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Beyond efficacy: The full public health impact of vaccines

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ABSTRACT

There is an active discussion in the public health community on how to assess and incorporate, in addition to safety and measures of protective efficacy, the full public health value of preventive vaccines into the evidence-based decision-making process of vaccine licensure and recommendations for public health use. The conference "Beyond efficacy: the full public health impact of vaccines in addition to efficacy measures in trials" held in Annecy, France (June 22–24, 2015) has addressed this issue and provided recommendations on how to better capture the whole public health impact of vaccines.

Using key examples, the expert group stressed that we are in the midst of a new paradigm in vaccine evaluation, where all aspects of public health value of vaccines beyond efficacy should be evaluated. To yield a wider scope of vaccine benefits, additional measures such as vaccine preventable disease incidence, overall efficacy and other outcomes such as under-five mortality or non-etiologically confirmed clinical syndromes should be assessed in addition to traditional efficacy or effectiveness measurements. Dynamic modelling and the use of probe studies should also be considered to provide additional insight to the full public health value of a vaccine. The use of burden reduction and conditional licensure of vaccines based on collection of outcome results should be considered by regulatory agencies.

1. Introduction

Traditionally, vaccine efficacy, i.e. the percentage reduction of disease in a vaccinated group compared to an unvaccinated group, has been used as the primary benchmark for vaccine licensure. However, efficacy provides a measure of proportionate reduction, is limited to etiologically confirmed disease, and focuses on individual level effects; consequently, it does not capture the full public health impact of a vaccination program. In addition to preventing infection in individuals, the ultimate goal of vaccination is to achieve a significant public health impact in the catchment population. Thus, there is a need to provide a broader measure of impact beyond efficacy and safety that encompasses the capacity of a vaccination program to reduce infection transmission, disease burden (incidence, mortality, sequelae), the pressure on health systems and health inequities between populations, as well as measure coverage and mechanisms of action, all of which help determine a vaccine's impact [1,2]. Additionally, the full public health impact will require additional measures, such as vaccine preventable disease incidence (VPDI), number needed to vaccinate, and a wider range of outcomes, such as under-five mortality, impact on syndromic disease, and indirect vaccine effects, as well as additional analytic or design strategies, such as dynamic modelling (i.e. statistical approaches used to express and model the behaviour of a system overtime) and the use of probe studies (i.e. that attempt to estimate the impact of vaccines against syndromes or disease states). These issues are often lost in regulatory discussions, where there is a focus on risk: benefit ratios, as measured only by vaccine efficacy and safety. The relevance of these issues is highlighted herein with reference to pneumococcal, rotavirus, malaria and dengue vaccines.

To consider approaches to expand regulatory and policy discussions towards integrating disease burden reduction and vaccine efficacy/effectiveness measurements, the Fondation Mérieux organized a conference from June 22–24, 2015 entitled: "Beyond efficacy: the full public health impact of vaccines in addition to efficacy measures in trials" in Annecy, France ("Les Pensières" Conference Centre). A multi-disciplinary group of experts drawn from academia, industry, international organizations and public health institutes gathered to discuss the public health impact of vaccination on preventable disease burden in the contexts of vaccine licensure, developing evidence-informed immunization program policy for public sector vaccination programs and of developing communication strategies for target populations. Key issues addressed included:

- The concept of moderately effective vaccines and the limits of vaccine efficacy
- Preventable disease burden outcomes and measurement
- Key examples from the past and potential examples from the future
- The role of modelling and probe studies in assessing preventable disease burden
- The potential for regulatory agencies to consider preventable disease burden as a criterion for vaccine licensure

This report provides a summary of selected issues discussed by participants, key findings and recommendations for future approaches to addressing the full health impact of vaccines.

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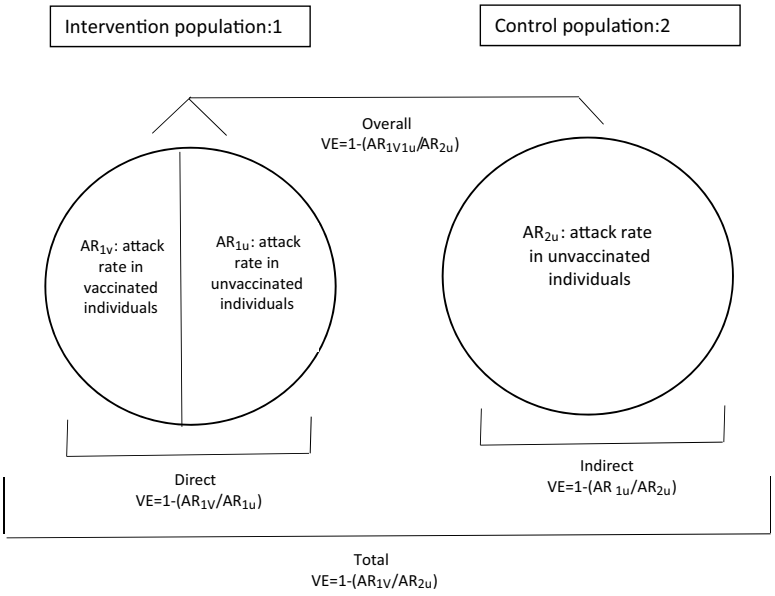

Fig. 1. Types of vaccine effectiveness as reported by Halloran [6], kindly provided by Ira Longini. AR, attack rates of disease; VE, vaccine effectiveness. Presence of unvaccinated individuals in the intervention population is explained by a coverage rate of less than 100%, which is in general never reached.

2. General concepts and methodological approaches

In the vaccine licensure pathway, randomized clinical trials, including those used for phase III trials, are designed to assess vaccine efficacy that is defined as: "the proportionate reduction of the incidence of the target infection in vaccinated subjects compared to controls" [3]. However, it is equally important to assess vaccine effectiveness, generally assessed in phase IV trials, which is defined as the actual performance of a vaccine at population level, or the balance of benefits and risks following introduction of a vaccine into routine immunization programs [3]. Both vaccine efficacy and effectiveness can be based on individual or cluster-randomized designs and can report direct and indirect effects of vaccines. Direct effect is the direct protective effect in a vaccinated subject. Indirect effects correspond to the reduction of infection or disease transmission in unimmunized subjects due to the presence of immune individuals [4,5]. Total vaccine effectiveness is the combined effects of the chosen vaccination strategy and direct protective effect in vaccinated subjects while overall vaccine effectiveness (i.e. herd effect) is the effect of vaccine in the population with immunized and unimmunized subjects as compared to if the population had not had the vaccination strategy [6] (Fig. 1).

Documentation of the overall vaccine effect (i.e. herd effect) is increasingly required as countries introduce new vaccines into their immunization programs. Its assessment is usually implemented post-licensure, but can face difficulties in the developing world due to the lack of adequate infrastructure for immunization records, surveillance and laboratory confirmation of the target disease. In these countries, cluster-randomized or group-randomized studies can be performed to evaluate vaccine effectiveness in parallel to vaccine efficacy during phase III vaccine trials. Schools [7], communities [8,9], dwellings or premises [10], and contagious geographical neighbourhoods [11,12] have been used as clusters in vaccine trials to assess herd protection. Cluster randomization allows more direct examination of the herd effect but requires minimal level of transmission between clusters, knowledge of the population before randomization and larger sample size. Extrapolation of the results to other clusters could be performed by using mathematical modelling.

Assessment of vaccine effectiveness characterizes the vaccine performance when implemented in a public health program, but it does not tell the full story of the impact of vaccines on disease burden. Indeed, most studies cannot have etiologic confirmation of 100% of true cases due to the limited sensitivity or specificity of laboratory tests for some pathogens. The inability to accurately document vaccine impact on disease burden using directly measured etiologically-confirmed cases is problematic since policymakers consistently mention the burden of etiologically-confirmed clinical disease as one of the most important factors in priority setting.

Measures beyond efficacy, such as vaccine preventable disease incidence (VPDI), may provide further information to inform economic assessment of vaccines. VPDI is defined as: outcome incidence in an unvaccinated population × vaccine effectiveness. It is a combined measure of vaccine effectiveness (or efficacy) and the baseline disease burden [13]. The measurement of VPDI during clinical trials in addition to traditional efficacy or effectiveness measurements can overcome limitations related to suboptimal sensitivity or lack of diagnostic tests, and allow measurement of the total burden of disease preventable by vaccine regardless of whether disease is etiologically confirmed or clinically suspected. Vaccine efficacy is usually used to confirm that a vaccine works, and thus is best documented against etiologically confirmed disease. By contrast, VPDI is used to estimate total disease burden reduction from a vaccine and is thus optimally calculated from vaccine impact on syndromic disease, as this approach also measures the contribution of the pathogen to the causal chain of illness regardless of where in the chain the pathogen occurs.

2.1. Vaccine probe studies

Vaccine probe studies emerged in the past 15 years and are particularly useful for pathogens for which the true burden may be hidden due to the absence of accurate laboratory testing or limited sensitivity of available diagnostics Vaccine probe studies can estimate VPDI, as well as the proportion of a syndrome caused by the pathogen, ideally, via randomized clinical trials [13] (note that while less precise, VPDI can also be estimated post licensure by evaluating changes in outcome incidence during the pre- and post-vaccine period and using time-series analysis can also be used).

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