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Pandemic vaccines: a formidable challenge for pharmacovigilance

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The COVID-19 vaccine effort was the most rapid global response to a health crisis in history. The challenge of managing unparalleled volumes of safety information provided unique opportunities to evaluate the robustness of current pharmaceutical industry pharmacovigilance practices and test novel approaches to strengthen safety signal detection, evaluation and communication.

Introduction

Pharmacovigilance (PV) systems are designed to monitor the safety of medicinal products and detect any change to their risk–benefit balance. They are used by industry organizations to ensure optimal communication of risk profiles to patients and healthcare providers in compliance with regulatory requirements relating to patient safety. PV systems require appropriate infrastructure, methodologies and resources to incorporate all available sources of safety information, including — but not limited to — literature, clinical and non-interventional trials, external database reviews and individual case safety reports (ICSRs) of suspected adverse reactions, for timely signal detection and management[1].

The unprecedented COVID-19 pandemic and the rapid development and global rollout of COVID-19 vaccines required adaptation of PV infrastructure and implementation of novel scientific approaches to perform near real-time signal detection and prioritization, and to enable prompt communication of vaccine benefit–risk balance. Here, we provide insights from AstraZeneca's experience during the distribution of >2.5 billion doses of the COVID-19 vaccine AZD1222 (ChAdOx1 nCoV-19) to >170 countries in 2021.

PV infrastructure requirements

Estimating incoming volume. Conventional PV approaches use the cumulative product safety profile and the size of the target population to forecast the volume of safety information that will be received after product launch. These estimates ensure that the necessary database capacity, resources and methodologies are in place to process the anticipated volume of ICSRs and to support the timely detection, evaluation and management of emerging potential safety issues.

During the pandemic, forecasting ICSR volumes for AZD1222 involved reviewing clinical studies for insights into adverse events (AEs)[2,3]. In addition, AstraZeneca used the literature on H1N1 influenza pandemic vaccines[4] to explore potential factors influencing ICSR volumes. Using this information, we estimated that ~400 ICSRs could be reported per 1 million vaccine doses administered. This preliminary forecast, and the planned supply of AZD1222 of ~2 billion doses, indicated the potential for ~800,000 ICSRs over 12 months (Supplementary Fig. 1).

After launch, substantial variance in country-level ICSR reporting rates was observed, with rates ranging from 1 to 6,154 ICSRs per 1 million doses administered (Supplementary Fig. 2). In addition, the rapid vaccine rollout further increased the volume of ICSRs received immediately post-launch, substantially exceeding initial forecasts (Supplementary Fig. 3).

Safety database capacity and PV resources. The safety database is an integral part of any PV system and is used to receive, collate, record and report safety information. The estimates of the ICSR volume during the pandemic indicated the need for sufficient database capacity to absorb all incoming case reports and the necessary workflows for efficient processing.

Before the launch of AZD1222, several servers were added to increase AstraZeneca's on-premise safety database capacity. In addition, the number of users who could concomitantly use the safety database was increased to ensure timely processing of incoming ICSRs. This preparation substantially increased the resource requirements and involved timely investment in safety database infrastructure. Ongoing updates to the ICSR volume estimate indicated the need to increase PV resources ~tenfold and to quickly recruit staff to process ICSRs. A vendor-based model offered the ability to reallocate resources to the most critical steps of the ICSR workflow and to rapidly adapt to the incoming volume.

PV processes: ICSR processing and prioritization. The processing of ICSRs supports the detection and management of safety signals. The process involves information extraction (including coding of drug–event pair associations and key ingredients) and database entry, prioritization based on predefined criteria, and local and global reporting. In safety databases, all steps of ICSR processing are defined in workflows. At AstraZeneca, automation of iterative steps such as data extraction and entry enabled the management of the incoming ICSR volume with a focus on those ICSRs that required close medical scrutiny. Fully automated workflows were used to accelerate the processing of certain ICSRs of adverse drug reactions that occur commonly with vaccines (Supplementary Fig. 4). The prioritization was agreed upon in close collaboration with major regulators, and was based on event seriousness and expectedness, as well as encompassing those in need of close surveillance.

Continuous monitoring and adjustments. AZD1222 was distributed in >170 countries during 2021, providing unique insights into regional variance in ICSR reporting rates (Supplementary Fig. 2). At the country

level, the structure of the AE collection system was an important contributor. Reporting habits and easily accessible reporting routes in certain countries, such as the Yellow Card system in the UK, led to surges of ICSRs. In addition, the incoming volume was driven by media attention and regional changes in vaccine eligibility. Because such variables were not static, frequent reviews and adaptations of forecasts were conducted throughout vaccine rollout (Supplementary Fig. 3).

Signal detection, validation and communication

Extensive clinical trials established AZD1222 as safe, with low incidences of serious AEs[2,3,5]. After marketing approval, increased exposure to large populations can lead to the detection of previously unknown events. Standard PV approaches for signal detection include quantitative disproportionality analyses, which compare a product's AE profile against a company's portfolio-wide safety database, and qualitative, focused surveillance for certain AEs of interest.

To strengthen its signal detection capabilities for AZD1222, AstraZeneca developed a hybrid proportional reporting ratio approach using US Vaccine Adverse Event Reporting System (VAERS) data for comparable vaccines (Supplementary Fig. 5). Additionally, to reduce the number of false signals, and per European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) requirements, we compared the observed AEs for specific events to estimates of the expected background rates for the same population (Supplementary Fig. 6) from March to December 2021. This 'observed versus expected' analysis provided further contextualization of safety signals in the population receiving AZD1222.

AstraZeneca used a knowledge graph to rapidly integrate public data on vaccine administration, AEs and population demographics and to then estimate AE background rates (Supplementary Fig. 7). Collaboration with health authorities and other COVID-19 vaccine manufacturers was crucial for obtaining accurate vaccine exposure data and developing case definitions for specific AEs. These novel PV surveillance approaches helped us take swift actions following initial indications of very rare safety signals with AZD1222, including conducting detailed evaluation and characterization of relevant data to facilitate early public communication.

This experience proved valuable as, during the AZD1222 rollout, AstraZeneca received urgent safety queries from health authorities including the EMA and the UK MHRA, who conducted their own surveillance, and from other authorities following their reviews of monthly safety summary reports. Providing responses involved separate data review and analysis of large volumes of cases, in addition to routine surveillance. Dedicated data management and response teams were established to address these requests.

Conclusions

Conventional PV infrastructure and approaches required agile, innovative adaptation to meet the challenges associated with rapid global rollout of AZD1222 during the COVID-19 pandemic. We identified several key lessons (Supplementary Fig. 8), including the need for dedicated infrastructure and resources, the importance of ongoing updates to and adaptation of ICSR volume prediction, the need for rapidly scalable PV systems and processes, and the value of ICSR prioritization and of near real-time safety signal detection and evaluation using comprehensive contextualization.

Our experience also informs future approaches for improved PV. For example, the enormous ICSR volume and condensed reporting timeframe highlighted the need for more agile and automated mechanisms for ICSR processing. For future safety databases, use of a cloud-based platform that maximizes automation — from ICSR receipt, through triaging, data entry, and medical review, to reporting — should be considered. To ensure report quality, additional technologies, such as artificial intelligence and algorithmic analysis, could be used in tandem with essential human input into medical and scientific assessment. Finally, novel contextualization approaches, including the use of detailed background prevalence data for the relevant populations, coupled with consistent frameworks for exposure data collection and ICSR reporting, will be valuable for improved signal detection and management in future pandemics. The safety of individuals when receiving any medicinal product remains the first priority for PV, and this focus will be further enhanced through the specific experience and lessons learned with COVID-19 vaccines.

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Competing interests

The authors are employees and shareholders of AstraZeneca.

Additional information

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