Digitalisation of Monitoring Side Effects Before, During and After COVID-19 Vaccines – Analysis of the Impact of the Pandemic on Reporting Side Effects in Republic of Croatia

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Abstract*. This paper presents the medicinal product's side effect reporting information system (OPeN) used by the Croatian Agency for Medicinal Products and Medical Devices. The paper aims to show the trend the trend in reporting suspected side effects before, during, and after the COVID-19 pandemic, as well as before and after the digitalisation of side effects reporting with the introduction of the OPeN. In this research collected data of reported side effects from 2014 to 2023 is analysed. This paper intends to show the process of reporting suspicions of medicinal product side effect reactions linked to the digitalisation of public services.*

Keywords. Digitalisation, Information System, OPeN, Side effect, COVID-19

1 Introduction and Literature Review

Public administration is under strong pressure related to improving its service delivery methods (Vestues et al., 2021). Current trends in public administration development emphasise collaboration between the public administration and the users of its services, focusing on the service users themselves (Fossheim & Lund-Tønnesen, 2023; Greve et al., 2016). Users can participate in public administration through the process of digitalisation, which has notably impacted the public sector, leading to substantial changes in the workings of public administration and to enhancing access to its services. The digitalisation process has accelerated under special conditions, such as the COVID-19 pandemic, which sped up the digitalisation of certain segments of public administration, creating opportunities for further development of the public administration system (Đanić Čeko & Guštin, 2022).

The process of digitalisation substantially influenced the healthcare sector, especially during COVID-19, where different digital technologies, such as telemedicine, various mobile health applications, and electronic health records were integrated, which led to more direct and improved healthcare (Balenović et al., 2022; Eşiyok et al., 2023; Moulay, 2023). The digitalisation of healthcare has also impacted the reporting side effects of medicinal product (somewhere called "adverse drug reaction" or "adverse effect"). Adverse drug effects were not only reported to the competent adverse effect reporting bodies. Some studies have used social networks to detect adverse effects available in the market (Farooq et al., 2021). Additionally, websites can impact the knowledge of pharmacovigilance by independently collecting patients reports to uncover harmful consequences caused by medicinal products, which clinical trials and national pharmacovigilance systems may not have recognised (Lentacker, 2024). Furthermore, some studies have utilised machine learning to extract extensive data for identifying adverse drug effects (Dubey et al., 2021).

Pharmacovigilance describes the process of monitoring and evaluating adverse effects and is an essential component of medicinal product regulation and public health programs. The impact of reported adverse effects contributes to the early detection of new safety risks associated with medicinal product use. In the Republic of Croatia, according to the Medicinal Products Act and the Ordinance on Pharmacovigilance (HALMED, 2024b), healthcare professionals are required to report adverse drug reactions. An adverse drug reaction is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention

related to the use of a drug, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards & Aronson, 2000). Sometimes this reaction may be characterised as a mild occurrence, and sometimes the consequences can be very dangerous for the patient's life (Kamble et al., 2023). Adverse drug reactions happen daily and affect patients' quality of life (Thomas, 2020). The adverse drug effects continue to be of interest to professional (pharmaceutical) and academic circles, considering how they begin in the medicinal product development phase (whether the drug is developed with a new or already known active substance), where possible adverse drug effects are initially explored (Elzagallaai, 2012). Furthermore, during the monitoring of drugs, new methods and ways of predicting possible adverse effects are defined, using the latest technologies, to reduce the occurrence of adverse effects or mitigate an adverse effect that may occur using a specific drug (Gawich & Alfonse, 2022; J. Wang et al., 2020; Mohsen et al., 2021).

The legal obligation to process reports of suspected adverse effects when using drugs in the Republic of Croatia is under the responsibility of the Agency for Medicinal Products and Medical Devices (HALMED, 2024b, 2024a). To fulfil its legal obligation more successfully, the Agency for Medicinal Products and Medical Devices began developing the OPeN information system in 2017, which is used for reporting adverse effects on medicinal products. The first significant upgrade to the OPeN information system occurred during the COVID-19 pandemic.

This paper aims to show the trend in reporting suspected adverse effects of medicinal products before, during, and after the COVID-19 pandemic, as well as before and after the digitalisation of adverse effect reporting. To our knowledge, this is the first paper that illustrates the process of reporting suspected adverse effects of medicinal products after significant changes in OPeN related to the digitalisation of public services. The paper is divided as follows. The first section presents the paper's goal and provides an overview of the area and literature. The second section describes the OPeN information system and the data collection method. The third section graphically presents the collected results. The paper concludes with a discussion, conclusion, and suggestions for upgrading the OPeN information system.

2 Information System for Reporting Side-Effects – OpeN

Until 2018, HALMED collected adverse drug reactions in various ways, most commonly using mail and email. In 2018, HALMED developed the OPeN information system for collecting adverse drug reactions to digitalise its pharmacovigilance-related services. The OPeN system is divided into two interconnected parts, as graphically illustrated in Fig. 1. The development of the OPeN information system was described by Rajh, Sudić, and Gvozdanović (Rajh, Gvozdanović, et al., 2018; Rajh, Sudić, et al., 2018).

The internal part of the system enables HALMED employees to streamline and facilitate business processes related to pharmacovigilance, which includes reporting suspected adverse reactions during drug use, recording and evaluating reported adverse reactions, and updating all additional information related to reported adverse reactions. In the internal part, employees are provided with the distribution of safety notices and the creation of various questionnaires within the educational module. This module represents HALMED's platform for educating healthcare professionals about activities undertaken to ensure the safe use of medicinal products and medical products, developed during the COVID-19 pandemic.

The external part of the OPeN system is intended for all external users of HALMED services, whether they are healthcare professionals (pharmacists or physicians), industry employees (i.e., marketing authorisation holders), or patients (or their legal representatives). External users can use the OPeN information system to report suspected adverse drug reactions and harmful events during the use of medical products. Additionally, healthcare professionals can use the functionalities of the OPeN information system to access the educational module, where they can access specific notices or respond to questions in the questionnaires. Healthcare professionals receive a predefined number of points for all activities within the OPeN information system, which serves to extend their licence at the respective chambers.

For the OPeN information system to successfully cover HALMED's business processes, the system is connected via web services and exchanges data with other information systems within and outside HALMED. Within HALMED, OPeN is connected to the information system for office operations and case management (Centrix), the document management system (DAIS), the National Medicinal Product Registry (NRL), and the OLIMP information system, in which the assessment of reports of harmful events on medical products is carried out. The OPeN information system is bidirectionally connected via web service to the VigiFlow information system, which manages reports of adverse drug effects and includes standardised medical terminology (Uppsala Monitoring Centre, 2024).

For the purposes of this research, secondary data were accessed and analysed, initially collected by HALMED within its legal authority and available in its business records. Data were collected from 2014 to 2023, such that from 2014 to 2018, open cases in the office operations system were summarised, and from 2019 to 2023, the number of open cases in the OPeN information system was summarised.

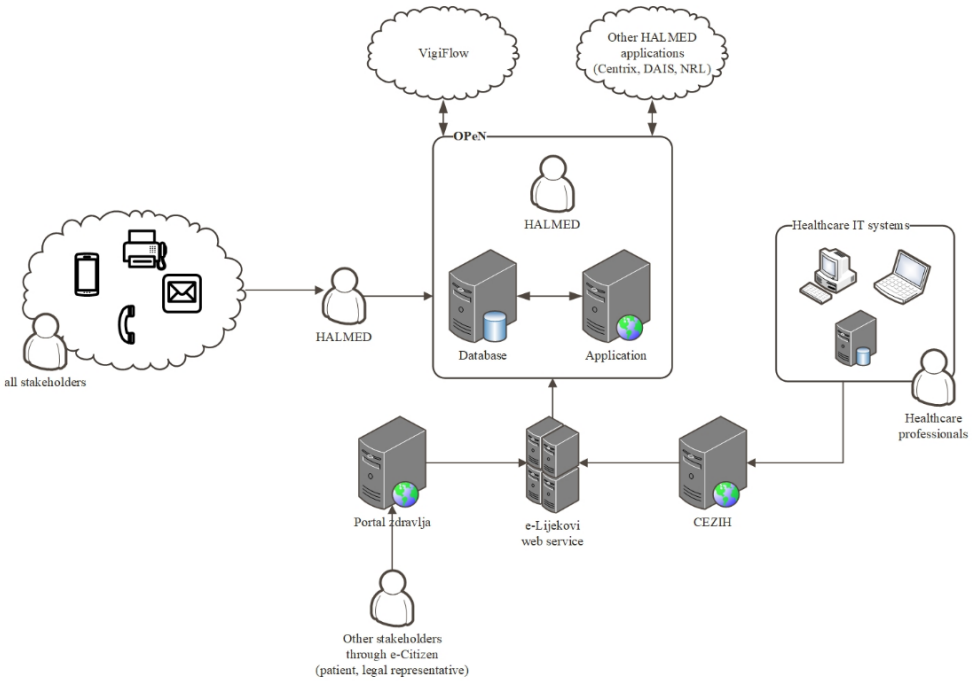

Figure 1. OPeN's structure scheme

3 Results

Results are graphically shown with Fig. 2 and Fig. 3. Fig. 2 graphically shows the number of reported adverse drug reactions from 2014 to 2023. From Fig. 2, it is evident that the highest number of adverse drug reactions was reported in 2021 (8491), while the fewest were reported in 2023.

Fig. 3 graphically represents the number monthly reported adverse reactions during the COVID-19 pandemic, between 2020 and 2023. In Fig. 3, the line represents reports of adverse reactions unrelated to COVID-19 (C-19), while the columns show reports of adverse reactions related to the COVID-19 pandemic. Observing this period, it is noted that the highest number of reports on suspected adverse reactions unrelated to COVID-19 was in March 2021, and the highest number of reports on suspected adverse reactions related to COVID-19 was in May 2021.

Fig. 4 shows the number of reported or analysed side effects through OPeN by reporter role between 2018 and 2023. The results in Fig. 4 shows that patients during COVID-19 reported far more side effects than any other reporter role.

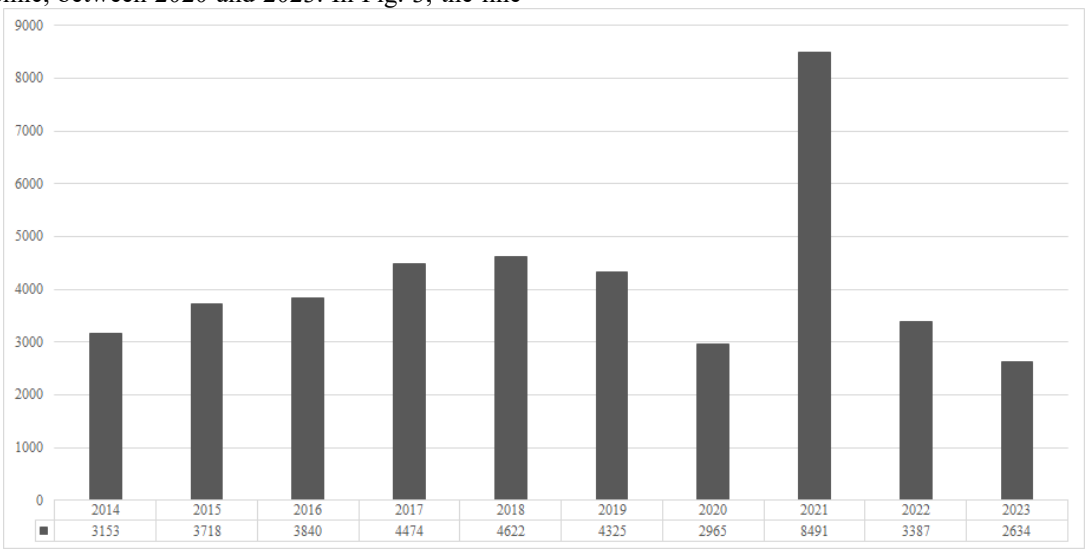

Figure 2. Number of reported adverse drug reactions

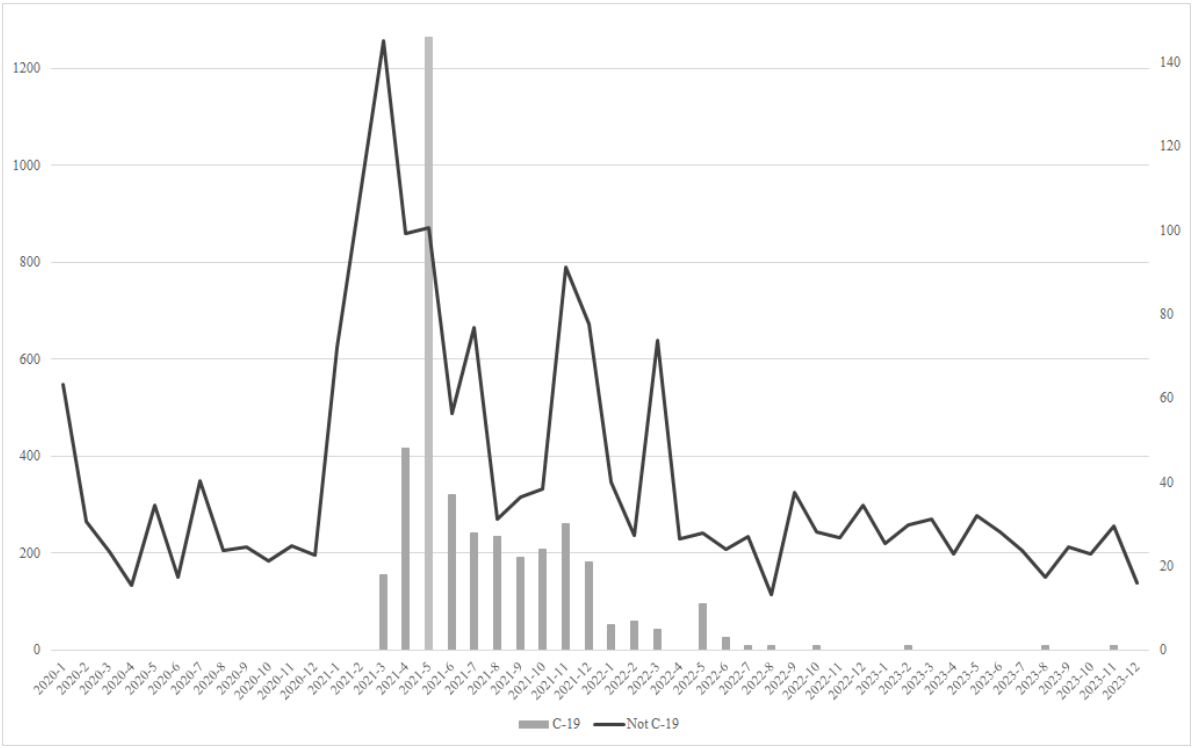

Figure 3. Number of reported adverse reactions by month during the COVID-19 (C-19) pandemic

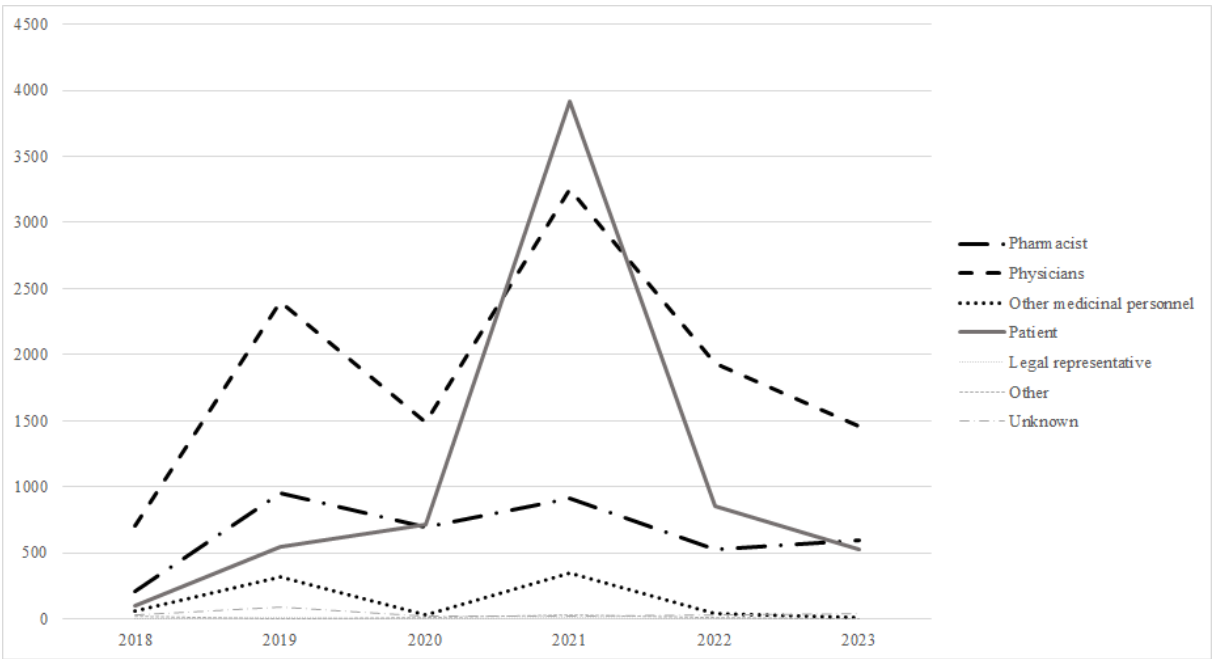

Figure 4. The trend of reporting adverse drug reactions by the reporter role

4 Discussion and Conclusion

Until 2018 in Croatia, adverse drug reactions could only be reported through traditional means—either by sending a paper form or an email to HALMED, the National Competent Authority (NCA). In 2018, HALMED launched the OPeN for electronic reporting of suspected adverse drug reactions. In addition to OPeN, it became possible to submit reports through a mobile application or by filling out a form on HALMED's website. This digitised the entire reporting

process, making access easier for all stakeholders in the pharmaceutical market. Additionally, the process of reporting adverse drug reactions has been promoted in various ways. Moreover, during the COVID-19 pandemic, HALMED significantly expanded the functionalities of the OPeN to adapt to pandemic conditions.

Discussion of Fig. 2 and Fig. 3. Fig. 2 shows that over the last decade, from 2014 to 2023, the number of reported adverse reactions was roughly consistent, with no significant fluctuations (with the exception of 2021). The highest number of reports was during 2021 due to the start of vaccination against the virus causing COVID-19 in Croatia. This is also evident from Fig. 3, which shows the peak of reports on COVID-19 vaccines in May 2021, when vaccination became available to all interested citizens, whereas previously only the most vulnerable groups were eligible. However, it is interesting to note that in 2023, the total number of reported adverse reactions decreased, despite an easy trend of reduction in reports since 2018 (except for 2021). While we cannot definitively state why there was a decline in reports in 2023, we have identified several factors that we believe contributed to this general reduction. First, we believe that the implementation of quality education and promotion of the reporting process led to fewer reports because stakeholders would not report expected and mild adverse reactions. Second, we think people have become more passive over time and less inclined to report adverse reactions, possibly due to the normalisation of certain side effects. Third, we believe there might be increased trust in medications, especially if they have proven effective and safe. Fourth, we think media coverage is responsible for reporting adverse reactions. Pharmacovigilance activities are not a common media topic (except during 2021 because of the COVID-19 pandemic), hence we believe this led to the peak in reports in 2021. If we consider the slight decline in reports after 2018, it could be attributed to "digital inaccessibility," i.e., the fact that some citizens in Croatia might not be able or willing to use digital tools.

Discussion of Fig. 4, which displays the trend of reported adverse drug reactions from 2018 to 2023, by role of reporter. Fig. 4 shows that all lines follow a similar trend – grow in 2019 and 2021, with drop in 2020, 2022 and 2023. Furthermore, from Fig. 4, it is apparent that the majority of adverse drug reaction reports are actually submitted by healthcare professionals (pharmacists and physicians), which is unsurprising given the legal obligation of these professionals to report (HALMED, 2024c), and also the fact that by reporting drug reactions, pharmacists accumulate points needed for issuing or renewing the Authorisation for Independent Practice (HLJK, 2024). In 2019 the grow on graph is because 2019 is first full year of using OPeN in HALMED. Furthermore, in 2021, there is a peak of reported adverse drug reactions from all stakeholders, especially patients which exceeds healthcare professionals, because patients reported the most adverse reactions during the vaccination campaign during the COVID-19 pandemic which started in 2021.

Moreover, using DATAtab (DATAtab, 2024), we checked if there is a correlation between number of reported adverse drug reactions from all stakeholders and Drug Utilisation Reports (we used DDD/1000/day value from each year) from 2019 until 2022 (HALMED, 2024d), because 2019 is the first full year of using OPeN, while HALMED did not publish Drug Utilisation Reports for 2023. The results of the Pearson correlation $(r(2) = 0.12, p = 0.882)$ showed that there was a low, positive correlation between the number of adverse drug reactions and the DDD/1000/day value of Drug Utilisation Reports ($r = 0.12$). However, the correlation was not statistically significant ($p = 0.882$), because p value greater than the significance threshold (0.05) suggests that the observed correlation could very well be due to random chance.

Currently, HALMED is upgrading the OPeN information system to enable reporting through hospital information systems and general practice information systems. We believe this is beneficial as it will allow for quicker reporting of adverse drug reactions with "one click," thereby encouraging healthcare professionals to be more active in the reporting process. Additionally, it will enable the possibility of reporting through the e-Citizens portal.

All these systems share a joint component base called eLijekovi, which contains information about all the medicines available in the Republic of Croatia. The data in eLijekovi are recorded in the form of the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP) standards (EMA, 2024) which the EMA has prescribed as the standard for recording and exchanging medicine data.

In this paper, we also proposed an extended model (Fig. 5) of the system for collecting side effects, which on the HALMED system side includes the use of artificial intelligence (AI) for receiving and processing data which could be used as a proof of concept (PoC) in the near future in accordance with HALMED's time and financial resources. Given the standardisation of medicinal product data at national and European levels, artificial intelligence could use coding lists with standardised terms to recognise and classify adverse event data while receiving an adverse reaction suspicion. Additionally, in the case when the received data are not in standardised form, AI could be trained to match the data to standardised form. This data can also be used also by an AI in the process of analysing, identifying, and classifying the adverse drug reaction as mild, moderate, severe or lethal, comparing the received reaction of the same drug and suggesting the correction measures if possible. For training the AI, all the data currently stored in OPeN could be used.

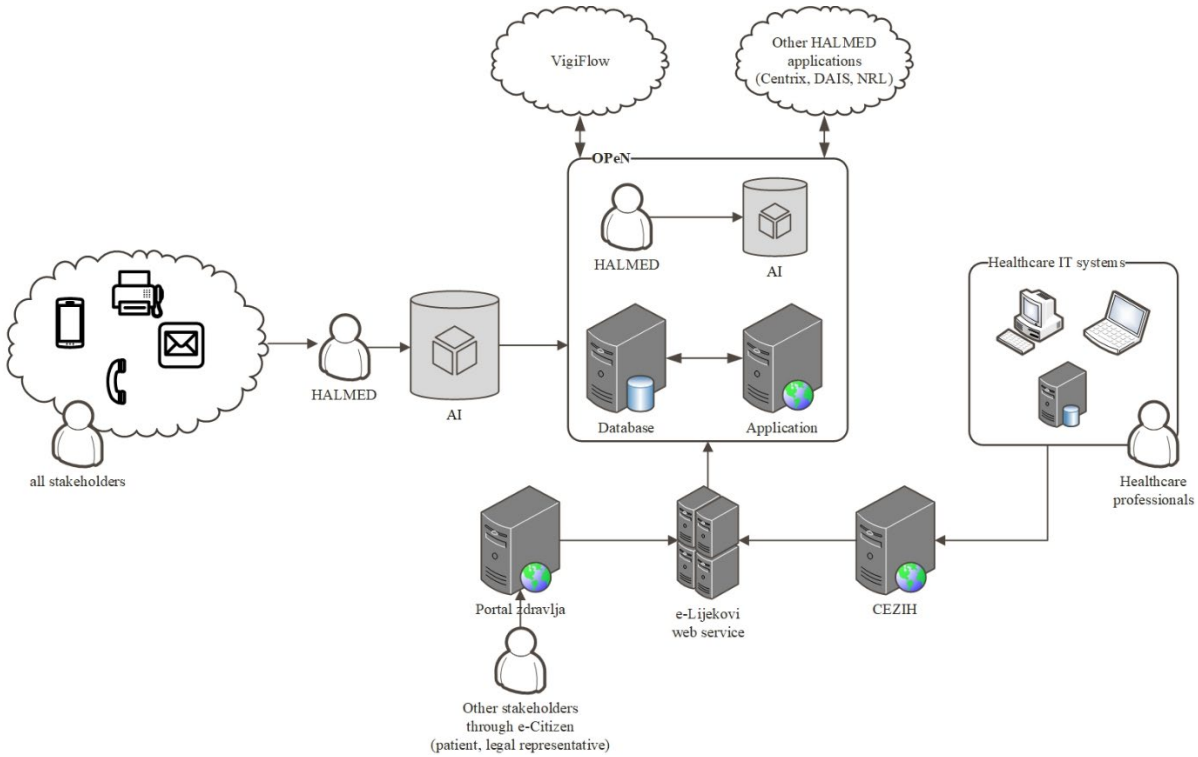

Figure 5: Proposed OPeN's structure scheme

This data were manually checked and all received adverse reaction suspicions were classified by HALMED's subject-matter expert.

The above mentioned process would speed up and simplify analysis and processing, as well as increase data accuracy. Suppose an adverse event report is received digitally, using artificial intelligence. In that case, the responsible HALMED employee only needs to verify the received data (without needing to overtype), expediting the business process of analysing received side effects.

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