An Overview of the Fundamental Vaccine Safety Concepts

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The rapid development of effective vaccines against COVID-19 is an extraordinary achievement. However, no medical product can ever be considered risk-free. Several countries have a pharmacovigilance system that detects, assesses, understands, and prevents possible adverse effects of a drug. To benefit from such huge data sources, specialists and researchers need advanced big data analysis tools able to extract value and find valuable insights

Keywords: COVID-19 ; vaccine ; big data ; adverse events

1. Introduction

In recent years, the ability to produce data has increased exponentially. Such data, commonly referred to as *big data*, contain valuable information about users' activities, interests, and behaviors, making it inherently suitable for an extensive range of applications [1]. For example, in bioinformatics applications [2], big data analytics provides appropriate techniques for storing, organizing, understanding, and interpreting the exponential amount of biological data that aims at solving problems in medicine and biology (e.g., fast analysis of massive DNA, RNA, and protein sequence data, fast querying on incremental and heterogeneous disease networks, and detection of complexes over growing protein–protein interaction data [3]).

Moving from science to society, social data and e-health are good examples to discuss. Social networks such as Facebook and Twitter have become very popular and are receiving increasing attention from the research community, since every day millions of people produce a huge amount of digital data that can be effectively exploited to extract insights concerning human dynamics and behaviors [4]. For example, social media users moving through a sequence of locations in a city or region can create a huge amount of georeferenced data that includes extensive knowledge of human dynamics and mobility behaviors [5][6]. In addition, an ever-increasing volume of urban-related data, with spatial and temporal attributes, poses several challenges related to city management and services, from weather and air quality to public transport to reduce emissions, traffic congestion, and energy costs [7][8].

The same occurs in the e-health domain, where big data analytics tools and systems can be used to help medical experts and epidemiologists design accurate and generalized models for predicting the different evolutionary stages of COVID-19 [9][10][11] or to support professionals and scientists in applying the natural language processing models able to detect and fight the COVID-19 infodemic on social media [12]. In particular, the pandemic demonstrated how important real-world (RWD) data are for informing health policy decisions and improving clinical trials. However, it is hard for many users to exploit such RWD, mainly due to the programming skills needed for implementing the appropriate data analysis methods.

2. Guide to Data Reading

Monitoring the safety of vaccines is a complex ongoing process. Comprehensive safety data are required to ensure that the benefits of a vaccination campaign outweigh the risks and reduce these to a minimum, allowing policymakers to make informed decisions about implementing a large-scale program among healthy citizens and ensuring that people are confident enough to accept vaccination. For the sake of clarity and for the reader's convenience, it is important to clarify the meaning of some terms that are used throughout the paper:

- An adverse event is any adverse episode that may appear after the administration of a vaccine, but which does not necessarily have a causal relationship with the vaccine;
- An adverse reaction is a response to a vaccine that is noxious and unintended. In order to distinguish between adverse events and adverse reactions, researchers must study potential causalities related to the vaccine;

- An undesirable effect is an unintended effect related to the properties of a vaccine, observed in a number of people, that is not necessarily harmful.

3. Signal Detection and Management

A safety signal is a notification about a new/known adverse event that can be related to a drug and requires further analysis. Several countries have a pharmacovigilance system that detects, assesses, understands, and prevents adverse effects or any other drug-related problems. For example, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) conduct post-licensure safety monitoring of US-licensed vaccines, the Medicines and Healthcare products Regulatory Agency (MHRA) verifies that medicines and medical devices work and are acceptably safe in the United Kingdom, and the Italian Medicines Agency (AIFA) controls the regulatory activity for pharmaceuticals in Italy.

In general, surveillance systems are based on two main approaches: *passive surveillance* and *active surveillance*. The first approach occurs when laboratories, physicians, or other healthcare providers regularly report cases or diseases to the local health department. Passive systems are most widely used to collect adverse events following immunization (AEFI) (an AEFI is any adverse medical event that follows immunization and is not necessarily causally related to vaccine use [13]. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease), and the system depends on receiving reports of adverse events, so data quality and completeness are difficult to ensure. An example of a passive surveillance system is the Vaccine Adverse Events Reporting System (VAERS) [14], which relies on information about unusual or unexpected events after vaccination from those who choose to voluntarily report their experience. The second approach provides accurate and timely information, since designated staff visit healthcare facilities, communicate with healthcare providers, and detect possible cases of adverse events of particular interest (AESI) (an AESI is a pre-specified medically significant event that can be causally associated with a vaccine product and must be carefully monitored and confirmed by further special studies. For example, AESIs associated with the administration of COVID-19 vaccines [15] cover all body systems, including immunological, cardiovascular, neurological, musculoskeletal, and dermatological manifestations) and review patient records; however, this is more resource and time-consuming than passive surveillance. An example of an active surveillance system is the Therapeutic Goods Administration system (TGA) [16], which exploits SMS messaging to directly ask people if they have experienced potential side effects.

4. Causality Assessment

It is very challenging to study the interactions between the vaccine, natural disease, and adverse reactions. Possible side effects differ with age, but if a high-incidence adverse reaction occurs shortly after introducing a vaccine, the temporal association can be easily misinterpreted as causal. To recognize whether an adverse reaction may be related to the administration of a vaccine, the WHO has developed an algorithm that considers: (i) the temporal connection between the administration and the notified reaction; (ii) previously reported evidence; (iii) the frequency of the event notification in the general population, vaccinated or unvaccinated; and (iv) plausibility from a biological point of view.

On the basis of all these factors, the evaluation process can output four potential suggestions:

- Related to the event, i.e., the causal connection between the event and vaccine is considered possible;
- Unrelated to the event, i.e., other elements and factors can explain the adverse reaction;
- Indeterminate, i.e., the temporal association is valid, but the collected data are not enough to confirm causality;
- Unclassifiable, i.e., all reports that lack sufficient information and for which further investigation is required.

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