Harnessing the potential of pharmacoepidemiology for public health

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Pharmacoepidemiology for public health

Pharmacoepidemiology aims to appraise and understand the use and effects — both beneficial and adverse — of medicines in real-world settings. As such it can be considered a bridge science, linking clinical pharmacology, epidemiology, public health and the social sciences. Unlike many other health disciplines, pharmacoepidemiology is relatively young. Its value was not internationally recognized until the mid-1980s. Since then, a proliferation of scientific research has been observable: starting from classical field studies, including those used in epidemiology, and culminating in refined analytics and bespoke approaches to address different needs. Additionally, the broad scientific community, as well as other stakeholders, can now access significant quantities of administrative claims data and population healthcare databases. This has overcome issues relating to mass-recruitment for studies and statistical power, even leading researchers and the American Statistical Association to question the concepts of p-value or confidence interval.[1]

In parallel, over the past decade, new public health paradigms have evolved as a result of three factors:

1. popularization of the One-Health[2] and other global health concepts which render inappropriate a focus on specific effects, to the exclusion of development of a global and objective view of beneficial vs. untoward effects, or of benefit vs. risk
2. awareness of new pandemic threats
3. advances in information technologies, statistics, and computing (such as “big data”, artificial intelligence and machine learning).

The need for pharmacoepidemiology

Medicines are public health tools. With regard to the quality and transparency of the assessment of their effectiveness and safety, they are increasingly subject to the expectations and requirements of patients, healthcare professionals and regulators. Those involved in the development and delivery of medicines must therefore take full account of the aforementioned paradigm shifts. Additionally, the arrival of novel therapeutic agents, such as gene therapy, biologics and mRNA vaccines, whose modes of action and interactions with living organisms have very little in common with those of the more traditional chemical medicines, has brought into question the classic elements of pharmacovigilance and pharmacoepidemiology, such as the dose–effect relationship, drug causation criteria and the determination of drug exposure.

Another challenge for post-market assessment of therapeutic effect and associated real world evidence lies in the pressure towards very early market launch. This is incompatible with the traditional product development standard (i.e. phases I to IV of clinical trials) that prevailed until recently.

Indeed, one of the biggest challenges facing public health derives from the increasingly early market launch and the massive use worldwide of innovative and costly medicines, as observed during recent immunization

[1] https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf

[2] One Health' is an integrated, unifying approach to balance and optimize the health of people, animals and the environment. It is particularly important to prevent, predict, detect, and respond to global health threats such as the COVID-19 pandemic. See more at https://www.who.int/health-topics/one-health#tab=tab

[3] Medicines in the context of this paper include chemical medicines, biological medicines, vaccines and products based on genes, tissues and cells.

campaigns against SARS-COV2 virus. Public concern (justified or not, regarding risk associated with use of these medicines was very marked. Yet anticipating and characterizing the fear associated with the accelerated introduction and widespread use of a new medicine — which represents a new occurrence — is difficult. The long-term safety of "conventional" medicines has also often been questioned.

In brief, in-depth assessment — to the extent possible in real time — of the added value and associated risks of not only innovative but also older (i.e. chemical medicines) would facilitate decision-making around selection and use of medicines. Such appraisal would take into account marked changes that can be induced by numerous factors including, for example, age, gender, background incidence of the disease in a given geographic area or population and access to care.

The paradoxes of pharmacoepidemiology

Yet pharmacoepidemiology as currently practiced mitigates against such in-depth assessment. This is due, in part, to the intense interest in technological development that has almost become an end in itself, and to an overly reductionist and streamlined approach to problems. Moreover, with its increasingly powerful tools and access to immense data, it appears to have turned away from the integrated and unifying One Health concept.

Problems also arise because public opinion and decision-makers increasingly expect immediate answers to questions concerning the use of medical products, often disregarding the time required to plan and carry out the sound scientific research needed for the development of meaningful responses to those questions. The recent COVID-19 pandemic and the so-called "infodemic" that hampered efforts to overcome it, perfectly illustrated this phenomenon. The release of the results of a multitude of narrowly-focused studies worked against development of a global perspective regarding the benefit–risk ratio of the new vaccines. Studies were carried out to investigate different aspects of vaccine effectiveness and a variety of adverse reactions (including myocardial infarction, cerebral thrombosis, myocarditis, pericarditis, musculoskeletal and neurological events). Yet in spite of the hundreds of studies carried out, and the considerable resources dedicated to them, real-time data that provided an overall view and precise assessment of the benefit–risk of the new vaccines, and their impact on the main populations concerned, was lacking. Instead, a single, identified risk would become the centre of attention, even though risk is inherently unpredictable and multifaceted, especially in the case of biological medicines. The result was that social networks and influencers, rather than facts or science, shaped public opinion, often greatly exacerbating vaccine hesitancy. It was also noticeable during the pandemic that the communications and decisions of health authorities were often made hastily, ignoring the time required for execution of sound epidemiological research, to the detriment of an objective view of the global benefit–risk balance of the new vaccines.

But a "sliced" and fragmented approach to pharmacoepidemiology is not new. Rather, it has been the rule in most of the debates that have animated pharmacoepidemiology in recent decades. Many studies, sometimes contradictory, have concentrated on limited aspects of the populational impact of a medicine, such as a given type of adverse reaction, and have not provided an overall assessment that would enable a definitive conclusion to be drawn about the benefits and risks associated with a given product, and/or an appropriate decision to be taken about its use. Examples can be cited with respect to even the most commonly used medicines. They include studies targeting the specific adverse effects of proton pump inhibitors or the effect of their long-term use on all-cause mortality.[3] Conversely, other badly-needed studies are notably absent: for example, on the overall benefit–risk (e.g. injury falls, increased risk of dementia, etc.) of certain psychotropic medicines such as benzodiazepines.[4]

Studies that cannot be justified, that are unlikely to provide any responses to the questions concerning the

[3] For example : Xie Y, et al. *Estimates of all-cause mortality and specific mortality associated with proton pump inhibitors among US veterans : cohort study*. BMJ. 2019. PMID: 31147311.

[4] For example : Horowitz MA ; Wright JM, Taylor D. *Risks and benefits of benzodiazepines*. JAMA. 2021 ; 325(21): 2208.

interactions between health products and public health, can even be deleterious to public health if they delay decision-making or lead to false conclusions about risk or benefit and the real contribution of a medicine to public health.

A new approach

Collection of randomized clinical data for pharmacoepidemiological research can be very costly. But the data sources now available mean that pharmacoepidemiological research can be conducted relatively inexpensively. Moreover, available tools can greatly optimize use of data, and help ensure that results are delivered in a timely manner.

Pharmacoepidemiology thus has the potential to help generate clear evidence of the (potential) impact and efficiency of any public health intervention, especially in the event of likely new treatment paradigms and public health challenges (which will impose difficult choices in the near future).

But without denying the tremendous conceptual and technical developments made during the past forty years, it can reasonably be asserted that criteria and guidance are required in order to eliminate the limitations of much current epidemiological research and to more precisely define the role and potential strengths of pharmacoepidemiology in assessing the contribution of medicines, including biologics, to meet global public health needs. Put alternatively, pharmacoepidemiology requires a new approach, to support strategy development and decision-making. This new approach would enable us to answer questions about when to conduct a study, on what, and using what data source(s).

Creation of a CIOMS Working Group — that will ensure diversity of expertise and opinion, independence, credibility and broad outreach — to develop guidance and recommendations on the integration of pharmacoepidemiology and global public health is therefore proposed. Its role will be to focus on the questions that pharmacoepidemiology can successfully address, rather than on good pharmacoepidemiology practices, or pharmacoepidemiology's technical, methodological and statistical aspects, such as determining which type of epidemiological or statistical method to use, how to implement it, and how to analyse the data collected. (Excellent examples of the latter, some of which serve as international references, have already been published, often under the aegis of health authorities and learned societies.)

The working group: harnessing the potential of pharmacoepidemiology for public health

In the context of available data sources (administrative claims databases, registries, population cohorts and recent advances in this field such as "big data", artificial intelligence (machine and deep learning), the guidance will define the most operational approaches to comprehensive assessment of the effects of a health product and its benefits–risks balance for global public health.

The guidance will help users to determine whether or not a study would be feasible and useful. In terms of resource optimization and management, this is important. Some topics have been explored repeatedly, without always leading to operational conclusions, while important issues, such as long-term effects or negative impact on disease, have remained unanswered for years. The guidance will also facilitate prioritization of studies to be carried out according to their potential to produce meaningful results and address population impact.

The Working Group will develop an inventory of situations, both real and theoretical, representing the challenges that the assessment of the impact of medicines on public health now entails. For each situation, the working group will define:

- whether a pharmacoepidemiological study could be appropriate or should be conducted
- what information it should generate
- what would be the timeframe for setting up this study and obtaining relevant results
- what would be the study limitations and possible untoward consequences

- whether a simpler and/or faster approach, always guided by common sense, should be adopted e.g. drug utilization data, meta-analysis of available data, modelling, could provide sufficient information on this issue.
- these assessments will be synthesized so that a set of recommendations for each situation can be drafted.

More specifically, guidance will consider to what extent the paradigms of One-Health and global public health, and the launch of novel health products such as biologics, bring into question the applicability of some of the key concepts and approaches of the current application of pharmacovigilance and pharmacoepidemiology. It has already been mentioned that confidence intervals and p value may no longer be relevant when dealing with entire populations. The relevance of approaches such as case series, case–control, case–population, case cross-over, and case time control design that focus on one type of effect also need to be reviewed.

The guidance will point out that pharmacoepidemiology, however effective it may be, is unable to provide a response to every question relating to medicines and public health. Several technical and conceptual reasons account for this and will be listed and illustrated with practical examples. Fortunately, in many cases, such situations can be managed and an appropriate decision taken.

Impact

The guideline will aim to serve as a reference worldwide for regulators, pharmaceutical and biotechnology companies involved in product development and marketing, and for health policy decision-makers working at national, regional or local level. The guidance will also be of interest to researchers, academics, healthcare professionals and patients. The CIOMS guidance will aim to reduce the incidence of:

- studies that are not necessary for decision-making purposes and that can even delay or complicate decision-making (for example, if the validity of results is questionable)
- studies that fail to address, or only partially address, the public health issue to be investigated.

More significantly, the guidance will promote implementation of appropriate studies that can answer important public health questions related to medicines.

Efforts to produce the guidance will also bring about cross-fertilization between regulatory authorities, industry and scientists, and foster further collaboration in the area of pharmacoepidemiology, including to enhance its impact and support meaningful research and benefit public health at a global level.

Composition of the Working Group

The panel of experts will include a broad representation of all stakeholders covering several WHO regions including academia, pharmaceutical industry, and regulatory authorities, to promote synergies and development of a global perspective. Ensuring the optimal involvement of health care professionals and patients will be discussed and determined during the first Working Group meeting.

Deliverables

The Working Group's first task will be to agree on a list of deliverables and to establish an operational calendar for their finalization. These deliverables will be formalized concisely so that, for each issue raised, an operational approach is defined. The drafting must take into account the diversity of their potential users: regulators, researchers, members of the pharmaceutical industry and CROs, and academics.

Each deliverable will be supplemented by an appendix recalling the context and whenever possible, practical examples to illustrate the proposed approach. In common with all CIOMS reports, a glossary will be included and later incorporated in CIOMS' cumulative glossary.

An additional deliverable, in the form of a comprehensive training package is also envisaged. Its aim will be to educate stakeholders regarding experimental and observational approaches, interpretation of their findings and conclusions, and their limitations. This will be one means of tackling the misinformation that can surround the introduction of a new health product or even arise in the case of well-known and much-used product.

Timelines

The Working Group is expected to finalize its report within three (at most four years). Timeline for development of the training package timelines may exceed those of the report.