to the effectiveness of vaccines and to the impact of vaccination programmes. We propose a bridge between the effects of vaccine, as defined in previous work [10,11], and epidemiological measures of public health impact. We describe relevant methods to measure these effects and discuss the assumptions and potential biases that are involved.

2. The concepts

2.1. Definitions

Vaccine efficacy is commonly defined as the direct effect of a vaccine measured in pre-licensure randomized clinical trials, where vaccination is allocated under optimal conditions (Table 1) [3,10]. It is estimated by comparing disease occurrence between vaccinated and non-vaccinated individuals in a population. When vaccination is randomly administered and blinding is ensured, it is assumed that any differences in disease occurrence can be attributed to the direct effect of the vaccine [3,11].

Most sources define vaccine effectiveness as a measure of protection attributable to a vaccine administered under field conditions to a given population [1,3,6,12]. It is measured by observational post-licensure studies. It can thus be clearly distinguished from vaccine efficacy [3,10,13]. Both vaccine efficacy and effectiveness (VE) are measured according to the following formula:

$$\mathrm{VE} = \frac{R_{\text{unvaccinated}} - R_{\text{vaccinated}}}{R_{\text{unvaccinated}}}$$

R: risk or rate

Although international agencies such as the World Health Organization (WHO) and the European Medicines Agency advocate the need to assess the impact of vaccination programmes on disease occurrence, we could not find a definition for the impact of a vaccination programme [1,2,6,9]. In the majority of studies, the impact of a vaccination programme is expressed as the proportionate reduction in disease burden, comparing incidences in the same population between a pre-vaccine and a post-vaccine period according to this formula [8,14–20]:

$$\mathrm{IMPACT} = \frac{IR_{\text{pre-vaccine}} - IR_{\text{post-vaccine}}}{IR_{\text{pre-vaccine}}} = 1 - IRR$$

IR: incidence rate, IRR: incidence rate ratio

However, a number of other studies assessed the impact of vaccination programmes by comparing changes in prevalence of an outcome (e.g. pathogen carriage), proportion of samples testing positive for the target disease, health care use or median age at infection before and after vaccination [22–26].

2.2. The different effects of vaccine and vaccination programme

In epidemiology, the effect of an exposure is defined as the amount of change (increase or decrease) in a population disease (or any other outcome) caused by this exposure [27]. Depending on the outcome measured, the effect is the change in incidence rate, proportion or prevalence of this outcome attributed to that particular exposure.

In vaccinology, the exposure classically consists in vaccination; more specifically individuals are exposed to a specific vaccine administered with a given schedule at a specific time. But a vaccination programme may also reduce the risk of disease by reducing transmission in the entire population, including the unvaccinated. In that case, the effect of the programme would be more than the sum of the effects of vaccination on those vaccinated, due to this indirect effect (see below). Thus in a population in which there is a vaccination programme, the entire population is exposed to the effect of the programme, even if only a fraction is vaccinated.

Halloran et al. distinguished four kinds of effect of vaccine and vaccination programmes (Fig. 1). The *direct effect* is measured by comparing vaccinated and unvaccinated persons belonging to the same population and exposed to the same vaccination programme to cancel the programme-specific effect [11,28]. In the indirect, total and overall effects, the exposure is the vaccination programme. These effects are measured by comparing two populations, the population exposed to the programme and a reference population without a vaccination programme (only unvaccinated individuals). *The indirect effect* is the population-level effects of widespread vaccination, as a result of reduced transmission – also