DEBATE
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Challenges and perspectives in surveillance of post-marketing/use

Desafios e perspectivas na vigilância sanitária pós-comercialização/uso

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ABSTRACT

This essay aims to discuss the challenges and perspectives posed for the post-marketing surveillance in Brazil. Based on a non-systematic literature review, some challenges are pointed out, such as: 1) the need to review the post-marketing/use risk management model; 2) the strengthening of work in the Sentinel Network; 3) the systemic analysis of notifications and integration between the information systems and 4) the effective implementation of the product traceability system. Only a few challenges have been brought into the debate, knowing that many others exist for the expansion and improvement of the post-marketing surveillance, considering the dynamics and globalization of the relations of production and consumption in the risk society.

KEYWORDS: Health Surveillance; Health Risk; Surveillance of Post-markting Products; Risk Management and Adverse Effects

RESUMO

Trata-se de um ensaio que busca refletir sobre os desafios e as perspectivas para a vigilância pós-comercialização/uso (Vigipós) no Brasil. Com base numa revisão não sistemática da literatura, são apontados alguns desafios como: 1) necessidade de revisão do modelo de gestão do risco na pós-comercialização/uso; 2) fortalecimento do trabalho da Rede Sentinela; 3) análise sistêmica das notificações e integração entre os sistemas de informação; e 4) implantação efetiva do sistema de rastreabilidade de produtos. Apenas alguns desafios foram colocados em debate, sabendo que muitos outros existem para ampliação e aperfeiçoamento da Vigipós, considerando a dinamicidade e a globalização das relações de produção-consumo no que se conhece por sociedade de risco.

PALAVRAS-CHAVE: Vigilância Sanitária; Risco Sanitário; Vigilância de Produtos Comercializados; Gestão de Riscos e Efeitos Adversos

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INTRODUCTION

Contemporary society is characterized by the massive consumption of technologies, including health technologies, which also leads to the emergence of new needs. It is, therefore, quite challenging, in this broader context, to manage the risks inherent in new technologies. When observing the field of biomedical and epidemiological sciences and the adoption of innovative technologies, it appears that life in society is increasingly complex and full of new elements of insecurity[1].

To better understand this perspective, it is important to reflect on the theory of the risk society designed by German sociologist Ulrich Beck[2]. According to Beck, contemporary society is undergoing profound changes that entail social, political, economic and industrial risks, which are taking on ever greater proportions and exceed national borders. The risk society lives in the midst of the consequences of scientific and industrial progress, surrounded by a plethora of risks. Some of these risks cannot be contained, neither spatially nor temporally, and coexist both on the visible and invisible levels. What's more, many of them are "institutionally manufactured" by science, by the market, by the government, among others[3].

It is noteworthy that behaviors and attitudes, individual and collective, are fundamental for the protection of health and the reduction of risks to which everyone is subjected. However, it is the role and duty of the State to adopt strategic measures to intervene or prevent the risks of diseases and other health problems in the population, as well as in the production-consumption of health products and technologies[4].

The notion of health security related to the risk/benefit ratio within the scope of product production-consumption is directly linked to risk control strategies. This includes concerns with the mastery of techniques and the work tools that are necessary for the intervention, with a view to health protection and promotion[5]. Examples include biotechnology, personalized medicines, 3D organ printing, biomarkers, robots that perform surgeries and information science to improve the regulatory decision system.

Health security can have several meanings in the context of use, especially when we consider the diversity of objects under health surveillance. A major challenge for public health is managing risk in the production-consumption of technologies, in the face of health problems in the risk society[5]. "In general, technological progress imposes the need for ever greater vigilance, more qualified and experienced professionals, more equipped structures and more intricate control systems"[6].

According to the World Health Organization (WHO), adverse events (AEs) are incidents that result in unintended harm and are a direct consequence of healthcare and unrelated to the natural evolution of the disease. Furthermore, in the activities of the Brazilian National Health Surveillance Agency (Anvisa), an AE is considered an unexpected or undesirable effect that compromises the health security of a citizen/patient. On the other hand, a technical complaint (TC) refers to any suspected change/irregularity in a product/company[7].

In this debate, the expanded concept of post-marketing/use surveillance (Vigipós) is adopted. It is understood as the integrated and systematic set of all health surveillance actions to monitor the safety of products used by the society, monitoring, evaluating, investigating, inspecting and communicating the risks arising from the consumption and use of these products[8]. It is important to clarify that the scope of this concept includes both monitoring and inspection actions aimed at AEs, as well as the TCs of all products – objects of health surveillance, including: medicines, cosmetics, health products, sanitizers, and food.

The publication of Ordinance/GM/MS n. 1.660, of July 22, 2009[9], which institutionalized the Health Surveillance Notification and Investigation System within the scope of the National Health Surveillance System, stands out as a milestone of post-marketing surveillance (SNVS) and was considered an important step in strengthening these actions and making them more practical. This normative act established the guidelines for the AE and TC surveillance system of products in post-marketing/use, with shared management between the Ministry of Health, Anvisa, state health departments, and municipal health departments. Vigipós' field of action comprises: biovigilance, cosmetovigilance, pharmacovigilance, hemovigilance, nutrivigilance, technovigilance and the surveillance of sanitizing products.

To provide some context of the amount of data, from 2012 to 2017, 274,071 reports including AEs and TCs were submitted to the Health Surveillance Notification System (Notivisa), with a significant increase of 58% (n = 20,126) in the interval of six years[10].

Since its institutionalization, Vigipós has made great progress in areas like regulatory framework, design and setup of an official information system, such as Notivisa, the establishment of practices aimed at monitoring and inspection, continuous training of professionals from the Sentinel Network and of risk managers in hospitals. On the other hand, studies point out challenges related to the complexity of the information system, underreporting, problems in data quality, biased reports and reports with missing information about the product, the company or the patient[11,12,13].

Considering this landscape, the purpose of this debate is to reflect on the challenges and prospects for post-marketing/use surveillance in Brazil.

What challenges and prospects?

Based on a non-systematic review of the literature, it is possible to point out some subsidies that support the debate on the challenges and prospects for strengthening post-marketing/use surveillance in Brazil.

Post-marketing/use risk management model

Some authors argue that it is necessary to review the reactive model of post-marketing/use surveillance, in which the process of investigating an incident begins only after receiving, screening and analyzing the complaint or report. These authors argue that it is necessary to rethink or redesign this model of action so that there is an active search for suspected AE cases, in a model known as proactive[10,14,15].

In a study of the risk management system, Barbosa[14] explained that the reactive process is composed of actions that aim to "remedy the effects of crises and correct problems on an emergency basis", while the proactive process is focused on the detection, analysis, and communication of risks, in addition to their continuous monitoring, "enabling managers to detect risks and opportunities and make the best possible decision" [14].

The World Health Organization – Uppsala Monitoring Center (WHO-UMC), Collaborating Center for Pharmacovigilance, clarified that spontaneous reports alone do not provide sufficient, reliable and comprehensive data on the harm caused by the use of health technologies. It highlighted that other methods of analysis and investigation should be adopted, like worldwide research projects, conducted by regulatory authorities, academics, professionals and manufacturers seeking alternatives to product monitoring. Direct reporting by patients, a strategy established in many countries, including Brazil, is recognized as an important and complementary source of information on product safety, and new electronic methods of generating reports, algorithms, online and mobile applications, for example, can contribute to enriching and expanding the information available for decision making[16].

Onakpoya et al.[17] stated that more effective methods are needed to detect, document and report severe AEs in patients using a certain product, seeking to reduce the time for decision-making after reporting. They advocate a more robust approach to decision making in relation to death reports and greater collaboration and coordination between international regulatory agencies.

The WHO[18] proposes that the post-marketing/use surveillance system be organized in a virtuous circle based on three main objectives: preventing, detecting and responding to products on the market.

> **Prevention** includes training and awareness-raising actions, legal provisions; clear and regular communication between civil society groups, healthcare professionals and the industry, in addition to a traceability system.
>
> In **detection** are border control actions, reporting systems, adequate risk management and access to laboratory support.
>
> In **response**, there is a set of alerts and recalls, sanctions, policies, process and procedures properly organized and based on evidence.

To enhance the performance of the model, we must address a systemic and continuous set of actions, which constitute the elements of the integrated post-marketing/use monitoring systems[19]:

- incentives and strategies to encourage healthcare professionals and patients/consumers to report suspected AEs;
- adoption of faster measures by regulatory authorities, considering temporary suspensions or restrictions during the investigation process;
- immediate responses from manufacturers of products subject to health surveillance, including recalls, when serious AE suspicions or quality deviations are reported;
- guidelines, guides or protocols for determining when a product should be withdrawn from the market;
- more rigorous monitoring and verification of deaths and reports of reasons for leaving clinical trials, with more transparency in the reporting of AEs and immediate access to reports of pre-market clinical studies[19].

The conclusions of Daniel Mota's research[11] on the evolution of pharmacovigilance in Brazil also reinforced the need for changes in different dimensions, like the legal and structural formalization of Vigipós; implementation of educational and restrictive measures to encourage reporting by both professionals and consumers, as well as the productive sector, in addition to the adoption of periodic, systematized and standardized assessments including methodologies, techniques, and parameters for the dissemination of analysis results, as a strategy to improve the credibility and applicability of post-marketing/use surveillance[11].

Another study that addressed management and pharmacovigilance in Brazil highlighted the need for further research to better understand the relationship between governance and product safety in the post-market in decentralized federal systems, as is the case of Brazil[20]. The findings of this study revealed that the investments made in the management of Vigipós (pharmacovigilance) produced significant improvement through several strategies, including transparency, accountability, policy, law, and regulation in the field of activity of Vigipós. However, they suggest the implementation of other mechanisms, like post-authorization and drug distribution safety protocols; use of new data and analyses to determine disease prevalence; managing resources where they are urgently needed and increasing the engagement of different stakeholders in decision making related to monitoring and inspecting products[20].

It is also necessary to consider the different perspectives between Vigipós specifically for medicines and for other products. Despite the particularities of the risks arising from the use of these technologies, empirically it becomes clear that there has been significant progress in promoting the rational use of medicines, encouraging reports of AEs and TCs of medicines and strengthening pharmacovigilance initiatives, in comparison

with other objects, like: health products (correlated), sanitizing products, food, cosmetics, which are still seeking to organize and systematize their work process, in addition to establishing the mechanisms and tools for action within the scope of the SNVS.

Sentinel Network

It is known that, not only in Brazil but throughout the world, knowledge about the occurrence of AEs in health does not always reach the competent authorities through a formally established system. These events, especially when they involve the transmission of serious illnesses or death, often gain prominence in the media even before formal communication to health authorities. Very often, this gap in the communication flow affects the credibility of healthcare and surveillance systems.

Therefore, with the purpose of strengthening post-marketing/use surveillance of healthcare technologies and products and care-related AEs, since 2002, Anvisa has maintained the Sentinel Network, which works as an observatory in 23 Brazilian states and the Federal District, totaling 260 institutions focused on health risk management, working together and effectively with the SNVS[8]. This Network is formed by a set of healthcare services – public and private institutions, from small to large, in addition to blood centers and basic health units – which work in partnership with Anvisa for notification of AEs and TCs.

A study done in 2017 described the profile of the Sentinel Network and found that these services can be both an environment conducive to monitoring the behavior of new health technologies and ideal spaces for the training of human resources to have a "sentinel vision" and report the occurrence of failure of health services and products[8].

Sentinel institutions also play an important role in producing information that supports health surveillance actions, in addition to AE and TC reports. For example: participation in targeted surveys that collect data to validate the available evidence to subsidize the work done by Vigipós.

In this sense, there is a need for Brazil-wide expansion and strengthening of the Sentinel Network, making it an official part of international networks for exchanging information and monitoring products worldwide. There are currently global coordination monitoring networks that work in broad partnerships to support the improvement of systems, workforce, tools, and skills that are needed to enhance product quality standards and protect people's health, enabling their safe access to health technologies[18].

Systemic analysis of reports and integration between systems

For Vigipós' performance to develop in a systemic manner, it is essential to build strategies and mechanisms that expand data collection, through reports of suspected TCs and AEs, after the use of drugs, health products, cosmetics, sanitizing products, food, blood products, cells, tissues, and human organs and healthcare. This would allow the creation of a reliable database, whose technical information on safety and efficacy can subsidize regulatory actions in the Brazilian market[8].

There are several channels to send reports to Anvisa, such as e-mails, ombudsman channels, companies' reports, the Agency's portal, among others. There is also some fragmentation in the information systems where all reports should be entered. There is the recently-deployed VigiMed system for medicines; Notivisa for other products and care, in addition to FormSUS forms for reports of biovigilance, nutrivigilance and reaction to donation in cases of hemovigilance, among others related to healthcare services, such as AEs of infection related to healthcare by mycobacteria of rapid growth.

In addition to the challenge of collecting qualified information from various sources, the quality and completeness of the data and the consolidation of a robust database, it is necessary to invest in new analytical approaches that use large volumes of data (big data) and integrate with other information systems on deaths, diseases, and injuries. Applying these data survey and mining strategies, in addition to using information or reports from various social networks, associated with artificial intelligence tools[21], greatly improves systemic analysis and decision making as to whether or not to withdraw a product from the market.

The prospect is that more and more progress be made in the use of modern technologies and social networks to seek complaints about the consumption of products and capture rumors. In a study published in 2015, the authors sought to determine how the data available on social media network platforms can be used at Vigipós. They considered that the potential value of these data seems to be greater for measuring awareness of emerging issues in the use of technologies and noted that most social media subscribers are part of a younger and healthier share of the population. They defended the need for further research to investigate and explore other social media platforms to further characterize their usefulness for post-marketing/use product surveillance[22].

After receiving, screening, classifying and investigating the reports, it is essential that health surveillance bodies pay attention to the generation of signs, i.e. sets of reports that may suggest a causal relationship between an AE and a product. In general, more than one report is needed to determine this relationship. It is necessary to establish the strength of association, the clinical importance (severity and impact on public health) and the potential for adopting preventive measures. In the first case, health measures can be triggered, with memos and alerts, and it is possible to propose changes in the drug labeling or even the suspension of its sales and distribution. In extreme cases, product marketing authorization may be suspended or revoked[23].

Mota and Kuchenbecker[21] considered establishing a causal relationship between the product used and the AE or harm caused to be a major challenge. They stated that most of the decisions in the field of health surveillance are not proven merely by the

nature of the technical-scientific evidence of causality, in view of the use of the precautionary principle and the complexity involved in determining the risks that may arise from the use of a drug, for example.

They will also be able to trigger inspection actions, done through inspections, laboratory analysis, the examination of advertising material, investigation of quality deviations and handling complaints related to events that are secondary to the use of health products and services, among others. Based on the results of this work, it is possible to detect problems and adopt measures that halt or minimize health risks. The information obtained in these processes is also used to feed control systems, support changes and improvements in work processes and guide citizens and health professionals toward risk prevention[7].

In 2018, the WHO published a report on the monitoring of irregular products and highlighted that this is a growing problem all over the world, associated with the complexity of globalized production and supply chains and increased e-commerce. "Globalized trade needs surveillance at a global level. An integrated approach at the national, regional and global levels is now crucial for the protection of patients in all our countries"[18].

To support these actions, the challenge is to integrate the laboratory sample management system, known as Harpya, implemented in the Official Laboratories (Lacen) and coordinated by the National Institute for Quality Control (INCQS) and Anvisa, to the work of Vigipós. It is a fundamental system for producing relevant information for post-market monitoring of product quality, since it has the reliability, safety, and traceability of the analyses done by the Lacen. In addition, this system provides for the unification, standardization and availability of the quality control analytical reports of the products monitored within the scope of the SNVS[24].

Traceability system

In a descriptive analysis of the products reported to Notivisa, Toda and Andre[25] concluded that the State, through regulatory agencies, should demand from manufacturers more investment in quality control, preventing them from marketing products with side or unwanted effects.

Costa[26] highlighted that, in the context of economic globalization, typical of our hyperconsumption society, the production of health technologies is fragmented, and components can be imported from several places. This situation necessarily implies the search for strategies and actions to control health risks at the international level. The author considered that one of the possible strategies is the implementation of the concept of traceability, since "it enables to detect and locate, in different territories, sources of harm and risks along the production-consumption chain"[26].

Through traceability, it is possible to check whether a product is genuine and follow the path taken from its manufacture to its delivery to the consumer, based on the records of all transactions in the production chain[27].

Regarding drug traceability, there is Law n. 11.903, of January 14, 2009, amended by Law n. 13.410, of December 28, 2016[28], which created the National Medicines Control System (SNCM). The system aims to follow them throughout the production chain, from manufacturing to consumption by the population, providing greater safety for patients and professionals in relation to the medicines they use. According to the above mentioned Law, it is up to Anvisa to implement the SNCM, with a goal set for 2022 to put the entire pharmaceutical chain in Brazil within the scope of the system, mainly in order to avoid the circulation of counterfeit medicine.

It is also necessary to mention the National System for the Management of Controlled Products (SNGPC), which has been designed to monitor the dispensing of medicines and narcotic and psychotropic substances and their precursors and the prescription and consumption habits of controlled substances in a given region of the country.

Since its implementation in 2007, according to the Anvisa Activity Report[7], the SNGPC has increased health control over the movement of controlled drugs and antimicrobials sold in pharmacies and drugstores, providing:

- improvement in the qualified access to antimicrobials in the country;
- greater security against fraudulent handling; and
- more agility in the preparation of reports on medication consumption and the production of timely information for decision-makers.

As for health products, the National Implant Registry (RNI) is being currently implemented. It is a traceability system designed to enable the recording of surgical procedures for implantation of osteoarticular prostheses (hip and knee) and coronary stents in Brazil.

Another challenge concerns the setup or structuring of the recall mechanisms for products subject to health surveillance, as an "instrument to defend the life, health, and safety of consumers and those around them"[29]. Alves and Kallas Filho[29] considered that this mechanism is the fulfillment of the principle of prevention/precaution, considering that after a TC is reported and confirmed, it is the direct responsibility of the manufacturer and/or supplier to make the risk communication and, at the same time, take action to collect the products and neutralize the risks to the population.

CONCLUSIONS

Only a few challenges were pointed out here for health surveillance in the post-marketing/use of products. We are, therefore, far from exhausting the subject, given the dynamism and globalization of new and old technologies in the risk society.

In fact, it is essential to know how risk is perceived and valued by different groups in society and how health surveillance works

and is present in people's daily lives. The effectiveness of Vigipós depends, to a large extent, on the role played by the population, who should adopt an active approach and try to stay informed about questions of product safety, quality, and efficacy[30]. Surveillance strategies will be more effective with the enhancement of health surveillance education initiatives, which include encouraging citizen participation in the communication of events and the improvement of post-marketing monitoring and inspection[31].

There is a lot of talk about deregulation, reducing bureaucracy and controls over the pre-market surveillance system, which includes all protection initiatives regarding products available to the population. However, it should be noted that health surveillance actions in pre-market and post-marketing are conceptually complementary and can, together, fulfill the purpose of protecting the health of the population. In practice, we should strike a balance in health surveillance actions, regardless of whether the product is on the market or not, depending on the integration with other areas of knowledge and the field of public health, such as epidemiology and social sciences.

The challenge of managing decentralized actions at Vigipós also stands out. In the Debate Cycle, there was an emphasis on the potential of the health surveillance coordinators' performance in post-marketing/use, even to improve and inform pre-market surveillance[31].

With the "What health surveillance does society need?" question, the reference text of the Debate Cycle reflects on the alignment of health surveillance actions with the concept of responsiveness, translated into the SNVS's ability to adapt and respond to political, economic and social needs and the circumstances of each case, without neglecting health security. In practice, this would mean adjusting and adding flexibility to regulatory instruments and practices based on risk management, in order to allow for a balanced and continuous adjustment between regulation and the behavior of manufacturers and consumers. It would take more pre-market regulatory requirements for products with higher risk or less known risk; depending on the intensification of post-marketing surveillance for products with fewer requirements in the pre-market phase[31].

Finally, further discussion on the topics addressed here is essential, so that future research can produce evidence to help overcome these and other challenges for Vigipós and effectively improve the prospects for the country.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.