Monitoring the Safety of Medicines and Vaccines in Times of Pandemic: Practical, Conceptual, and Ethical Challenges in Pharmacovigilance

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Abstract

In this paper, we analyse some of the challenges that pharmacovigilance, the science of detecting and assessing possible adverse reactions from medical interventions, is facing during the COVID-19 pandemic. In particular, we consider the issue of increased uncertainty of the evidence and the issue of dealing with an unprecedented amount of data. After presenting the technical advances implemented in response to these two challenges, we offer some conceptual reflections around such practical changes. We argue that the COVID-19 emergency represents a chance to push forward critical thinking in the field of pharmacovigilance, and that contributions from epistemology, ethics and philosophy of science are necessary to increase resilience in the face of this and future health emergencies.

Keywords: COVID-19, Pharmacovigilance, Resilience, Big Data.

1. Introduction

The coronavirus disease (COVID-19) pandemic emerged in Wuhan, China, in 2019 and rapidly spread globally during 2020. COVID-19 is not only a crisis for public health and healthcare. It is also a challenge for the established structures of knowledge production, use and communication (Meng 2020). The COVID-19 crisis is forcing us to improve the way we make science-based decisions in the face of uncertainty. This is necessary in order to increase resilience for this and future pandemics or other health emergencies (Leonelli 2021).

In this paper, we argue that the COVID-19 emergency represents a chance to push forward critical thinking in the field of risk assessment of medical interventions. A health crisis requires urgent action from healthcare, but such urgency cannot come at the cost of patient safety. When a medicine enters the market, its safety is only partially known. Effects on vulnerable groups are often undetected within

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pre-marketing clinical trials; for this reason, a system of post-marketing monitoring is in place in order to identify evidence of possible side effects as early as possible. The aim of this paper is to show that improving safety of medicines and vaccines in cases of global health emergency is not only a practical, but also a conceptual challenge. As such, it should be met not only with technical improvements of existing processes, but also by incorporating contributions from epistemology, ethics and philosophy of science. The ultimate aim is a more self-critical, interdisciplinary and resilient practice of risk assessment of medicines and vaccines.

Pharmacovigilance is the science of detecting and assessing possible adverse reactions from medical interventions. Although in pharmacovigilance all types of evidence, including laboratory research, observational studies and anecdotal reports are potentially crucial, most of post-marketing safety monitoring is based on the so called 'passive surveillance'. The cornerstone of this process is the spontaneous reporting of potential adverse reactions by manufacturers, health professionals or patients. Analyses of adverse reaction reports generate hypotheses about causality between medicine or vaccines and the reported symptoms. Such hypotheses of causal connections are sometimes called 'signals'. In pharmacovigilance, a signal is defined as a hypothesis of a risk from a medicine with data and arguments that support it (Uppsala Monitoring Centre 2021a).

During the COVID-19 pandemic, the challenges and complexities of safety monitoring in pharmacovigilance have been amplified (Ferreira-da-Silva, Ribeiro-Vaz, Morato & Polónia 2021). Arguably, this extra-burden is due to three factors that have changed during the COVID-19 pandemic. These are:

- *Increased uncertainty,* as a result of the novelty of the disease and the novelty of certain medicines and vaccines, often approved with a lower level of safety evidence as compared to medicines approval in non-urgent situations.
- *Increased amount of data to be handled and processed*, mainly because of massive COVID-19 vaccination programs in place globally.
- *Increased public attention,* due to the public perception of the state of emergency and to the extensive media coverage of issues around drugs and vaccines safety.

In the literature there are recent accounts on how manufacturers and drug authorities evolved in order to face these issues (Ferreira-da-Silva et al. 2021). Notably, much of the focus of the innovation process is set, especially by manufactures, on digitalization, automatization, and the development of more sophisticated data-mining algorithms and artificial intelligence technology to increase the effectiveness of existing procedures (ICON 2020; Pharmafile 2021). This optimistic trend rightly sees technological innovations as an important part of the solution, and some manufacturers have gone so far as saying that the COVID-19 emergency offered the chance to innovate the company's pharmacovigilance procedures, which had been otherwise stagnating and conservative. Even more optimistically, media reported that

> Using smart technology to manage the […] process not only simplifies what can be laborious and time-consuming work for humans, but can also help to reassure members of the public who are concerned about the safety of newly developed drugs (Pharmafile 2021).

However, although technological improvements are an important part of the solution, it is also known that technological innovation alone will not lead to a sustainable improvement of medicines' and vaccines' risk assessment (Naidu, Sushma, Jaiswal & Asha 2020). Here, we urge that equal attention should be given to practical, technological advances *and* to the critical reflections necessary to make such advances meaningful and efficient. Only this way can the COVID-19 experience be harnessed to improve risk and safety assessment of medical interventions.

In the following, we are going to analyse in detail two of the three COVID-19 related challenges: the issue of dealing with increased uncertainty, mainly in relation to safety monitoring of COVID-19 treatments, and the issue of handling increased amount of data, mainly in relation with safety monitoring of COVID-19 vaccines. For each of the two challenges, we first outline a general description; secondly, we give an overview of the practical implemented measures so far; finally, we present the related critical reflections and indicate some conceptual advances pushed by each specific COVID-19 related challenge.

Before starting the analysis, the next section briefly introduces the process of pharmacovigilance.

2. Safety Monitoring and Risk Assessment in Pharmacovigilance

The paradigmatic case that started the modern pharmacovigilance structure, was the thalidomide disaster, where the drug used as an antiemetic during pregnancy provoked rare limbal malformations in the new-born (Dally 1998). After this, the WHO Programme for International Drug Monitoring (PIDM) started a collaboration between the drug authorities of by now 148 countries for systematic global monitoring of all medical treatments before and after being released on the market (Letourneau, Wells, Walop & Duclos 2008).

The standard procedure of the so called 'passive surveillance' in pharmacovigilance is that observations of suspected adverse effects of medicines and vaccines, collected during regular clinical use, are reported by marketing authorization holders, health professionals or the public to the national authorities of each country member of PIDM. These reports are registered into national databases and often shared, together with some reports from pre- and post-authorization clinical trials, in international databases curated by WHO (VigiBase) and other international agencies (e.g. EudraVigilance, curated by the European Medicine Agency). For this, one needs to digitally transcribe and code the reports using standardised international terminology both for medicines, vaccines and symptoms (Mugosa, Stankovic, Turkovic, & Sahman-Zaimovic 2015). A valid adverse reaction report must contain at least coded information about an identifiable reporter, an identifiable patient, a suspected adverse reaction and a suspect medicinal product (CIOMS working group VIII 2010). Only when the data are in standardised format, can they be retrieved from databases, accessed and analysed by pharmacovigilance experts to detect new possible causal relationships between reported reactions and medicines.

Typically, the knowledge accumulation about a new adverse effect follows the shape of an S curve with three phases. A first slow generation of suspicion, followed by a rapid accumulation of case reports (signal strengthening) and a final slower period of confirmation, typically including post-marketing observational studies (Meyboom, Hekster, Egberts & Gribnau 1997).

In pharmacovigilance agencies, new hypotheses of causality do not get assessed until a sufficient number of cases accumulate. The final phase of confirmation is usually based on clinical trials and/or pharmacoepidemiological research studies, which traditionally have taken long in relation to the timelines of decision makers. Often, a preliminary regulatory decision has to be taken already during the second phase of signal strengthening and possible confirmation.

For the process of hypothesis-generation, a vast spectrum of information is used: from preclinical studies, to clinical experiments, active surveillance and observational studies. However, post marketing hypothesis generation in pharmacovigilance is primarily based on passive surveillance, as described above.

Based on the information retrievable from national and global databases, pharmacovigilance experts need to assess whether the drug is likely to play a causal role for reported symptoms, or not. There are three complementary approaches to this task:

- Single case assessment: each single report goes through an independent causality assessment. There are several methods for causality assessment in the single case, however they all have some common points (Meyboom, Hekster, Egberts & Gribnau 1997). These include: (I) considerations of temporality; (II) the presence of confounders, such as illness or other drugs, which could equally well (or better) explain the symptoms; (III) evaluations of the symptoms over time (see table 1, excerpt from WHO-UMC methodology for causality assessment).
- Analysis of case series: when a series of relevant cases is collected and identified, the hypothesis of causality is assessed by verifying whether the putative effect is consistent, robust and specific through the available cases. The Bradford-Hill criteria are often used to test the causal hypothesis, and this usually implies the consideration of many different types of evidence (pre-clinical, clinical studies, safety profile of similar drugs, etc.) (Shakir & Layton 2002).
- Statistical methods: when numbers of reports/drug event combinations are too large to be individually manually analysed, statistical measures are used as a tool to detect signals. In these cases, the likelihood of a causal hypothesis is judged by the amount of reports linking the drug to the same symptom. *Disproportionality* measures calculate whether the combination drug-symptom is reported into the database more times than expected if the combination happened by pure chance (CIOMS working group VIII 2010. Once detected as disproportionate, signals may subsequently be analysed manually.

With this short introduction to the process of hypothesis generation in pharmacovigilance, we are now going to look in more details at the way this system was challenged during the pandemic.

3. Pharmacovigilance and COVID-19 Treatments: Dealing with the Challenge of Increased Uncertainty

3.1. Why Is Evidence of Adverse Effects from COVID-19 Medicines Uncertain?

One of the issues challenging pharmacovigilance during the COVID-19 pandemic is, as mentioned, increased uncertainty. What is this uncertainty due to, and why does it impact pharmacovigilance considerably?

On one hand, we are dealing with a new human corona virus, SARS-CoV-2. The virus causes mild to severe pneumonia with a pathogenesis that is still to a certain extent unknown and has been gradually but still only partially elucidated during the course of the pandemic. To complicate the picture, the pathophysiology or the illness has turned out to be a particularly complex one. Respiratory distress syndrome is the primary cause of SARS-CoV-2 mortality, but the disease may affect multiple organs where heart failure, thrombo-embolic events, severe single or multiorgan dysfunction are common among causes of COVID-19 fatality (Machhi et al. 2020). It has thus been difficult, especially in the first year of the pandemic, to evaluate whether a certain reported symptom might or not be caused by the underlying COVID-19.

On the other hand, we are dealing with a health emergency in which many severely ill patients were co-medicated with a huge arsenal of medicines in the lack of an acknowledged therapeutic approach (Desai 2020). It is difficult to disentangle the causal contribution of so many medicines, given that a medicine repurposed for COVID-19 patients might have a different safety profile in this particular context. Moreover, several new treatments for COVID-19 have so far been approved for emergency use, with limited knowledge of their safety profile. COVID-19 adverse effect reports often contain a long list of co-medications, and it is difficult to evaluate whether a certain reported symptom might partially or entirely be caused by one of them (Gérard et al. 2021).

Finally, some undesired effects might be provoked by a combination of the medicine(s) used, the COVID-19 infection, and the background medical history of the patient. Indeed, risk groups for developing severe COVID-19 are weak, old and some chronically ill patients (Machhi et al 2020). At the same time, these patient groups may similarly be partly susceptible to adverse drug reactions because of declining organ functions, for instance of the liver and kidney (Mühlberg & Platt 1999). It is clinically reasonable to suppose that some of these patients may be predisposed to be hurt by a certain treatment which is otherwise safe in the majority of the population. At least in some cases, then, a certain adverse effect can be generated by the interrelation of different causal contributions in the individual patient.

To understand the extent to which this situation hinders pharmacovigilance recall that, for the causality evaluation of single adverse event reports, one decisive factor is whether the symptom can be explained by another medicine or underlying condition (see section 2). Let's consider an example. Imagine that a patient without any history of allergy and skin diseases has a rash after the initiation of an antibiotic. Say also that timing of the rash onset is compatible with the biology of the drug-body interaction, and the symptom disappears after drug cessation. According to most of the causality assessment methods (table 1), causality in this case will be categorised as 'probable' because other acknowledged causes of the event have been excluded. If, however, the patient had episodes of rash in the past, or has an infection that could explain the rash, or is already using a medicine which is associated with rash, the causality would be classified as only 'possible'.

Similarly, since it is uncertain whether a specific symptom associated with a COVID-19 treatment could be explained by the underlying COVID-19 infection, or by (a multitude of) other concomitant COVID-19 medicines, causality in the vast majority of the adverse reaction reports will at best be classified as 'possible', without further possibility of discerning among them (Desai 2020).

Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes the relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Table 1. Excerpt from WHO-UMC methodology for causality assessment (Uppsala Monitoring Centre, 2021b).

3.2. How to Cope with Increased Uncertainty? Practical Implemented Measures

In this complex situation, causality assessment methods that rely on an evaluation of the difference made by each single causal factor, are of limited help. Some experts have even predicted early in 2020 that the causality assessment of single COVID-19 related reports would be impossible, and that "causation needs to be viewed for the study drug with a public health perspective" (Desai 2020).

One predominant way to face this situation has indeed been to focus on the population level, in the lack of precise single case causality assessment. This was done, for instance, for the novel antiviral remdesivir, which was granted emergency authorisation for the treatment of COVID-19 (Saint-Raymond et al. 2020). Since preclinical studies showed a potential renal toxicity, and clinical trials produced unclear results about this potential side effect, it was important to further assess the risk (Saint-Raymond et al. 2020). One explorative approach has been to search databases for the number of adverse reaction reports containing the term 'remdesivir' together with one of more terms indicating renal failure. Using a statistical disproportionality measure (called Information Component, IC), it was possible to assess that remdesivir was reported in correlation with terms of renal failure more often than expected (Gérard et al. 2021). Authors point out numerous caveats, not least the persistence of many confounding factors, nevertheless they argue that this evidence reinforces the hypothesis of harm. However, other statistical designs have reached different conclusions. For instance, a retrospective cohort study on COVID-19 patients who received remdesivir did not find a statistically significant association between the medicine and renal impairment, concluding that this particular safety warning may be a 'clinical lore' rather than a valid precaution (Ackley, McManus, Topal, Cicali, & Shah 2021). Ultimately therefore, statistical evidence is still contradictory, and whether experts adopt a cautionary mode still depends largely on their interpretation of the preclinical toxicity and pharmacology studies (Gevers, Welink, & van Nieuwkoop 2021) alongside clinical study results.

In parallel to the mainstream focus on statistical strategies to control for confounders, a second tactic was promoted by drug agencies of countries such as Norway and France (Grandvuillemin, Drici, Jonville-Bera, Micallef, & Montastruc 2021). These experts emphasise the need of efficacy and responsiveness of the system in times of health emergency and to control for confounders by improving the clinical *quality* over the quantity of the data:

> Although COVID-19 is a confounding factor per se, owing to its potential for multi-organ damage including the heart and kidney, the *quality of the transmitted data* in adverse drug reaction reports, the *timeliness of feedback from clinicians*, and the real-time pharmacological and medical analysis […] made it possible to swiftly identify relevant safety signals (Ibid: abstract, emphasis ours).

In these systems, pharmacovigilance experts use their decentralised national network of clinicians and pharmacists who contributed with detailed clinical investigations of some cases. Decentralised national pharmacovigilance systems allowed to promptly detect signals of harm for some of the COVID-19 treatments. An example is the Intracranial Venous Sinus Thrombosis, in combination with thrombocytopenia, a rare syndrome that was detected and confirmed in some individuals after immunisation with certain COVID-19 vaccines and which was quickly detected in countries such as Norway and Denmark (Norwegian Medicines Agency 2021). Moreover, the French medicines agency claimed that their system allowed early detection and communication of the cardiac adverse events occurring in some COVID-19 patients treated with hydroxychloroquine (Grandvuillemin et al. 2021). Their conclusion is that:

> Some pharmacovigilance systems are working on automated signal detection by using tools connected to very large databases. However, for the time being, these methods enable the identification of signals, but do not allow for any conclusion on a causal link, for which a medical and pharmacological evaluation remains essential. Moreover, a real-time medical and pharmacological analysis is crucial in this type of health crisis (Ibid: 407).

Clearly, 'normal business' pharmacovigilance would not see these two strategies as mutually exclusive. As explained in part 2, it is normal practice to integrate statistical and clinical approaches for causality assessment. However, it appears that in the COVID-19 emergency the role of single case assessment and clinical expertise for facing increased uncertainty is under discussion. Most experts would probably agree that in an ideal world there would be resources to both improve the sophistication of statistical studies, for instance by joining different databases and registries, *and* build up decentralised networks of clinical experts. However, resources are limited and need to be wisely allocated. Clinical causality assessment in pharmacovigilance is a resource- and time-consuming task, especially if it needs to happen in parallel with a health crisis requiring extra healthcare resources (Desai 2020). The question then becomes: is it worthy to maintain and invest resources in improving qualitative evidence of this type? Would it ultimately help building resilience to deal with future situations of increased uncertainty?

This is a practical question that hides a conceptual issue about the role of qualitative evidence for knowledge-building, and the type of scientific discoveries we seek in pharmacovigilance.

3.3 Uncertainty and Scientific Discoveries in Pharmacovigilance: A Critical Reflection

The field of pharmacovigilance is generally struggling with a tension between the need of prompt regulatory action to safeguard the health pf patients and minimize the impact of the detected adverse effects and the need of sufficiently good evidence to support the action taken, a tension that is emphasised in times of emergency. Partially, this tension is due to the low epistemic[1] role that is traditionally assigned to single case reports and qualitative evidence. There is a growing resistance against establishing causality, or expanding scientific knowledge, based on few outlier cases (Howick 2011). In the evidence-based medicine pyramid of evidence, evidence from case studies and expert opinion are rank the lowest for the purpose of establishing causality (Howick 2011). The best way of looking for causal links is generally considered controlled experimentation, where confounding factors are controlled for.

Nevertheless, the epistemic role of single case in pharmacovigilance is clearly higher than normally granted by evidence-based medicine (see part 2). The legislation states that safety warnings in the product labels should be based on "at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies *and/or on an evaluation of causality from individual case reports*" (European Commission Enterprise and Industry Directorate 2009). A hypothesis of harm from a medical treatment, therefore, does not *in principle* need to be supported with statistical evidence and could be formulated on the basis of as few as three cases, or even less (ibid). Traditionally, pharmacovigilance emphasises causality assessment in the single case, and is close to a *singularist* view of causation (Uppsala Monitoring Centre 2021b). In this view, the causal link is best investigated by studying in detail the causal context and by understanding the causal processes at place (Anjum & Rocca 2019).

What, then, when the problem of confounding is major and the uncertainty is high, like in the case of the COVID-19 emergency? Should pharmacovigilance emphasise the statistical approach to try to control confounding factors, getting closer to the EBM pyramid of evidence? Or should more effort be invested in the clinical investigation of single cases, maintaining a singularist take on causation?

This question requires that we critically reflect on why pharmacovigilance has traditionally acquired such a different epistemological take on causal evidence compared to other medical disciplines.

One answer could be that pharmacovigilance is mainly an exploratory activity, which needs curiosity and "prepared minds" to identify unexpected risks (Trontell 2004). As such, it was categorised as a specific process of discovery, namely *serendipity* (Rocca, Copeland & Edwards 2019). Serendipity is the process of making a discovery when not looking for it. Serendipitous discoveries are based on the emphasis of unexpected but valuable findings (ibid). This view accurately describes the first, explorative phase of pharmacovigilance, largely based on passive surveillance and on a multitude of different types of evidence. In this sense, discoveries in pharmacovigilance are different from other discoveries in medicine, that are instead intentionally derived from an established theory (the efficacy of a

[1] In the paper, by 'epistemic' we mean 'knowledge-related'.

drug, for instance). An argument for the favourite status of the single case in pharmacovigilance is that rigid study designs are unfit for discovering the unexpected (Osimani 2013). On the contrary, successful drug safety monitoring must succeed in catching the significance of unexpected clinical observations (Rocca, Anjum & Mumford 2017). What counts for serendipitous discoveries is the quality, and not the quantity, of the observation (Copeland 2017).

A resilient pharmacovigilance system, then, would be one that promotes serendipitous discoveries, especially when a prompt reaction to crisis is needed (Rocca, Copeland & Edwards 2019). How could this be done?

There is no easy answer to this question, however some conceptual ground has been laid regarding this issue. Recent advances in serendipity research acknowledge the importance of the social context, trans-disciplinary networks, diversity of expertise and plurality of methodological perspectives (Copeland 2017). In other words, chance and the prepared mind (or sagacity, as it is also called) are not enough to catch the unexpected. An interesting observation that is not followed up by the scientific community, for instance because dismissed as "low quality" according to the dominant standards of evidence, does not lead anywhere.

Interdisciplinary responsive networks are typically formed in response to virus outbreaks. As we experienced during 2020, knowledge about the SARS-CoV-2 progresses exceptionally fast, because different disciplines collaborated closely under the perception of a common problem to solve (Leonelli 2021). In these circumstances, observations are picked up and considered by different disciplinary perspectives. Because of this, communities fighting virus outbreaks have been explicitly called "sites of serendipity" (Michener et al. 2009).

Following this reasoning, pharmacovigilance systems that emphasise decentralised network of clinical experts and encourage in-situ clinical assessment of the single cases seem in line with the promotion of a serendipitous, responsive network in which clinicians and pharmacovigilance experts collaborate with the purpose of catching unexpected clinical observations in real time. If we think in terms of serendipity, we can say that in time of pandemics the importance of informative narratives is crucial. Understanding the causal story in its contexts, including patient-generated evidence and hypotheses of inherent mechanisms at place in the specific patient, is as challenging as crucial. The French national Agency of Medicine recommendation, of keeping the clinical analysis as essential for early detection of possible side effects during the pandemic (Grandvuillemin et al. 2021), is in line with our critical reflection here.

In summary, in this session we have outlined the challenge of dealing with increased uncertainty, due to confounding from a new virus and new use of medications during the COVID-19 pandemic. We have shown that the pharmacovigilance community tried opposing strategies, from downplaying the difficult task of causality assessment in the single case in favour of a population approach, to allocating extra resources for the specific task. Finally, we have made our main point: that predicting which strategy is the most effective requires critical thinking about the specific task of pharmacovigilance and the type of evidence needed to promote it. When such considerations are made, clinical expertise and in-situ causal evaluation appear even more important when uncertainty is high.

4. Pharmacovigilance and COVID-19 Vaccines: Dealing with Big Data

4.1 Why is Big Data an Issue for Pharmacovigilance During the COVID-19 Pandemic?

As already mentioned, most of the world's countries have in place a system for the safety surveillance of medicines and vaccines on a large, population scale. In developed countries it is becoming increasingly common to base this surveillance in electronic healthcare databases, and data are often shared in common databases among countries. For instance VigiBase, the WHO global database of individual case safety reports, contains over 20 million reports of suspected adverse effects of medicines, shared, since 1968, by member countries of the WHO Programme for International Drug Monitoring (Lindquist 2008). National and international databases are periodically analysed with data-mining approaches. Such analyses may be more or less systematic depending on the mandate of different institutions. Regardless, the aim of data mining approaches is always to identify drug-symptom combinations that are interesting for further safety evaluations, for instance because they are reported more often than expected. This is an efficient but time-consuming system, since adverse reaction reports need to be digitally transcribed, usually by the national medicine centres (if not in digital format originally), coded and structured in a form that can be processed with traditional analytic tools (Lindquist 2008). Standardisation and codification are indeed an essential step to make database useful. Pharmacovigilance experts unanimously agree that "The quality of what you get from the database depends on the quality of what you put in" (Barwick 2020), an issue that the pandemic made even more visible, as we are going to describe.

During the COVID-19 pandemic, the global dimension of the therapy and vaccination programmes, together with the need for close safety monitoring of the marketed products due to scarce pre-marketing information, have generated extraordinarily large amounts of spontaneous adverse effect reports. Since January 2021, over 1.100.000 adverse effect reports of COVID-19 vaccines have been shared into VigiBase,[2] which is an unprecedented affluence. The first problem to face was that market authorisation olders and national centres are not equipped to deal with these amounts, which require more trained professionals to process the data than available at the moment. As a result, there were substantial backlogs in handling of reports even at normally resource-rich centres (Norwegian Medicines Agency 2021b).

On the other side, spontaneous reports are only part of the potentially useful data that are being produced in increasing amounts. Clinical trials, health registries, claim registries, and even experiences largely shared in social media might give insights for safety monitoring (Hussain 2021). These represent big potentials as well as big challenges. First, joining different registries, databases and health records requires expanded standardisation and a common language for coding (Leonelli 2019). Second, healthcare data are protected by privacy and cannot readily be shared among different stakeholders (Benzschawel & Silveira 2011). Third, processing unstructured data, such as clinical cases and patient narratives,

[2] Data retrieved from the website http://www.vigiaccess.org/, which provides public access to VigiBase.

requires more sophisticated analytical tools than the ones currently used to mine structured data (Hussain 2021). The issue of dealing with increased amounts of data during the pandemic, therefore, have been described predominantly as a series of practical challenges.

4.2 How to Cope with Bigger Amounts of Data? Practical Implemented Measures

The current situation has been described as an unprecedented opportunity for technological innovation (Ferreira-da-Silva et al. 2021; Hussain 2021; ICON 2020; Meng 2020; Pharmafile 2021).

Manufacturers, companies offering pharmacovigilance services, and national agencies have implemented new technologies, often based on artificial intelligence, with among them the following aims:

- Automatic coding of the adverse drug reaction into standardised medical terminology (Pharmafile 2021).
- Automatic translation into and from different languages (Pharmafile 2021).
- Increased efforts for the implementation of existing methods for automatic removal of patient sensitive data from clinical narratives, in order to share healthcare data among different databases (Meldau 2018).
- Improved mining of unstructured data, such as narratives, clinical studies and social media (Hussain 2021).

Researchers have also applied to pharmacovigilance databases data analysis methods from other disciplines, such as time series analysis (Beninger 2021). Moreover, previous efforts to link health data from different electronic registries (Hripcsak et al. 2015) have been harnessed and developed to answer COVID-19 related questions, including questions about safety of treatment (Morales et al. 2021). Finally, the European Medicine Agency, recognising that "Big Data can complement clinical trials and offers major opportunities to improve the evidence upon which we take decisions on medicines", have set up a Big Data Taskforce to build technical skills, capacity and tools for the joint analysis of different type of data sources (European Medicines Agency 2020).

4.3 Epistemology of Big Data Pharmacovigilance: A Critical Reflection

Although the success of data-centric research is based on technological and practical innovations, it also depends on a solid base of theoretical knowledge and human judgement. Philosophical issues linked to big data are comparatively less visible in mainstream discussions but should not be overlooked. While epistemology and ethics of big data have been discussed in other disciplines dealing with big databases, such as biology and climate science (Leonelli 2016), the time is ripe for applying them to pharmacovigilance, too. The aim is to acknowledge the *full* range of skills necessary to develop an efficient use of pharmacovigilance data, in normal times and even more importantly in times of crisis.

A crucial philosophical issue to consider, when critically reflecting on the acceleration of big-data pharmacovigilance during COVID-19, is the debate between objectivity and constructivism, or else the question of theory-laden obser-

vations. The empiricist ideal that scientific explanations somehow emerge directly out of the data seems to be having a revival in era of big data (Leonelli 2016). This is in line with the evidence-based medicine paradigm, in which expertise and theory have the lowest epistemic status, and statistical evidence from controlled studies the highest (Howick 2011). Data-driven research has been saluted as 'the death of subjectivity' and is believed to lend objectivity and clarity even to fields that have been traditionally less amenable to quantification, such as sociology (McKie & Ryan 2016). Is this view, that clear explanations derive primarily from data rather than from people and expertise, applicable also to COVID-19 pharmacovigilance (and pharmacovigilance in general)?

In her analysis of data-centric biology, philosopher Sabina Leonelli writes:

> Far from being 'the end of theory', the computational mining of big data involves significant theoretical commitments. The choice and definition of keywords used to classify and retrieve data matters enormously to their subsequent interpretation. Linking diverse datasets means making decisions about the concepts through which nature is best represented and investigated. In other words, the networks of concepts associated with data in big data infrastructures should be viewed as theories: ways of seeing the biological world that guide scientific reasoning and the direction of research, which are often revised to take into account new discoveries (Leonelli 2019: 2).

We are going to show that just like theoretical understanding of natural phenomena is crucial for linking datasets in the field of big data biology, as pointed out by Leonelli, clinical and pharmacological reasoning are necessary for the meaningful organisation of data in pharmacovigilance databases. How so? And how does this matter for COVID-19 related pharmacovigilance?

We will use two examples to illustrate that the success in COVID-19 vaccine safety monitoring, although being data-driven, has not emerged directly from the data, but from a genuine collaboration between data science, pharmacological theories and clinical expertise. Our aim, in other words, is to show that big-data pharmacovigilance is theory-laden and its success in times of crisis depends on a network of different types of expertise, rather than predominantly on data science. Nurturing such network and interdisciplinary dialogue is then a central part of improving pharmacovigilance in the face of health emergency.

As a first example, consider that without proper "query" systems it is not possible to retrieve data relevant for COVID-19 specific (or any other) safety questions in an efficient way. In other words, one thing is the much-discussed technical issue of coding large amounts of data, something that seems to be possibly facilitated with artificial intelligence. Another, more fundamental need is to develop the common terminology that coders (whether human or not) use to classify the data and integrate them together (Leonelli 2019).

Let us introduce some background information before we apply them to the COVID-19 vaccine safety monitoring. When entering case safety reports in a pharmacovigilance database, marketing authorization holders and national agencies need to code the name of medicines and vaccines with a standardised international classification. One classification in use at the moment is provided in the *WHO Drug* dictionary. *WHO Drug*, created by the WHO Programme for International Drug Monitoring, is constantly updated, and the magnitude of this labour is demonstrated by the fact the big task force dedicated to maintaining it at the

Uppsala Monitoring Centre (Lindquist 2008). One *WHO Drug* feature classifies medicines based on various different and *relevant criteria*, such as their pharmacological effect, indication for treatment or metabolic pathway, in Standardised Drug Groupings (SDG) (Uppsala Monitoring Centre 2020). The SDGs are not mutually exclusive and as such any drug may be listed in several SDGs. Such grouping criteria are relevant for different purposes. For instance, a medicine manufacturer might set up a clinical trial to test a certain medicine which is metabolised by enzyme E, therefore all medicines interacting with E might interfere with the study medicine. The manufacturer then will exclude from the trial all the participants that take any of the medicines listed in the *WHO Drug* SDG of "medicines inhibiting E". This was indeed the initial purpose for setting up the SDG classification: helping *WHO Drug* users from the pharmaceutical industry to manage the inclusion-exclusion criteria in their clinical trials.

Soon enough, *WHO Drug* SDGs were repurposed and integrated in the toolbox for safety monitoring analysis (Chandler & Lagerlund 2019). Imagine for instance that I suspect that a medicine X causes a certain adverse effect because it inhibits receptor R. Being able to retrieve a group of safety reports containing medicines similar to the medicine of interest X, in that they all inhibit receptor R, is important. It allows me to check, for instance, whether there is a significant correlation with the adverse effect of interest in the total number of reports at the SDG group level. This gives an indication to support (or not) the hypothesis of mechanism.

It should be clear at this point that the ways the database can be used is determined by the types of possible 'group queries'. The more relevant the SDGs or similar groupings are for a specific purpose, the more efficient may be the data mining of coded data.

Let us now consider how SDGs were used for the safety monitoring on COVID-19 vaccines. When in need of enhanced efficiency such as during the COVID-19 pandemic, *WHO Drug* specialists created new SDGs for the new purpose of facilitating the safety monitoring of COVID-19 vaccines (Uppsala Monitoring Centre 2020). In doing so, decisions were made on how adverse effect reports related to different types of COVID-19 vaccines should be linked together. Curators made decisions about how clinical and pharmacological interactions are best "represented and investigated", in Leonelli's own words. Does it make clinical sense, for instance, that RNA-based vaccines might interact with the body in different ways than vaccines containing inactivated viruses? If so, SDGs should be grouped based on the vaccine platform. This would make it possible to easily and efficiently retrieve, for instance, all reports containing RNA-based COVID-19 vaccines together with a certain symptom and check whether there is a disproportional reporting at group level. Notice now the crucial point: the idea that the type of vaccine platform has something to say about the adverse reactions it may provoke did *not* emerge directly from the data. Rather, it is a hypothesis anchored in clinical and pharmacological thinking, obtained by reasoning about the mechanism of action of different types of vaccines and the molecular mechanisms possibly at place in the patient. The SDG example then indicates that collecting more data, and improving data technology, represent only a part of the knowledge developments necessary for COVID-19 vaccine safety monitoring.

Clinical and theoretical reasoning are fundamental for a spectrum of steps in the process of curating a pharmacovigilance database. Here is a second example. What do we mean, in statistical measures of disproportionality, that the pair vaccine-symptom is reported more than expected in the database background? Which

background should be used to calculate the expected statistic? Normally, the number of reports expected if the combination happened by pure chance are calculated considering the whole database. In the case of COVID-19 vaccines, however, there might be more useful background measurements. One could choose to calculate 'background expectations' using a more relevant background, for instance using only the adverse reaction reports relative to vaccines in general. Or, to narrow it down even more, one could use as background only reports relative to vaccines for agents that access the host through airways. When narrowing down the background, one aims to detect disproportionately reported reactions that are specific for the COVID-19 vaccines, while a broader background would tend to identify reactions typical to vaccines in general. Each of these choices generate different statistical results, and there is likely no unified view on the best methodology compared to what could be considered the gold standard, the full database background. Again, the crucial point is that the reason for considering one statistical method more suitable than the others for the purpose of COVID-19 vaccine monitoring does not emerge directly from the data. If that was the case, indeed, there would be only one answer to the question of which method is the best: the answer provided by "pure facts". Rather, the method one favours to calculate disproportionality depends on clinical and pharmacological reasoning, as well as on the priorities set by different evaluating bodies.

We have argued, using examples from pharmacovigilance practice, that the data-driven approach to COVID-19 vaccine safety monitoring should be seen as constructed. Indeed, it relies on judgement, theories, and clinical/pharmacological expertise as much as on data and technological development. Why is it important to point out the fundamental role of clinical and pharmacological reasoning? The first reason, already made by Leonelli for biology data-centric research, is a question of awareness and transparency. Since the theoretical reasoning underlying data processing influence the way in which data can be used, researchers and pharmacovigilance practitioners should understand and be critical of the conceptual choices made by others, that ultimately shape their own data-based research. For instance, a recent analysis tested whether mRNA vaccines are disproportionately reported together with MedDRA terms describing facial paralysis (Kamath et al 2020). The type of statistical analysis described by the authors assumed that vaccinated and non-vaccinated people have similar likelihood of reporting an event. Evaluating whether such assumption is viable, however, is job for pharmacists and sociologists, who can assess whether for instance media campaigns might have influenced the reporting rate of vaccinated people.

A second reason for pointing out the importance of judgement and expertise in data-centric COVID-19 pharmacovigilance concerns the type of knowledge and skills we, as a scientific community, need to encourage in order to increase its efficiency, especially in times of emergency. The European Medicine Agency's Big Data Taskforce highlighted the need of more data scientists and AI professionals (European Medicines Agency 2020). However, from our arguments here stems the additional need of nurturing and reinforcing the interdisciplinary work of medical doctors, pharmacologists, and data scientists.

4.4 Ethics of Big Data Pharmacovigilance: A Critical Reflection

Increasing reliance of big data requires a parallel increase of reflections about good practices of big data research. The field of *data ethics* was recently created to

study "moral problems related to data, algorithms and corresponding practices, in order to formulate and support morally good solutions" (Taddeo & Floridi 2016: abstract).

In pharmacovigilance, one dominant concern in the sphere of data ethics is the protection of patient privacy and sensitive health data (Callréus 2013). As in all epidemiological research where health data are shared between different databases, there is a tension between the potential public health benefits of accessing personal health-related information and the privacy rights of single persons (Rocca & Anjum 2020). While this tension brings about an important and still unsolved hinder to data sharing, which was also acknowledged to slow down the progression of COVID-19 data-based research (The Alan Turing Institute 2021), there is more to be discussed.

For example, we believe that some straight-forward observations about the pharmacovigilance databases should be brought to the attention of data ethicists and might raise discussions about the inclusiveness of the current system. For instance, 80% of COVID-19 related adverse reaction reports shared into VigiBase in 2020 were from the WHO regions of Europe and the Americas, and only 1% came from the African region (Rocca et al 2021). This extreme difference is more pronounced for the COVID-19 reporting than for the database and supports the observation that global differences in medicines availability and quality of healthcare have become more pronounced during the pandemic (McMahonid, Peters, Iversid & Freemanid 2020).

When considering the state of patient safety in the African continent these numbers are not surprising. Only a few countries in the WHO African region, for instance Tanzania and Ghana, have functional regulatory and pharmacovigilance systems according to international standards, and it was predicted that other governments will not be in the economic situation to prioritise pharmacovigilance in the near future (Ogar, Mathenge, Khaemba & Ndagije 2020). Arguably, the issue of limited resources is also accompanied by a language barrier. Although coding dictionaries are offered in a number of languages, pharmacovigilance protocols and reports are predominantly issued in English, something that makes it necessary for a pharmacovigilance professional to master this language. Finally, the social structures and cultural heritage of certain countries might make it less immediate for citizens to report what can be seen as a 'failure of the system', regardless of the pharmacovigilance structures in place. At the same time, regional experts warn that the COVID-19 emergency poses a particular threat to patient safety in sub-Saharan Africa, where lack of medical literacy, misinformation, lack of sufficient professional guidance in a context of panic and fear might lead to irrational use and abuse of medicines and traditional remedies to a higher extend than elsewhere, in the attempt to prevent or cure COVID-19 (Ogar et al. 2020).

It is important to highlight that when we are strengthening big-data pharmacovigilance, AI and data processing, we are representing almost exclusively European countries, the Americas and a handful of other countries globally. One side of the problem is then that global pharmacovigilance data are biased because they are incomplete. We have little information on the level of access to and the impact of COVID-19 treatments and vaccines for a large proportion of the global population.

The bias inbuilt and hidden in data-centric research is one of the dominant themes in data ethics. The concern is that cultural assumptions hold the false belief that datasets and algorithms increase objectivity of the research because they

are less partial and less discriminatory than single researchers, single experiments and small datasets. Instead, it is often the case that there are inbuilt systematic discriminations, which are carried on no matter how big the datasets and how sophisticated the algorithms (D'Ignazio & Klein 2020). Although bigger studies and systematic reviews increase beliefs of objectivity due to bigger dataset, the picture is not complete until the systematic discrimination has been taken care of.

In the presented case, it seems that until social structures and inequalities are addressed, capacity building and awareness is raised and funds are allocated in order to strengthen the culture and the structures of patient safety globally, it will not be possible to at least decrease, if not overcome, the incompleteness of global pharmacovigilance data on which patient safety action is based. It seems then reasonable to argue that an increased reliance on algorithms and databases to improve drug safety needs to be accompanied by an increased effort of adapting to the social and technical structures of developing countries. Failure to do that will result in a system that contributes to increase the global inequalities of healthcare by increasing the disproportionate amounts of safety data on medicines from specific world regions.

In summary, in this session we have outlined the challenge of dealing with increased amount of data, due to the high number of drugs and vaccines with less established safety profiles that are distributed globally during the COVID-19 pandemic and potential similar future health challenges. We have shown that the pharmacovigilance community in parts of the world has implemented a number of technical innovations, based on smart algorithms and artificial intelligence, to attempt to face such challenges. Finally, we have made the point that the increased reliance on databased and algorithms must be paralleled by an increased reflection about the full manual or human skills that are necessary to make data-centric pharmacovigilance efficient in COVID-19, as well as reflections about the structural inequalities that underlie global pharmacovigilance. When such considerations are made, efforts to increase the interdisciplinarity between data-science skills and clinical expertise seem vital, together with considerations on how to improve technical know-how in developing countries.

5. Concluding Remarks

The aim of this paper was to indicate that an improvement of pharmacovigilance systems in the face of a pandemic requires the critical consideration of foundational issues at the side of technological development. Our analysis pointed out that both high uncertainty and increased focus on big data require to strengthen interdisciplinary networks between clinicians, pharmacovigilance experts, regulators, data scientists and curators of databases, data-ethicists and philosophers of science. At the moment, there is generally an increasing demand of interdisciplinary practice, however education, research funding, scientific journals and regulatory systems maintain a disciplinary focus. In particular, interdisciplinarity between the research and practice of pharmacovigilance and the humanities is still at an embryonic stage (Rocca 2020). The next question is how such interdisciplinarity should be implemented, and who is in charge of implementing it. We urge that the pharmacovigilance community should give space to this question, together with other foundational reflections on the epistemology and ethics of pharmacovigilance, in discussion fora, platforms, specialised journals and social media.

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