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Review

Ongoing pharmacovigilance on vaccines

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ABSTRACT

Vaccines have peculiar characteristics as well as their surveillance. Specific requirements, needs and challenges for the vaccine vigilance are discussed in the perspective to improve the whole system in order to guarantee a safer vaccine use and the keeping of the public confidence in vaccinations. Key elements for the routine safety monitoring, new regulations and some available tools are taken into account. Finally, the Italian experience is shortly described.

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Introduction

The vaccines are subject to a strict safety surveillance and, more increasingly, to the monitoring of effectiveness. Both are generally included within the pharmacovigilance activities. Vaccines have peculiar characteristics and if only the pharmacovigilance rules are considered for surveillance purposes this could be not enough. The decreased frequency of the diseases that they prevent, the potential replacements of circulating strains, the importance of risk communication, the heterogeneity of the stakeholders (including subjects against the vaccinations) represent some of the issues to deal with daily which may complicate not only the surveillance itself but also may negatively affect the immunization programs.

The specific needs to conduct a proper vaccine-vigilance are well known [1–4]; however, new requirements have been identified following the experience gained during the last pandemic, thus representing a challenge to improve the whole system contributing to a safer vaccine use in the interest of patients [5–7]. The features identified by several countries as crucial for an effective surveillance and which should be strengthened pertain to the capability to quantify risks, the analyses of the burden of disease data, the identification of the target groups for vaccination (and the related strategies to convince them to get vaccinated), the better communication of safety and efficacy data on vaccines, the capacity for generating timely data. Moreover, for a general improvement of the vaccine-vigilance, an increased collaboration both at national and at international level was deemed mandatory.

Key elements for the routine vaccine safety monitoring

Overall, the key elements to set up a routine monitoring of the vaccine safety should consider the following issues:

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(i) The vaccines are used to prevent diseases, consequently they are administered mostly to healthy individuals, primarily children.
(ii) Each product, although with the same composition of a similar vaccine, is strongly dependent on the manufacturing processes. This may result in differences between batches of the same vaccine. Each batch is subject to the specific controls before being marketed, and, according to the new pharmacovigilance legislation and the Good Vigilance Practice (GVP), the reports of adverse reactions should specify the brand name and the batch of the vaccine involved.
(iii) The vaccines are biological products, often composed by different antigens; the majority of official immunization programs provide for a concomitant administration of different vaccines in the same session. Moreover, an Adverse Event Following Immunization (AEFI) could temporally overlap with the natural diseases. Given such complexities the surveillance requires the ready availability of data and appropriate tool to analyze them to ensure rapid and informed actions. For a quick decision-making process a closer collaboration among the relevant stakeholders involved (regulatory authorities, public health authorities, healthcare professionals, academia, companies, parents/citizens and vaccines manufacturers) is required.
(iv) The risk communication is often difficult and requires appropriate expertise since today the widespread use of the web, allows everyone to search for medical information. The communication remains a great opportunity but it is to consider also the possibility of misinformation and if the misinformation is not adequately balanced by official and quick information, they may turn to be harmful thereby increasing the vaccine skepticism which ultimately may result with possible outbreaks of vaccine-preventable infectious diseases.

Adequate tools for data analysis, the strengthened pharmacovigilance rules, together with an increased transparency can improve the vaccine-vigilance and ultimately the public confidence in the vaccines. The development of the vaccine-vigilance is still ongoing, although a lot of work has been already made in the last years. Some aspects of such development will be summarized in this paper, both in general and then with focus to the Italian situation.

The regulatory issues

Important regulatory changes in pharmacovigilance took place in Europe with the entry into force of new legislation [8–11]. The new provisions aimed at further protecting health of patients, sharing the work among Member States, saving resources, and improving the efficacy of the actions taken. The main changes of the new legislation involve the collection and the analysis of the relevant information concerning medicines, the regulatory process and the communication with the stakeholders.

First of all it was introduced an extension of meaning of adverse reaction to include the cases coming from abuse or misuse of drug, medication error, overdose and professional exposure; secondly tools for the ADR collection, the signal detection and signal management were specified and the Pharmacovigilance Risk Assessment Committee was established.

Some of other major changes introduced by the new legislation concern the content and the structure of the safety documents provided by the Companies to the Regulatory Authorities and the possibility from the latter to request legally bound post-authorization studies. The Periodic Safety Update Report (PSUR) has now a new format and is called Periodic Benefit Risk Evaluation Report (PBRER) which presents and discusses not only the safety issues such as adverse reactions, signals and risks, but also includes an evaluation on the benefits based on the efficacy and effectiveness data; thus, the PBRER provides an updated overall benefit/risk evaluation of each product.

The new legislation extends the submission of the Risk Management Plan (RMP) to all new marketing authorization applications. The RMP is a stand-alone document containing a detailed description of the risk management system used by the companies and is defined in the Directive as "*a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions*" [12].

When new concerns on authorized products emerge, the new legislation enable the possibility to require the conduction of a post-authorization safety study defined as a study "*. . .conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measure*" [13]. Furthermore, it has been introduced the possibility to require studies on the efficacy or effectiveness when accumulating evidence suggests that previous efficacy evaluations might have to be revised significantly.

Most of the above-mentioned provisions are not specific for vaccines. However, the new legislation impacts also the vaccine-vigilance and a dedicated GVP module has been recently published (Guideline on good pharmacovigilance practices. Product or population specific considerations I: vaccines for prophylaxis against infectious diseases) [14]. This document focuses on vaccine-specific aspects to be considered when setting up pharmacovigilance activities for vaccines. Indeed, for vaccines, the need of post-approval safety and efficacy data become necessary to confirm the benefit–risk of vaccination in the real world, in different target groups (often excluded from registrative studies), or to better study the immunogenicity (for the evaluation of long-term protection or different vaccine schedules).

Even the RMP includes the discussion on aspects considered peculiar of vaccines; for example, the waning of immunity, the co-administration with other vaccines, the "syndrome close resembling wild-type disease", the adverse events of special interest (AESI), the monitoring of breakthrough infection cases, and the reversion of the virulence (for live attenuated vaccines) are part of the evaluation.

The tools

A dedicated GVP module and specific procedures have been established to conduct signal detection routinely [15]. However it should be pointed out that, even if the signal detection and management have been improved by the new legislation, they still relied on passive reporting systems. The vaccines safety surveillance has now evolved towards a real time data monitoring and to better investigate safety concerns up to risk quantification. Thus, it is expected an increasing use of complementary active systems of surveillance especially those based on the use of different large database of electronic medical records routinely collected [16]. The combination of different database for the vaccine safety monitoring requires the capacity to link the adverse reactions or hospital discharges to the immunization data. The analysis of different database could be even more powerful if databases from different countries are available and if data analyses are performed using harmonized procedures and tools [17]. The analysis of data coming from different countries also increases the size of the populations studied; this can be very relevant in case of rarer adverse reactions that cannot be appropriately studied in a limited geographic area. An example of such experience could be represented by the Vaccine Adverse Event Surveillance & Communication (VAESCO)