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Safety and perception: What are the greatest enemies of HPV vaccination programmes?

Paolo Bonanni, Beatrice Zanella, Francesca Santomauro, Chiara Lorini, Angela Bechini, Sara Boccalini *

Department of Health Sciences, University of Florence, Viale Morgagni 48, 50134 Florence, Italy

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ABSTRACT

Vaccines stimulate a person's immune system to produce an adequate reaction against a specific infectious agent; i.e. the person is protected from that disease without having to get it first. As vaccines are administrated to healthy subjects, they are held to the highest standards of safety. Regarding human papillomavirus (HPV) vaccines, at present three prophylactic vaccines are licensed (bivalent HPV 16/18, quadrivalent HPV 6/11/16/18 and the nonovalent HPV 6/11/16/18/31/33/45/52/58 vaccine). Pre- and post-licensure studies (i.e. not yet for nonovalent HPV vaccine) confirm that HPV vaccines are generally safe and well-tolerated, site injections symptoms are the most common adverse events (AEs) reported, and pain is the most frequently referred local symptom. Serious AEs are rare and not associated with severe sequelae, at least no vaccine-related deaths have occurred. Despite these scientific evidences, it is still difficult to explain to the population the importance of a good vaccination programme. There are many determinants for HPV vaccines hesitancy which represent a barrier that must be overcome in order to increase vaccine coverage, including psychological reactions, religious or cultural aspects, and fear of possible AEs (demyelinating diseases, Complex Regional Pain Syndrome – CRPS, or Postural Orthostatic Tachycardia Syndrome – POTS). A weak communication strategy which frequently suffers due to spread of unverified news by media and websites may lead to the failure of a vaccination programme. Such a situation happened in Japan (2013), due to which a great number of women remain vulnerable to HPV-related cancers. In order to resolve the issues around HPV vaccines acceptance, it is necessary to use good communication strategies. Multicomponent and dialogue-based interventions seem to be the most effective, especially if an adequate language is used, customized according to the vaccination programme target.

1. Introduction

Vaccines stimulate a person's immune system to produce an adequate reaction against a specific infectious agent, protecting the person from the disease without having to get it first [1]. Unlike most medicinal products that treat or cure diseases, vaccines prevent them [2]. Vaccines act at both individual and population levels (herd immunity) and can modify the immune status and the epidemiology of an infectious disease (ID) also reducing the circulation of an infectious agent.

As the aim of vaccines is preventive and not therapeutic, they are administrated to a large number of healthy subjects (usually children or adolescents); thus, even the smallest adverse event (AE) is perceived as not tolerable. For this reason, vaccines are held to the highest standards of safety. The potential for any risk is considered less acceptable in the case of vaccines than in that of disease treatment. It will be an increasing challenge to spread the benefits of vaccination in the apparent absence of the disease but with the possible presence – even if mild – of adverse events following immunization (AEFIs) [3].

Safety – a major issue for any vaccine – is assessed at every step of vaccine development (preclinical and clinical studies) and after licensure; as a matter of fact, health authorities require an ongoing commitment for post-licensure analysis of safety [4]. The Global Advisory Committee on Vaccine Safety (GACVS) – an independent scientific advisory board – provides the World Health Organization (WHO) with strict advice on vaccine safety issues of global importance [5].

Broad community confidence in the vaccines' safety is critical for generating maximum public health benefit. One reason for this is herd immunity effect, which is achieved when the vaccine

* Corresponding author.
E-mail addresses: paolo.bonanni@unifi.it (P. Bonanni), beatrice.zanella@unifi.it (B. Zanella), francesca.santomauro@unifi.it (F. Santomauro), chiara.lorini@unifi.it (C. Lorini), angela.bechini@unifi.it (A. Bechini), sara.boccalini@unifi.it (S. Boccalini).

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coverage in the population is sufficient to prevent the circulation of the infectious agent among those who remain susceptible. This is only possible if the public has confidence in the safety of a vaccine. The study of AEs of vaccine is not only an effort to provide individuals with a basis for deciding whether to vaccinate, but also an effort to improve the safety and effectiveness of vaccines and to increase confidence in societal decisions, which weigh the costs and benefits to the society [6].

The aim of this paper is giving an overview about the main determinants, which influence in a negative way, an immunization programme, focusing especially on HPV vaccination, trying also to provide some advices in communication strategies for overcoming this issue.

2. Vaccine surveillance

Vaccine safety is continuously monitored to identify and evaluate potentially occurring rare and/or serious AEs that are temporally linked to vaccination (sudden deaths, immune-mediated disorders, narcolepsy). The Vaccine Adverse Event Surveillance and Communication (VAESCO) is an European research network, funded by European Centre for Disease Prevention and Control (ECDC), which collects data on AEFI in Europe and compare them in order to provide high quality vaccine information [7]. The Vaccine Adverse Reporting System (VAERS) – sponsored by Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) – and New Vaccine Surveillance Network Extended System (NVSN-ES) cooperate with the aim of gathering information about AEs, that may occur after the administration of vaccine licensed for use (VAERS) and to better evaluate the impact of new vaccines or new vaccine's policies (NVSN-ES) in the US area [8]. When needed, studies are planned to assess safety signals and distinguish between possible causes and likely coincidence [9–11].

The passive vaccine surveillance is carried out with the voluntary reporting of AEs from healthcare providers, vaccine-takers, and others (parents, relatives, friends, etc.) [12] and can be designed to recognize new or rare AEs and changes in rates of previously reported AEs [12,13]. Nevertheless, the variability of reporting, reporter bias, and potential underreporting are limitations that hinder the defining of a causality relationship [12,14]. Instead, active vaccine surveillance is a systematic procedure for identifying clinically significant events that occur within a defined period and/or population; this can assess whether a specific AE is significantly associated with the immunization [15,16].

Vaccines are also associated with the theoretical risk of adverse immunological responses that may lead to immune-mediated disorders: this could be due to homology between vaccine antigen and a human protein, or non-specific immune enhancement properties of the vaccine adjuvant [4,17,18].

Surveillance is an essential tool to generate signals and hypotheses but cannot be used to prove them. A well-designed and controlled study allows researchers to test hypotheses and to assess whether there is evidence and what is the size of the effect. The main methods used in this evaluation – case-control studies, cohort studies, and case-only methods – require the implementation of statistical calculation to support quantitative signal detection through Proportional Reporting Ratio (PRR [*]), 95% PRR Confidential Interval, and χ^2 test.

$$PRR = \frac{incidence\ of\ an\ AE\ after\ receiving\ a\ given\ drug}{incidence\ of\ the\ same\ AE\ in\ the\ whole\ surveillance\ database} \times [*]$$

The PRR measures a reporting relationship between a medicinal product (e.g. vaccines) and an AE, based on the relative increase in proportion of individual cases related to an AE [19]. In essence, PRR is the proportion of all cases related to an AE reported after the administration of a vaccine, on the total number of cases of the same AE reported for all vaccines. If the expected value is one, AE is reported after the vaccine at the same probability as after all vaccines. If the value is greater than one, the AE is reported with more likelihood after that vaccine compared to what is reported after the totality of the vaccines [20].

3. Vaccine hesitancy: main determinant categories

According to WHO and the Strategic Advisory Working Group (SAGE WG), *Vaccine Hesitancy* is "the delay in acceptance or refusal of vaccines despite availability of vaccination services" [21,22]. It is a complex issue that is context-specific, varies across times, places, and vaccines, and includes complacency, convenience, and confidence as the main determinant factors [21]. Among the global population, during the last few years, it is raised a significant sense of criticism and alarmism to vaccines: immunization programmes have successfully reduced the incidence of vaccine-preventable diseases, leading to an increasing proportion of healthcare providers and parents with little or no personal experience about vaccine-preventable diseases. For their risk-benefit analysis, they have to rely on the historical descriptions of such vaccine-preventable diseases. The public is no longer used to seeing these diseases and may think that vaccines are no longer needed. Moreover, the AEs of vaccines become more evident due to the absence of the disease the vaccine is supposed to prevent [17]. Therefore, on one side there is the perception that an ID may not be harmful. On the other side, there is the perception that a vaccine could be dangerous for any possible AE. People are also aware that vaccines are usually accompanied by some degree of personal distress and pain, and the apprehension is generally associated with each immunization. In addition, parents searching for information about vaccines on the Internet are likely to encounter websites that encourage vaccine refusal or emphasize the risks of vaccines. Likewise, the media may sensationalize vaccine safety issues or – in an effort to present "both sides" of this topic – fail to provide perspective. The combination of these factors may have an influence on parental beliefs about immunization [17]. A national telephone survey in United States found that, although the majority of parents support immunizations, 20–25% have misconceptions that may gradually erode their confidence in vaccines [23].

4. HPV vaccines

Currently, three prophylactic HPV vaccines are licensed: the bivalent HPV16/18 virus-like particle (VLP) vaccine, the quadrivalent HPV 6/11/16/18 VLP vaccine, and the latest nonovalent HPV 6/11/16/18/31/33/45/52/58 VLP vaccine, which offers a broader coverage than the bivalent and quadrivalent vaccines [24]. The nonovalent HPV vaccine should provide protection against HPV types representing ~90% of cervical cancer cases and ~90% of genital wart cases, using the average of HPV-type prevalence [25]. They are highly immunogenic and protect mostly against the HPV types included in the vaccines, with little cross-protection against non-vaccine HPV types [26–30]. All the vaccines are administrated in males and females from the age of nine years; boys and girls aged 9–14 (bivalent and nonovalent vaccines) or 9–13 (quadrivalent vaccine) should follow a two-dose schedule, while for people aged more than 14 years, the vaccine is generally given according to a three-dose regimen [31–33].

Though the new nonovalent HPV vaccine has five additional antigen types and a double quantitative of adjuvant (500 μg of amorphous aluminum hydroxyphosphate sulfate) compared to the quadrivalent vaccine [34], a combined analysis of seven

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